20TH EADO CONGRESS

April 4th–6th, 2024

PARIS, FRANCE

PALAIS DES CONGRÈS VERSAILLES

EADO
European Association of Dermato Oncology

BOOK OF ABSTRACTS

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ABSTRACTS

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Table of Contents

- Patient with metatypical metastatic Basal Cell Carcinoma treated with Vismodegib.
- Patient-orientated evaluation of treatment of non-melanoma skin cancer with Rhenium-188 compared to surgery
- Primary radiotherapy in older adults with basal cell carcinoma: results of the prospective, multicenter BATOA cohort study on treatment burden, short-term outcomes and a comparison with surgically treated patients
- Right-Sided Lateralisation of Basal Cell Carcinoma and Squamous Cell Carcinoma in a UK Cohort
- The use of High Frequency Ultrasound in Cutaneous Oncology Surgery
- Topical Rhenium-188 ionizing radiation therapy exerts high efficacy in curing non-melanoma skin cancer- Final study results
- What is the quality-of-life impact of basal cell carcinoma in older patients? A multicentric cross-sectional study.
- **Cutaneous sercoma**
- Incidence, local recurrence, metastasis, disease-specific survival, and overall survival in patients with cutaneous rhabdomyosarcoma: A nationwide cohort study of 24 patients
- Cancers of the skin and mucous membranes in people living with HIV compared to the general population.
- Clinical features and treatment patterns of patients with classic Kaposi sarcoma in Greece.
- Evaluating the performance of a clinicopathological prognostic nomogram and utility of the 40-gene expression profile (40-GEP) test in refining risk of metastasis in high-risk cutaneous squamous cell carcinoma (HR-cSCC) patients
- Evaluation of efficacy and tolerability of a repairing protective cream containing the postbiotic Aquaphilus Dolomiae extract G2 for onco-dermatological indications
- Multimodal skin imaging of a dermatofibrosarcoma protuberans using line-field confocal optical coherence tomography, ultra-high frequency ultrasound and reflectance confocal microscopy
- Optimizing Healing: Evaluating Ozone Therapy's Impact on Skin Cancer Surgery Reconstruction at the Amazon Head and Neck Surgery Center
- Stratified processing of skin lesions through deep learning
- Sun awareness and prevention in chemotherapy patients: a comparative study

Cutaneous T- and B-cell lymphoma

- Dermoscopic, Reflectance Confocal Microscopy and Line-field Optical Coherence Tomography features of Cutaneous Lymphomas
- Insights on different erythroderma features in Sezary syndrome: a prospective validation study
- Integrated transcriptomics reveals cellular and molecular interactions in pruritic cutaneous T-cell lymphoma
- Leg lymphoma not leg type lymphoma
- Updates on CTCL diagnostic and therapeutic trends amidst the COVID-19 pandemic: insights from a referral center

Melanoma – Epidemiology and diagnostics

- Phenocopies in melanoma families with germline mutations in CDKN2A are associated to MC1R polymorphisms and high total body nevus count
- Level of satisfaction with treatment and clinical care at the Skin Cancer Unit in patients with cutaneous melanoma - A single specialist referral centre analysis.
- ANALYSIS OF GLOBAL Skin-Cancer Epidemiology and Correlation with Dermatologist Density and Population Risk Factors
- Analysis of the long-term survival of patients with thin melanomas using comprehensive, population-based Australian data.
- Assessment of facial pigmented lesions using Line-field Confocal Optical Coherence Tomography and its correlation with Reflectance Confocal Microscopy and histopathology
- Assessment of performance in clinical risk prediction tools for cutaneous melanoma in the UK population
- Assessment of the impact of a dermoscopy training associated with an artificial intelligence on general practitioner residents
- Augmented intelligence using 2D and 3D total body photography for melanoma screening: Patient and dermatologist perspectives in real-world application
- Breslow thickness depends significantly on the individual suspecting melanoma: the importance of guaranteeing access to a dermatologist.
- Changes in the pigmentation of melanocytic nevi associated with the use of self-tanners: a diagnostic challenge in patients at risk of melanoma
- Characterization of 10 cutaneous tumors with ex vivo LC-OCT: A novel tool in dermato-oncological surgery with margin control?
- Cost-of-illness of skin cancer: A systematic review
- Developing a patient-informed conceptual model of advanced and metastatic melanoma
- Diagnosis of vulvar pigmented lesions with confocal microscopy
- Diagnostic criteria for melanocytic lesions in LC-OCT
- Early detection of skin cancer: a nurse-initiated consultation to improve dermatology access.
- Epidemiological indicators of melanoma in the Republic of Uzbekistan
- Estimating Occupational Exposure to Ultraviolet Radiation Using the Canadian Occupation Exposure Matrix (CANJEM) in a Nationwide Cohort of French Adults
- Gamification of Dermoscopy Education Using a Smartphone Mobile Platform: A Pilot Study
- Incidence Of Skin Melanoma And Mortality From It Among The Population Of The Republic Of Belarus (epidemiological data from a 30-year study)
- Is melanoma a death sentence in Black Africans? A three-year institutional study from a resource limited setting
- Long-term survival of melanoma patients according to primary tumour thickness – an Australian population-based study
- Loss of AMBRA1 expression in the tumour endothelium as a potential biomarker to identify AJCC stage I/II melanomas at high risk of metastasis.
- Melanoma Diagnostic Accuracy in a Total Body Photography System with an AI Dermoscopy App

- Melanoma in Children, Adolescents, and Young Adults: The Spanish Cohort of the MELCAYA Consortium
- Melanoma Prognosis and Associated Risk Factors: A Retrospective Cohort Study Using Semantic Map Analysis
- Nationwide study of the treatment options of lentigo maligna and recurrence rates in the Netherlands
- New designed, non-invasive diagnostic tools for the diagnosis of oral mucosal lesions.
- New differential diagnosis of melanoma. ¿Induced?
- Novel, non-invasive method for classification of melanocytic lesions using a direct illumination multispectral imaging camera
- Prediction of melanoma metastasis using dermatoscopy deep features. An international multicenter cohort study
- Pregnancy-associated melanoma- a pilot study
- Prospective multicenter comparative study of dermoscopic images of a standard dermatoscope and an Autonomous TBP/Dermoscopic Imaging device (Deviskan^{R}) ("Deviskan QS"-Quality Study)
- Psychological distress and need for psycho-oncological support in high-risk patients for melanoma and melanoma survivors: Patient-reported outcomes of a prospective study
- Risk factors on developing brain metastasis from melanoma: A sistematic review
- Role of the COVID-19 pandemic on the incidence and stage at initial diagnosis of cutaneous melanoma: a retrospective national study from the French Clinical Database of Melanoma Patients (RIC-Mel).
- Sarcopenia as a prognostic indicator in advanced melanoma; a retrospective cohort study.
- Single-cell and spatial transcriptomic analysis of primary (nevus-associated)-melanoma
- Staging of Mucosal Melanoma of the Head and Neck
- The health economic impact of the 31-gene expression profile test for treatment and surveillance management plans in patients with cutaneous melanoma
- The interest of dermascopy X400 technique interpreted by non dermatologists and an artificial intelligence software in the identification of pigmented genital lesions.
- Unlocking Potential in Clinical Practice: A Comprehensive Assessment of an Artificial Intelligence Based Clinical Decision Support System for Cutaneous Melanoma Detection
- Usability of a smartphone app for skin cancer detection.
- Use of 3-dimensional total body photography and digital dermoscopy with artificial intelligence algorithms for early melanoma detection in high-risk patients
- Using a clinicopathologic and gene expression model to predict prognosis in stage I-II primary cutaneous melanoma: a multicenter Danish cohort study
- Validation of the Melanoma Institute Australia Prediction Tool for Sentinel Node Metastasis Risk Amongst Patients with Cutaneous Head and Neck Melanoma
- “One spot check”; a new strategy to increase dermatology access for worrisome skin lesions.

Melanoma – Experimental and translational studies

- ALDH1A3-acetaldehyde potentiates melanoma heterogeneity
- AMBRA1 is a predictive biomarker of melanoma response to targeted therapy
- Cell cannibalism: a possible source of therapy resistant melanoma-fibroblast hybrids
- Circulating tumor DNA: a promising biomarker in stage III BRAF+ melanoma
- Discoidin domain receptor 1, a melanoma immunomodulator
- Effects of temozolomide on tumor mutation burden and microsatellite instability in melanoma cells
- Elevating MAPK Pathway Suppression with Combinatorial ERK Inhibitors
- Gene Signatures predict immune-related skin adverse events in melanoma patients
- High dose Vitamin D supplementation does not improve outcome in a cutaneous melanoma population: results of randomized a double-blind, placebo-controlled study (ViDMe trial)
- Identification of patients at high risk for relapse by Merlin Assay (CP-GEP) in an independent cohort of patients with melanoma who did not undergo sentinel lymph node biopsy: head and neck subgroup analysis
- Immunohistochemical analysis of AMBRA1 and loricrin expression reveals maintained expression in the epidermis overlying a range of benign melanocytic naevi but which may be altered in some melanoma in situ cases.
- Is There a Distinctive Molecular Identity for Sinonasal Malignant Mucosal Melanoma Compared to Cutaneous Melanoma?
- Kindlin-3 inactivation mediates melanoma agressiveness through crosstalk with the collagen-activated tyrosine kinase receptor DDR1
- Macrophages: A Key Population for the Resistance Acquisition in BRAF Mutant Melanoma
- miR-146a-5p and miR-21-5p as Potential Biomarkers of Malignant Melanoma
- Next generation sequencing (NGS) in melanoma patients: a descriptive study of a Canarian cohort with suspected cutaneous melanoma-dominant syndrome.
- PBX1 deregulation promotes melanoma progression and metastasis through alternative splicing
- Redefine Individual Melanoma Patient Stratification with Artificial Intelligence and Computational Analysis
- RNA helicase DHX9 enables PBX1 mRNA translation by unfolding RNA G-quadruplex in melanoma
- Role of eIF6 in Modulating Response to BRAF Inhibitors and Acquired Resistance in Cutaneous Melanoma
- Targeting autophagy as a therapeutic intervention in BRAFV600E melanoma cells through ULK-1 inhibition
- Tebentafusp effect on the tumoural landscape in metastatic uveal melanoma – a post-mortem study
- The Dutch Early-Stage Melanoma Study (D-ESMEL): a Discovery Set and Validation Cohort to Predict the Absolute Risk of Distant Metastases in Stage I/II Cutaneous Melanoma
- Tumor microenvironment (TME) features and serum cytokines in patients with metastatic uveal and cutaneous melanoma treated with tebentafusp

- Unraveling the Impact of Microbiome on Immunotherapy Efficacy in Melanoma

Melanoma – Immune checkpoint inhibitor (ICI) therapy

- A case of delayed onset immune-related optic neuritis after combined immunotherapy treatment for metastatic melanoma
- A phase 3 study of the efficacy, safety, and pharmacokinetics profile of subcutaneous vs intravenous nivolumab + relatlimab fixed-dose combination in previously untreated metastatic or unresectable melanoma (RELATIVITY-127)
- A systematic review of changes in melanocytic naevi during immune checkpoint inhibition and targeted therapy
- Adjuvant lymph node radiotherapy and immunotherapy in stage III melanoma
- Benefit of immunotherapy for advanced melanoma in two patients with xeroderma pigmentosum.
- Comparative Analysis of Pembrolizumab Dosing Schedules in the Adjuvant Treatment of Malignant Melanoma
- Complete response as prognostic marker of prolonged survival in metastatic melanoma
- Dermatological adverse events due to oncotherapy: the necessity for a new classification
- Dupilumab for the treatment of bullous pemphigoid triggered by melanoma immunotherapy
- Early recurrence in a pooled international cohort of melanoma patients treated with adjuvant nivolumab in a real-world setting
- Exploring “Decision regret” in Adjuvant-Treated Melanoma Patients– results from a cross-sectional survey on 200 participants
- First-line Nivolumab plus Ipilimumab in patients with advanced melanoma previously treated with adjuvant systemic therapy
- Hypertrophic Lichen Planus associated with Pembrolizumab
- Immune-related adverse events with adjuvant anti-PD-1 therapy in high-risk resected melanoma: a single-center experience
- Immunotherapy after progression to immunotherapy: Pembrolizumab and Lenvatinib versus conventional chemotherapy for patients with metastatic melanoma after failure of PD-1/CTLA-4 inhibition
- Impact of Immune-Related Adverse Events on Melanoma Outcomes: A Comprehensive Analysis
- InterPATH-001 trial in progress: Adjuvant V940 (mRNA-4157) with pembrolizumab versus placebo in patients with high-risk stage II-IV melanoma
- Ipilimumab and nivolumab in uveal melanoma: report on toxicity and treatment intensity
- Phase 2 Study of aTezolizumab, bevAcizumab, and Cobinetinib (TACo) in patients (pts) with PD1 refractory metastatic brain metastases (MBM)
- Prognostic value of tumor microenvironment molecules in the response to immunotherapy in advanced melanoma
- Quality-of-Life Assessment in Spanish Stage III Immunotherapy Patients: A Prospective Observational Study
- Radioimmunotherapy Sequence Impact on Clinical Outcomes of Patients with

Melanoma Brain Metastases: A Meta-analysis of Comparative Studies

- Real-World Evaluation of ImmuCare Patient-Reported Outcomes in Melanoma Patients Treated with Immune-Checkpoint Inhibitors
- Real-world outcomes for advanced melanoma in the adjuvant and unresectable setting: Single-center registry analysis
- RESCUE STUDY – International Survey on training of Dermatology Residents in Supportive Oncodermatology
- Sex differences and its impact on treatment outcomes of advanced melanoma in Germany – a DeCOG study on 2032 patients of the multicenter prospective skin cancer registry ADOREG
- Title: Survival Analysis of Patients with Non-Cutaneous Metastatic Melanoma Treated in a Reference Center in Northeast Mexico.
- Updated outcomes of AdjuMel study: real-world data in patients with resected stage III-IV melanoma treated with adjuvant nivolumab in France
- Use of Immune Checkpoint Inhibitor (ICI) Therapy for Cutaneous Melanoma from 2014 to 2021 in Norway: Insights from Real-World Data

Melanoma – Surgery

- Clinical characteristics and surgical approach of patient with SAMPUS/ Melanoma and pleomorphic dermal sarcoma on face
- Does the interval between melanoma diagnosis and surgery have an impact on outcomes? A systematic review and meta-analysis.
- Higher intraoperative detection rate of suspicious non-palpable lesions using wire marking in skin cancer patients
- Lymph Node Operative Experience in the UK – What's Changed?
- Patients who forego sentinel lymph node biopsy after 31-GEP testing are not harmed: A prospective, multicenter analysis
- Predicting sentinel node positivity in patients with primary cutaneous melanoma: an international multicentre study validating and refining the MIA risk calculator
- Prognostic impact of the surgical deep margin distance of invasive acral melanoma of the sole: A multi-institutional retrospective study
- Surgical treatment of external ear skin melanoma: literature review and one-center experience
- The practice of using Vacuum-Assisted Closure in combination with free skin grafts in the treatment of wound defects after removal of malignant skin neoplasms
- Time interval between Sentinel Lymph Node Biopsy and Excision of Primary Melanoma does not impact long term outcomes in a large UK cohort
- Total skin micrografts with punch for repair of surgical defects in acral skin

Melanoma – Systemic therapy other than ICI therapy

- Adjuvant therapy for Asian patients with resected stage III/IV BRAF V600-mutant melanoma with more than 3 years of follow-up: A multicenter retrospective study in Japan
- Complete remission of malignant lung metastasis of melanoma with stereotacticradiotherapy (Case report)

- Exceptional response to rechallenge of BRAF/MEK inhibitors in patients with primary acquired resistance to targeted therapy
- Gastric Melanoma: Primary or Secondary Forms? 2 case reports
- Patient treatment preferences in unresectable/metastatic BRAF-mutated melanoma: a qualitative study
- Real-world outcomes of adjuvant therapy in melanoma: an Italian referral center experience.
- The clinical utility of comprehensive genomic profiling tests for patients with advanced malignant melanoma in a real-world setting: A retrospective analysis from a single cancer center
- The RoMEO study: a real-world, observational, prospective investigation of dabrafenib and trametinib combination treatment in patients with BRAF V600 unresectable or metastatic cutaneous melanoma.

Merkel cell carcinoma

- All-trans retinoic acid activity in Merkel cell carcinoma cells: implication of the retinoid pathway
- Merkel cell carcinoma cells proliferation is inhibited by the DNA methyltransferases inhibitor guadecitabine via methylome modulation
- Prognostic significance of sentinel node tumor burden in Merkel Cell Carcinoma.

Rare tumors

- A retrospective multicenter study on the real-world efficacy of chemotherapy in 204 Japanese patients with advanced extra-mammary Paget's disease
- Atypical granular cell tumor - a case for worry?
- Atypical spitzoid lesions: A molecular and histological analysis of two NTRK driven cases
- Autoimmune Bullous Disorders induced by Cyclin-Dependent Kinase 4/6 inhibitors – first case series from the EADV Task Force “Dermatology for Cancer Patients”
- BRCA1-associated-protein 1 tumour predisposition syndrome (BAP1-TPDS) presenting with multiple BAP1-inactivated melanocytic tumours – a rare hereditary tumour syndrome
- Clinical and dermatoscopic features of multiple piloleiomyomas - a case report
- Evaluation of anticancer therapy- related dermatologic adverse events: insights from fda's faers dataset
- First description of atypical fibroxanthoma in Line-Field Confocal Optical Coherence Tomography and comparison with Reflectance Confocal Microscopy
- Genetic sequencing and Novel Therapeutic Targets in Perianal Extramammary Paget Disease
- Kissing lesions on penis – a very rare case report
- Localized multiple spiradenomas are caused by somatic mosaicism in ALPK1 hotspot mutation
- Paediatric Spitzoid Neoplasms : a 10-year retrospective study
- Pembrolizumab treatment for advanced pleomorphic dermal sarcoma, a three-case series in a spanish tertiary-level hospital

- Skin adnexal carcinomas DNA genomic profiling uncovers oncogenic pathways and potential therapeutic targets.
- Slow Mohs Micrographic Surgery in the management of Extramammary Paget’s Disease
- Squamoid Eccrine Ductal Carcinoma: A Case Series of Three Patients
- The risk of subsequent skin cancer in patients with atypical fibroxanthoma or pleomorphic dermal sarcoma compared to the general population: a retrospective cohort study
- Ultrasonography for the diagnosis and follow-up of extramammary Paget's disease (EMPD). A case-report.
- Unresectable endocrine mucin-producing sweat gland carcinoma revealing an actionable somatic CHEK2 gene mutation
- Whole transcriptome sequencing: Optimizing molecular classification and management of rare skin cancers.

Squamous cell carcinoma

- A Phase 1 study of fianlimab in combination with cemiplimab in patients with anti–PD-1/L1-experienced cutaneous squamous cell carcinoma
- A Randomized, Double-Blind, Phase 2 Study of Perioperative MK-4280A (Coformulation of Favezelimab and Pembrolizumab) vs Pembrolizumab in Patients With Resectable Cutaneous Squamous Cell Carcinoma
- A successful treatment of locally advanced squamous cell carcinoma with cemiplimab in a patient with multiple myeloma
- Age over 90 years is an unfavorable prognostic factor for resectable cutaneous squamous cell carcinoma
- Analysis of risk factors in melanoma survivors for the development of non-melanoma skin cancer
- Anhidrotic ectodermal dysplasia with multiple cutaneous squamous cell carcinomas in sun-exposed areas
- Beyond tropical verrucose syndrome: new associations of skin cancer and verrucous lesions.
- Cemiplimab Immunotherapy in the Treatment of Cutaneous Squamous Cell Carcinoma
- Cemiplimab in the treatment of locally advanced cutaneous squamous cell carcinoma: a case series study.
- Clinical response to immune checkpoint inhibitors in immunocompromised patient with metastatic non-melanoma skin cancer.
- Complete regression of Bowen's disease after incisional biopsy: case report
- Cost -effectiveness of Surgical Excision versus Photodynamic Therapy and 5-Fluorouracil Cream in Treatment of Bowen’s Disease: a trial based economic evaluation
- Delphi Consensus of Tumor Stage Based Treatment Approach to High-Risk Cutaneous Squamous Cell Carcinoma
- Desmoplasia, a risk factor for recurrence and metastasis in cutaneous squamous cell carcinoma: an interobserver agreement study among dermatopathologists.
- Examining the Association Between Ruxolitinib and Aggressive Cutaneous

Squamous Cell Carcinoma: Is There a Justified Need for Screening Programs?

- Factors Influencing the Risk of Involved and Close Squamous Cell Carcinoma Excision and Recurrence: A Comprehensive Analysis over a 7-Year Period.
- Flow cytometry-based strategy to characterize the microenvironment of skin tumors as a tool for preclinical research
- HPV vaccination practices among organ transplant recipients in France.
- IL-17 mediates angiogenesis in Basal Cell Carcinomas and Squamous Cell Carcinomas
- Incidence and surgical treatment trends of non-melanoma skin cancer in Denmark 2002-2021
- Integrating a Clinicopathological Risk Prediction Model into the European Guideline for Cutaneous Squamous Cell Carcinoma
- Malignant transformation during anti-TNF treatment of Hidradenitis suppurativa
- Management and outcomes following the first cutaneous squamous cell carcinoma in kidney transplant recipients: the United Kingdom COAST (Contemporary Outcomes After cutaneous SCC in Transplant recipients) study
- Neutrophil-lymphocyte ratio as a predictive marker for progression free survival in patients with advanced cutaneous squamous cell carcinoma prior to Cemiplimab treatment – a real-life setting
- Patient reported outcomes in the multidisciplinary treatment of patients with high-risk cutaneous squamous cell carcinoma in the head-neck area.
- Performance of a new classification system based on the eight most relevant prognostic factors for cutaneous squamous cell carcinoma: a retrospective cohort study showing limits to risk stratification with clinical and histopathological risk factors.
- Perineural invasion for risk stratification in cutaneous squamous cell carcinoma: a scoping review.
- Phase 2 study of intratumoral vidutolimod in combination with intravenous cemiplimab in patients with selected advanced cancer or metastatic cancer: trial in progress
- Porokeratosis Ptychotropica: The risk of cancerization and treatment options
- Predictors of recurrence and progression in poorly differentiated cutaneous squamous cell carcinomas: insights from a real-life experience.
- Prognostic factors for treatment failure of photodynamic therapy and5-fluorouracil in Bowen’s disease
- Proteomic Profiling of Cutaneous Squamous Cell Carcinoma Samples from Solid Organ Transplant Recipients and Immunocompetent Patients
- Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator (SUNTRAC): Perspectives from the EUSCAP database in a cohort of kidney transplant recipients
- Slow Mohs Micrographic Surgery: A Service Evaluation
- Sun Protection Patterns Among Organ Transplant Recipients and Non-Organ Transplant Patients with Skin Cancers
- Survival Outcomes in T3N0 versus N1 in Head and Neck Cutaneous Squamous Cell Carcinoma – Implications for Neoadjuvant Immune Checkpoint Inhibitor Immunotherapy
- The Correlation Between Clinical and Pathological Tumor Size in Cutaneous Squamous Cell Carcinoma and the Risk of Erroneous Downstaging
- The Dutch Keratinocyte Cancer Collaborative: real-world linked health care data to

identify and follow-up patients with advanced cutaneous squamous carcinoma on a nationwide level

- The treatment of elderly patients with locally advanced or metastatic cutaneous squamous cell carcinoma using Cemiplimab monotherapy or Cemiplimab associated with palliative radiotherapy: A single centre experience from the United Kingdom.
- Using the free flap to repair the postoperative defect of the head and neck squamous cell carcinomaUsing the free flap to repair the postoperative defect of the head and neck squamous cell carcinoma

Amount of abstracts: 224

Actinic keratoses

A-303

Efficacy and safety of tirbanibulin 1% ointment for the treatment of actinic keratosis in routine clinical practice in Spain and Italy (TIRBASKIN study)

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Background
Efficacy and safety of tirbanibulin have been evaluated in two Phase III trials in the US [1]. However, there is currently no clinical experience with tirbanibulin in Spain and Italy. The objective was to evaluate the efficacy and safety of tirbanibulin administered to patients with actinic keratoses (AKs) in routine clinical practices in Spain and Italy.

Methods
TIRBASKIN is a multicenter, single-cohort, phase IV, low-interventional, clinical study conducted among adult patients with 4-8 non-hyperkeratotic non-hypertrophic AK lesions of the face or scalp in an area of up to 25 cm^2 not previously treated in the last 6 months on the same area. Patients applied tirbanibulin 1% ointment for 5 consecutive days. Efficacy was assessed by the percentage of patients with complete (100%) clearance (CC) of all lesions within the application area and the percentage of patients with partial clearance (PC), defined as a reduction of at least 75% in the number of lesions within the application area, at Day 57. Safety was assessed by incidence and severity of adverse events (AEs) and local tolerability signs (LTS) (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosions/ulcerations) on a grading scale ranging from 0=absent to 3=severe.

Results
A total of 205 patients (mean age: 75 years; male: 84%; Fitzpatrick skin type II: 59%) with AK on face (46%), scalp (53%) or both (0.5%) completed study assessments at Day 57. At Day 57, there was a change from baseline of -75% in the number of lesions. CC was achieved by 52% of patients, and PC was achieved by 72% of patients (Figure 1), similar to the results obtained in Phase III trials [1]. At Day 8, 49% of patients provided information on LTS; LTSs were mostly mild or moderate erythema (37%), flaking/scaling (19%) and crusting/scabs (16%), resolved at Day 57. As AEs of special interest, two patients experienced basal cell carcinoma outside the application area. Neither AEs leading to death nor serious AEs occurred.

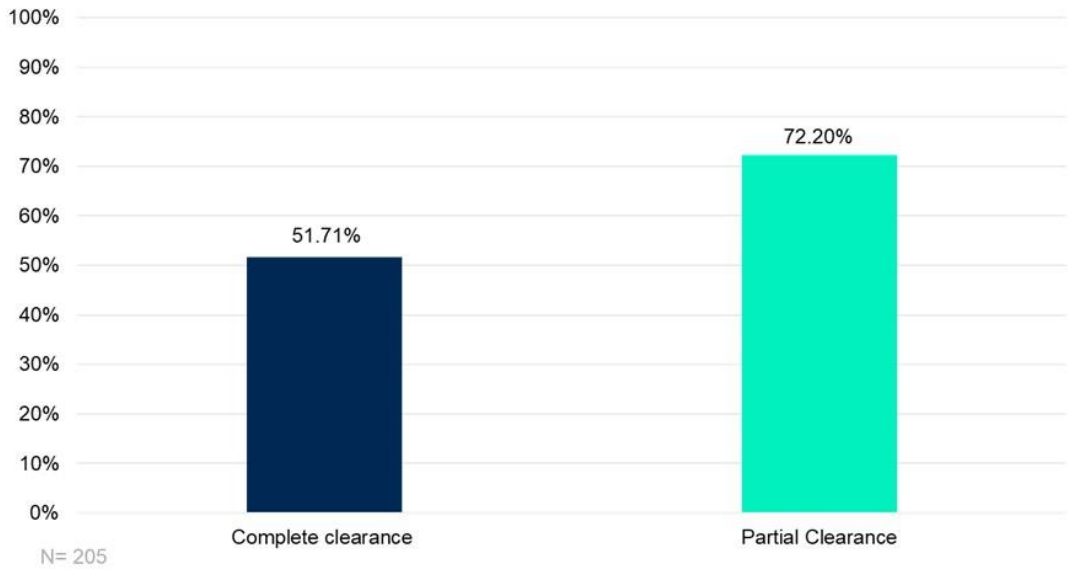

Figure 1 Complete and partial clearance after treatment with tirbanibulin for AKs

Conclusions
Tirbanibulin 1% ointment is effective, safe, and well tolerated, consistently with results reported in pivotal trials [1]. These results in clinical practice consolidate tirbanibulin as a valuable choice among AK available treatments.
References:

[1] Blauvelt A et al., (2021), Phase 3 Trials of Tirbanibulin Ointment for Actinic Keratosis, N Engl J Med, 384(6):512-520

A-124

Enhancement of sun-damaged skin qualities with tirbanibulin (SunDamage Study)

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Background
Actinic keratosis (AK) is caused by photo damage, distinctly by ultraviolet (UV) radiation. Subclinical stages of AK are present in epidermal layers before becoming clinically visible. The objectives were to assess efficacy and safety of the treatment with tirbanibulin, and the quality of sun-damaged skin before, immediately after and 2 months after the treatment by standardized VISIA® photography.

Methods
"SunDamage" is an interventional, monocentric, national, single-arm, uncontrolled, open, prospective phase IV study. Adult patients diagnosed with sun-damaged skin on the face applied tirbanibulin every night for 5 consecutive days. Disease specific skin parameters (AK lesions, subclinical lesions, sun damage, local skin reactions [LSRs] and other changes of the skin, including those not clinically relevant) were assessed both according to clinical routine and by VISIA® UV imaging (Figure 1)[1] at baseline, Day 8 (±2) and Day 57 (±7). Safety was analyzed by means of adverse events (AEs). LSRs were recorded and graded separately.

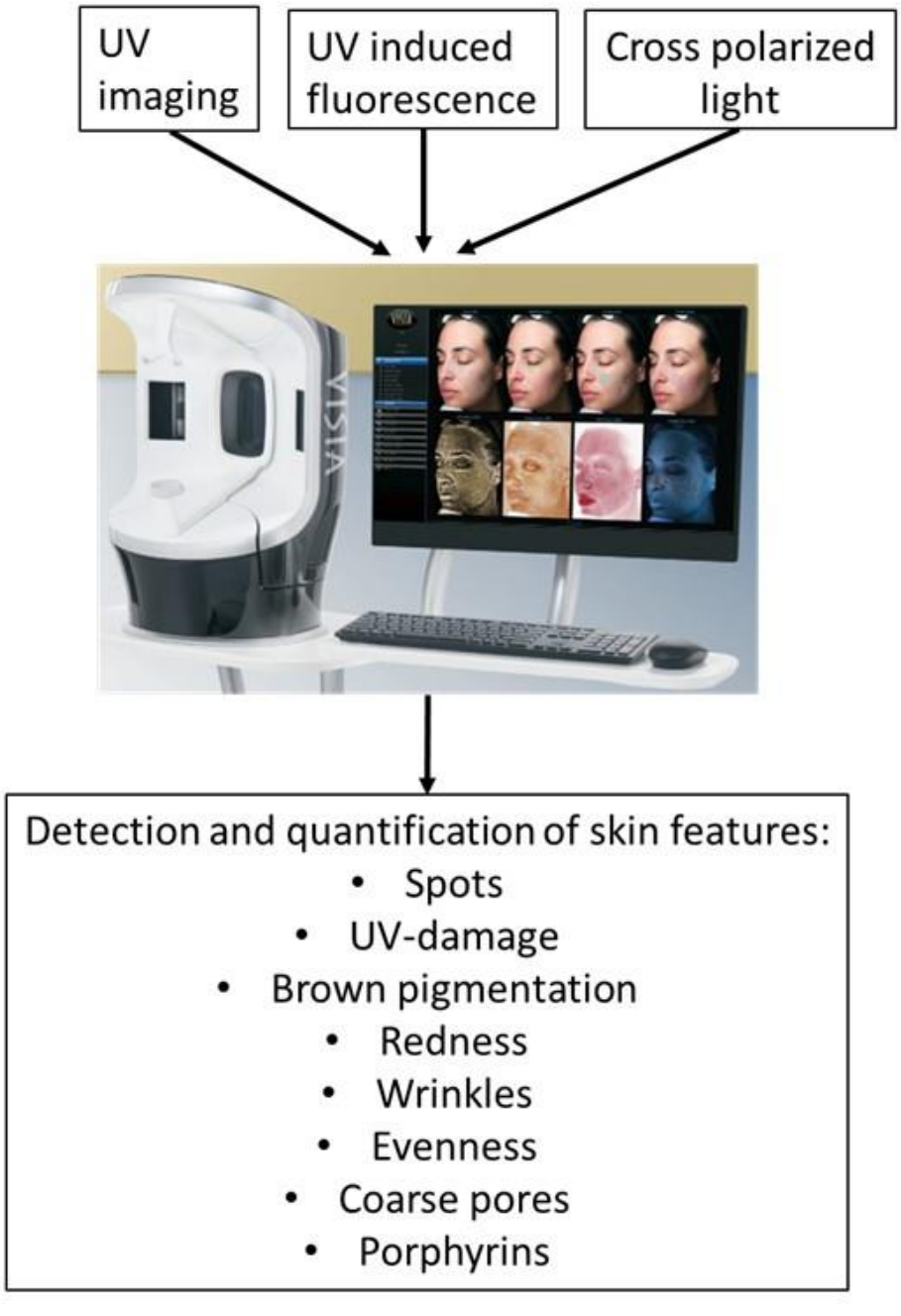

Figure 1 Description of VISIA® system

Results

A total of 26 patients completed the study (average age: 68 years; female: 58%). All patients presented sun-damaged skin, but no visible AKs. At Day 7, VISIA® measurements of the erythematous skin revealed higher values of redness by 8% points and roughness of the skin of 7% points. Thus, representing the mild LSR to tirbanibulin unmasking very early stages of subclinical AK as a symptom of sun damage (Figure 2). At Day 57, VISIA® measurements revealed improvement in all qualities of the skin in measured percentage points: spots: + 1.8, UV-damage +4, brown pigmentation +3.17, redness +2.8, wrinkles +2.46, evenness +4.5, coarse pores +1.32, porphyrins +2.73, revealing enhancement of sun-damaged-skin qualities. All patients developed mild erythema after application of tirbanibulin being visible on Day 7. At Day 57 there was no visible erythema. No safety concerns were observed.

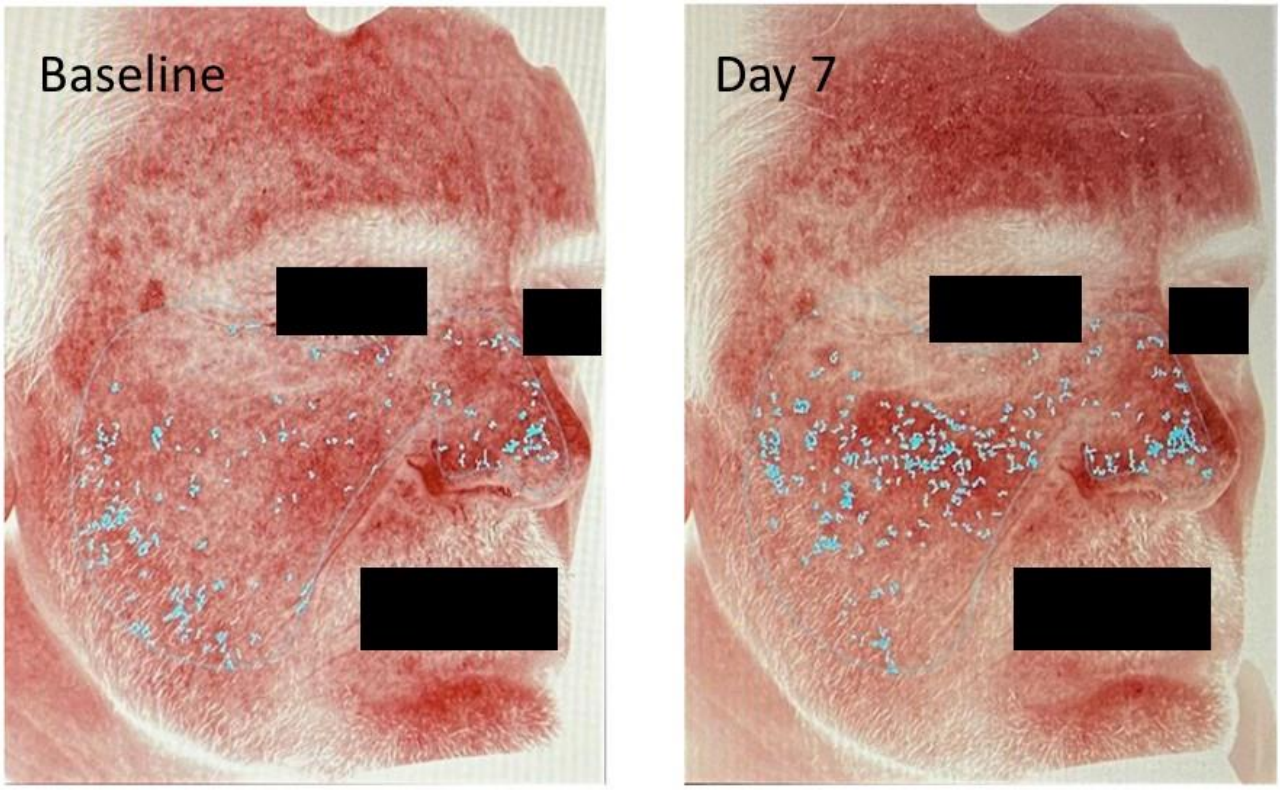

Figure 2 VISIA® measurements of erythema at baseline and at Day 7

Conclusions

These results confirm tirbanibulin to be effective, safe, and well tolerated in adult patients with facial sun damage. Moreover, tirbanibulin showed enhancement of 8 skin qualities measured by the VISIA system: spots, UV-damage, brown pigmentation, redness, wrinkles, evenness, coarse pores, and porphyrins. VISIA® can contribute to the characterization of sun damage severity and the monitoring of tirbanibulin treatment.

References:

[1] Canfield Scientifc, VISIA: Redefining the Vision of Skin Care 2022., https://www.canfieldsci.com/imaging-systems/visia-complexion-analysis/, 2024-01-01

A-236

Identification of two transcriptomic subgroups in actinic keratosis: differentiation between normal skin and cutaneous squamous cell carcinoma-like profiles using RNA-seq

L. Corchete-Sánchez[1,2], R. Corchado-Cobos[1], N. García-Sancha[1], C. Cardona-Machado[1,3], G. Baeza-Hernández[1,3], J. Pérez-Losada[1], J. Cañueto[1,3]

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Background

Actinic keratosis (AK) is the most important independent risk factor for the development of cutaneous squamous cell carcinoma (CSCC). The description of AK is essentially clinicopathological and its molecular characterization is not completely defined. We set out to evaluate a spectrum of aggressiveness from normal skin towards CSCC, with particular attention to AK and we aimed to evaluate whether there are distinguishable groups of actinic keratosis at the transcriptomic level.

Methods

An RNA-Seq study was performed, including normal skin(N=7), clinically similar grade II AKs (N=8), low-risk SCC(N=10), and high-risk SCC(N=9). Total RNA was extracted from the QIAGEN Kit samples(ref: 74134). The quality and quantity of the RNA were evaluated using the Bioanalyzer(Agilent) (RIN>8.5, 10 ng/µL). Sequencing was done on the Next-seq500 on the Flowcell Mid 150 to generate 75 bp long, paired-end reads. 75 million readings were performed per sample. Sequencing data processing using STAR and DESeq2. Biological pathways and gene set analyzes were performed by GSEA using the ClusterProfiler R package, focusing on cancer Hallmark pathways from the msigdbr package to obtain biological information. The rMATS tool was used to carry out an analysis of alternative splicing.

Results

Our study has delineated two distinct subtypes of AK, distinguished by 651 differentially expressed genes (DEGs). Transcriptomic analysis revealed that one subtype exhibits a profile closely aligned with that of Normal Skin (NS), hereby referred to as NS-like AK, while the other subtype mirrors the expression profile characteristic of CSCC, thus termed CSCC-like AK. This distinction implies divergent paths in the progression toward tumorigenesis. Further, enrichment analysis highlighted a pronounced presence of pathways associated with proliferation and inflammation within the CSCC-like subtype in comparison to the NS-like subtype. Notably, we observed significant differences between the two AK subtypes not only in their transcriptomic landscapes but also in their profiles of alternative splicing isoforms

Conclusions

RNA-seq analysis has successfully identified two molecularly divergent subgroups of AK, characterized by distinct transcriptomic signatures and alternative splicing isoform profiles. One subgroup is transcriptionally akin to normal skin, while the other bears greater resemblance to SCC, suggesting different stages in the evolution toward malignancy.

A-304

Patient and physician-reported outcomes with tirbanibulin 1% ointment for actinic keratosis in routine clinical practice in Spain and Italy (TIRBASKIN study)

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Background
Patient-reported outcomes such as treatment preference or satisfaction have not been assessed in patients treated with tirbanibulin for actinic keratoses (AKs) in Spain and Italy. The objective was to evaluate patient- and physician-reported outcomes following treatment with tirbanibulin ointment 1% once daily for 5 consecutive days in routine clinical practice.

Methods
TIRBASKIN is a multicenter, single-cohort, phase IV, low-interventional, clinical study conducted among adults with 4-8 non-hyperkeratotic, non-hypertrophic AK lesions of the face or scalp in an area of up to 25 cm^2 not treated in the last 6 months on the same area. Patients completed Treatment Satisfaction Questionnaire for Medication Version 9 (TSQM-9) survey at Day 57 comprising 3 domains: treatment effectiveness, convenience of use and global satisfaction with the treatment. Both patients and physicians completed the Expert Panel Questionnaire at Day 57, rating the overall skin appearance, satisfaction with improvement in “how skin looks” and “skin texture”, overall satisfaction, and likelihood to consider to be treated with tirbanibulin again (if needed), on a 5-point adjectival response scale from 0 to 5. Physicians’ version refers to physician’ experience/observation of tirbanibulin effects on their patients.

Results
A total of 205 patients with AK lesions on face (46%), scalp (53%) or both (0.5%) completed the study (mean age: 75 years; male: 84%; Fitzpatrick type II: 59%). Of them, 65% received previously at least one AK therapy. At Day 57, patients reported high levels of tirbanibulin satisfaction for all the 3 domains of TSQM-9 (Figure 1). 96% of physicians and 93% of patients rated overall skin appearance after tirbanibulin ointment to be much/somewhat improved and 91% of physicians and 88% of patients were extremely/very satisfied or satisfied with tirbanibulin to improve “how skin looks” and “skin texture”. Moreover, 88% of physicians and 85% of patients reported tirbanibulin to be much/somewhat better compared with the previous topical treatment and both (87%) reported much/somewhat likelihood to consider tirbanibulin again, if needed.

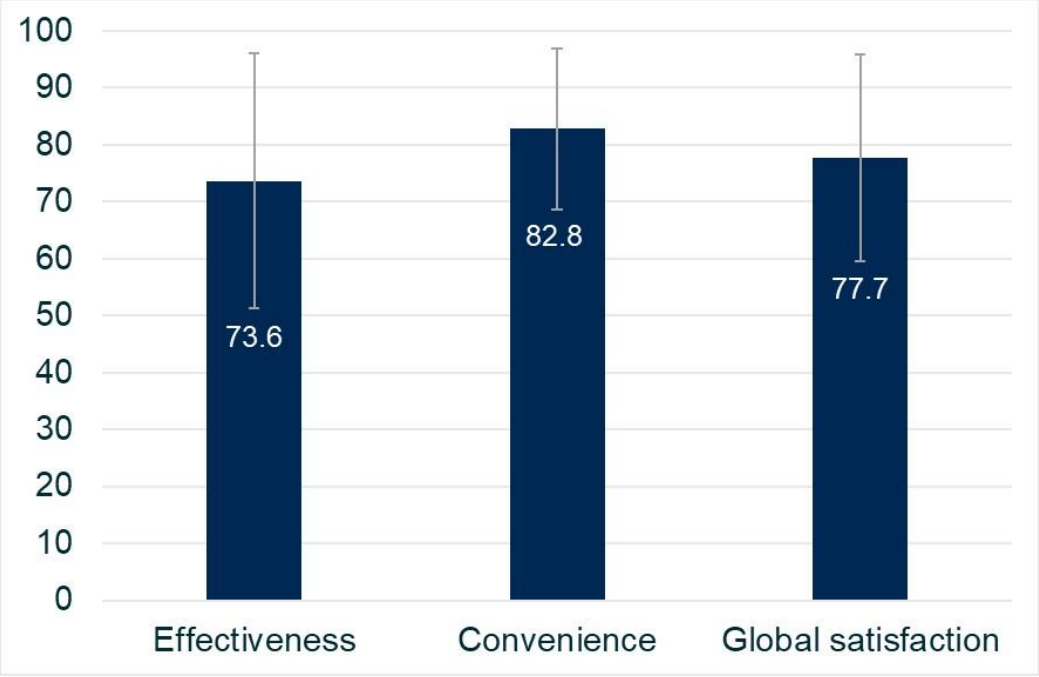

Figure 1 Tirbanibulin satisfaction scores at Day 57, reported through TSQM-9

Conclusions
Physicians’ and patients’ overall satisfaction with tirbanibulin for 5-days was high, and both reported great (much/somewhat) likelihood to use tirbanibulin in future, considering tirbanibulin as a valuable option for treating AK lesions.

A-329

Pre-treatment with topical tirbanibulin of surrounding Non Melanoma Skin Cancer cancerization field to improve surgical outcome

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Background
Basal (BCC) and Squamous cell carcinoma (SCC) are the most common skin cancers, and they represent a significant economic burden to health services because of a large volume of affected patients. Surgical excision, with histological assessment of the margins, is widely considered the mainstay of treatment. Incomplete excision is an important prognostic indicator of local recurrence or progression. Moreover, incomplete exeresis, leads to the need for further surgery, with a substantial impact on patient and on health system costs. Some studies underline that actinic keratoses are more frequently found in the lateral margins of excised non melanoma skin cancer (NMSC). Histopathological features found in the perilesional skin of surgical specimens, demonstrate the presence of actinic keratoses and actinic damage both in SCCs in BCCs. Therefore, improving the clearance of surgical margins before excision is a fundamental task. For this reason, "cleaning up" the cancer field surrounding a NMSC, appears to be a concrete possibility to improve surgical outcome. In this study, we treat the cancer field surrounding NMSC lesions scheduled for surgery with tirbanibulin to verify if the surgical outcome, in terms of the percentage of margins affected by residual neoplasia after surgery, improves.

Methods
Ten consecutive patients scheduled for surgery presenting 7 SCCs and 3 BCCs in the context of the cancerization field and/or severe photodamage constitute the study group. Patients performed a single course of topical tirbanibulin (1 application per day for 5 consecutive days) in the perilesional area around the target lesion. All treated areas (including NMSCs and the field of concretization) were clinically and instrumentally (Photodinamic Diagnosis, Digital picture, Vectra, thermographic image) evaluated, before topical treatment and after 30 days. Primary outcome is the percentage of positive margins in the study group, compared with a control group of 30 previously treated lesions matching for location, size and type, optained from our register. Secondary endpoint are the modifications of NMSC target lesions.

Results
Pretreatment with tirbanibulin, significantly improves the surgical outcome and reduces NMSC diameters.

Conclusions
Preliminary data suggest that pre-treatment with tirbanibulin cleans perilesional skin and reduces tumoral lesions, helping in the management of surgical patients affected by NMSC.

Basal cell carcinoma

A-294

A Multicenter Prospective Study of Electronic Skin Surface Brachytherapy for Keratinocyte Carcinoma: Long-term Follow Up and Correlation with Reflectance Confocal Microscopy

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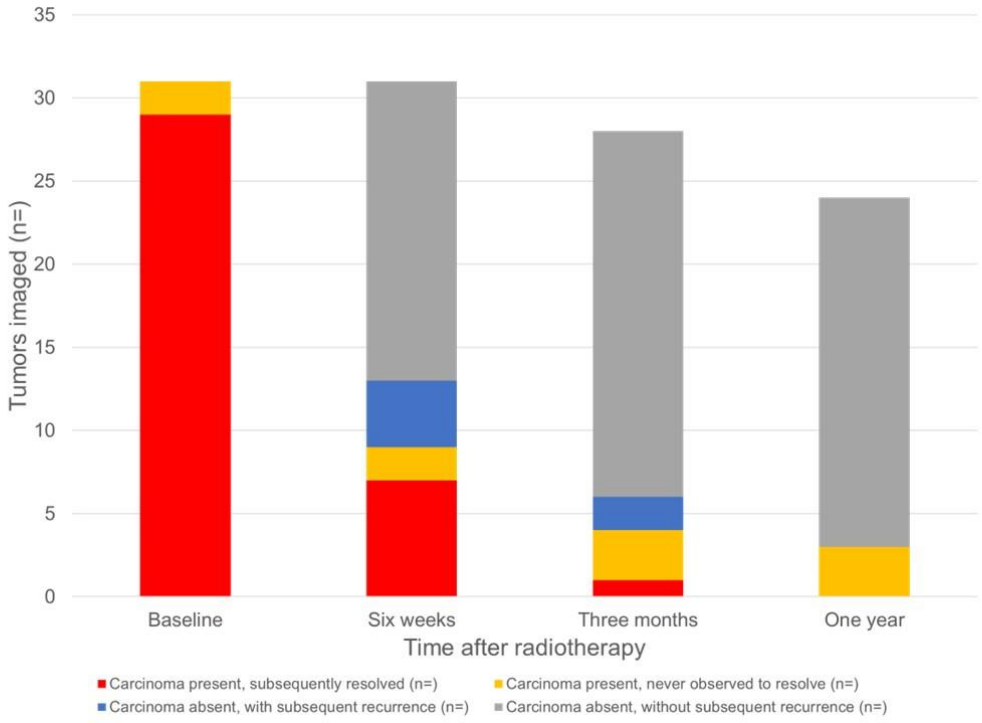
Background
Early-stage keratinocyte carcinomas (KCs) can be effectively treated with a variety of methods. This study examined the efficacy of a novel form of radiotherapy (electronic skin surface brachytherapy, ESSB) and used reflectance confocal microscopy (RCM) to assess response.

Methods
Patients with early-stage, low-risk KCs were recruited to this multicenter study. ESSB was delivered using Esteya® (Elekta AB, Stockholm) giving a dose of 42 Gy in 6 fractions of 7 Gy over 2-3 weeks to a depth of 3 mm beneath the skin surface. RCM was performed using a VivaScope® 3000 (Caliber ID, Rochester, USA) before at 6, 12 and 52 weeks after completing treatment to examine the perimeter and cross-sectional area of the irradiated KC. Image analysis was performed to characterize microscopic effects of ESSB and associate these with long-term outcomes.

Results
Thirty-four patients were enrolled at 2 centers, with preliminary results previously reported ([Kuo2023]). With median follow up of 5 years, no recurrences have been observed clinically. RCM was performed in 31/34 participants and detected carcinoma in 31/31 patients (100%) prior to treatment. Following treatment, resolution of carcinoma by RCM assessment was observed in 22/31 (71%) at 6 weeks, 24/28 (86%) at 12 weeks, and 21/24 (88%) at 52 weeks after treatment. (see Figure1). Previously described features of radiation effect on skin were observed following treatment ([NavarreteDechent2021]). These features will be correlated with clinician assessed late adverse events and patient-reported quality of life assessments for future presentation at the congress.



Presence of carcinoma on reflectance confocal microscopy before and after radiotherapy for keratinocyte carcinoma

Conclusions

ESSB is an effective mode of treating KC. Resolution of KC can be detected by RCM and may be more sensitive to detecting microscopic disease than clinical assessments. We are currently conducting a follow up trial at our center which correlates RCM and optical coherence tomography findings with histopathologic assessment, following radiotherapy.

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A-202

Adverse Effects in Elderly Patients (≥ 85 years old) with Advanced Basal Cell Carcinoma Treated with Sonidegib: A multicenter retrospective study

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Background

Introduction & Objectives: Locally advanced basal cell carcinoma (laBCC) is a significant therapeutic challenge, particulary in elderly patients within an increasingly aging population. Sonidegib, a Hedgehog pathway inhibitor, is effective in treating laBCC; however, the safety profile in the elderly population remains underexplored. This study aims to comprehensively evaluate the adverse effects experienced by elderly patients undergoing sonidegib treatment for laBCC.

Methods

Materials & Methods: A multicenter retrospective study was conducted on a cohort of elderly patients (age ≥ 85) with laBCC who received sonidegib therapy for more than 12 weeks. Clinical data, including adverse events, treatment responses, and patient characteristics, were collected and analyzed.

Results

Results: A total of 65 patients were included. With a meanage of 90.2 years old and a 51% of males, 68% of the patients presented EADO stage III. The most common histology was infiltrative (77%) and the most common locations were the periocular area (32%) and the nose (21%). A total of 41 patients (63%) experienced side effecs, being the most common muscles spasms, alopecia and dysgeusia . None of the patients experienced any grade 3 or 4 side effect.

We also examined the impact of these adverse effects on treatment adherence. The side effects caused interruption in 15 (23%) patients and required dose adjustment in 13(20%). Only 1 case developed an irreversible side effect and 7 cases could undergo treatment rechallenge (7/15).

Conclusions

Conclusions: This study sheds light on the safety considerations of sonidegib in elderly individuals, providing valuable insights for clinicians managing laBCC in this age group. Understanding the nuances of adverse effects in elderly patients is crucial for optimizing treatment strategies, ensuring patient well-being, and advancing the therapeutic landscape for laBCC

A-257

Cellular Origin of Basal Cell Carcinoma via Reflectance Confocal Microscopy

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Background
Basal cell carcinoma (BCC) derives its name from histological similarities of cells in the basal layer of the epidermis. In recent years, the pathogenetic study of BCC and the discovery of the Sonic Hedgehog signaling pathway, along with the evolution of immunohistochemistry and molecular biology techniques, have led to various hypotheses about its origin. The hypotheses focus on two possible origins: cells in the basal layer of the interfollicular epidermis or stem cells of the follicular bulge.
The aim of our study is to attempt to provide an answer regarding the anatomopathological origin of cells forming this tumor.

Methods
We analyzed three cases of very early BCC with Reflectance Confocal Microscopy (RCM) (Vivascope 1500) and confirmed by biopsy. It has emerged that it is one of the most sensitive and specific techniques for the diagnosis and subtyping of BCC. RCM is a non-invasive imaging technique that allows cellular-level resolution and imaging depth of approximately 200-300 µm. The power of cellular resolution imaging along with in vivo tissue studies has contributed to understanding the cellular origin of skin tumors, including BCC.

Results
This could constitute in vivo evidence that some BCCs originate directly from the hair follicle itself. Specifically, RCM revealed, in the first case, that the BCC perfectly centered the adnexal structure without altering it due to its early stage of development. In the other two cases, multiple tumor islands with alignment and clefting originating from a single hair follicle were visible through RCM. There is evidence supporting the follicular origin of BCC; indeed, the Sonic Hedgehog (SHH) pathway plays a key role in the pathogenesis of BCC and in the development of the embryonic hair follicle and during the hair cycle.

Conclusions
Our cases might represent the first in vivo evidence supporting the theory that at least a subset of BCCs originates from stem cells of the follicular bulge rather than from the interfollicular epidermis.

A-234

Comparison of the efficacy of skin examination using 3D total body photography to clinical and dermoscopic examination

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Background

Non-melanoma skin cancer (NMSC) is the most common malignant tumor that poses a worldwide problem for health services. Three-dimensional total body photography (3D-TBP) is currently used as an adjunct to skin examination, particularly to monitor melanocytic lesions in patients at high risk of melanoma. In this study, the efficacy and limitations of a skin examination for NMSC performed solely with 3D-TBP without patient contact are investigated.

Methods

130 patients with 167 skin lesions with suspected NMSC underwent skin examination with dermoscopy and subsequent surgery. In addition, a 3D-TBP was performed, which was subsequently assessed by an independent dermatologist and compared with the initial skin examination and histological results.

Results

Using 3D-TBP, a significantly lower sensitivity for the diagnosis of BCC (0.44 vs 0.77), a lower sensitivity for SCC (0.70 vs 0.78; p=0,754) and a significantly lower sensitivity for invasive skin tumors overall (0.66 vs 0.88; p<0,001) was achieved compared to clinical skin examination with dermoscopy. The location of the skin tumor did not influence the effectiveness of 3D-TBP. More advanced skin tumors with a greater tumor thickness (p<0,001) or a higher infiltration level were detected more frequently with 3D-TBP (p=0,001).

Conclusions

The results of this study show that 3D-TBP alone is inferior to traditional skin examination with dermoscopy. However, more advanced NMSCs were more likely being detected with 3D-TBP. Further studies need to investigate whether the effectiveness of 3D-TBP alone can be improved by using additional photographs of poorly visible areas of the body or digital dermoscopy.

A-212

Cumulative sum analysis-integrated e-learning for differentiation between basal cell carcinoma and non-basal cell carcinoma on optical coherence tomography: a diagnostic cohort study

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Background
Optical coherence tomography (OCT) may replace biopsy for diagnosing basal cell carcinoma (BCC) if BCC can be differentiated from non-BCC with high confidence. However, clinical implementation of OCT is limited by a shortage of OCT assessors. Cumulative sum analysis (CUSUM) is a statistical method which can be used to monitor OCT assessor training. Integrating CUSUM with e-learning may alleviate the OCT assessors shortage by enabling remote and simultaneous training of new OCT assessors. The objective of this study was to evaluate whether CUSUM-integrated e-learning is suitable for training healthcare professionals in achieving and maintaining an acceptable error rate for differentiating BCC from non-BCC on OCT. Furthermore, we explored the diagnostic accuracy for high-confidence BCC diagnoses by newly trained OCT assessors.

Methods
We developed a CUSUM-integrated e-learning with a theoretical module followed by 600 practice cases. Trainee performance was monitored by CUSUM (**Figure 1**). The diagnostic error rate; sum of false-negative and false-positive OCT results divided by the total number of cases was used to evaluate performance. Acceptable and unacceptable error rates were set at 16% and 25% respectively. After achieving and maintaining an acceptable error rate, newly trained OCT assessors were asked to differentiate BCC from non-BCC on 100 OCT scans for a subsequent diagnostic accuracy study. Diagnostic certainty on BCC presence was expressed on a 5-point confidence scale. Only the highest score was considered a positive OCT test result (high confidence). Histopathology served as reference standard.

Figure 1. CUSUM-analysis-based learning curve for differentiating basal cell carcinoma from non-basal cell carcinoma on optical coherence tomography

This CUSUM-analysis visualizes the learning curve of a trainee. The Y-axis represents the CUSUM-score, while the X-axis displays the index number of attempts. Horizontal lines on the graph represent acceptable and unacceptable boundaries. Successes result in a subtraction (S-1) from the CUSUM-score, whereas failures lead to an addition (S). The rising trend over the first three quarters of the graph indicates frequent failures and causes the CUSUM-graph to traverse unacceptable boundaries, thereby resetting the 0-line. Around attempt 225, the CUSUM-score starts a declining trend, signifying an achieved acceptable diagnostic error rate. This declining trend persists, indicating the trainee's ability to maintain an acceptable error rate over time.

Results

Seventeen trainees successfully completed the e-learning. Adequate performance was achieved and maintained after assessing a median of 385 scans (IQR:314-429). Sixteen novice OCT assessors participated in the diagnostic accuracy study. The pooled area under the curve (AUC) as measure for the ability to differentiate BCC from non-BCC lesions was 0.852 (95%CI: 0.833-0.870). Pooled specificity and sensitivity for a high-confidence BCC diagnosis were 95.4% (95% CI:93.2-96.9) and 31.1% (95% CI:24.2–39.0), respectively (**Table 1**).

Table 1. Duration of training and diagnostic accuracy of a high-confidence diagnosis by novice OCT assessors trained by CUSUM-integrated e-learning.

	Duration of training		**Overall diagnostic performance**		**Diagnostic accuracy of high confidence diagnosis**					
	Hours *Median* (IQR)	No. Scans needed *Median* (IQR)	AUC	95% CI	Sensitivity (% (x/n))	95% CI	Specificity (% (x/n))	95% CI	DOR	95% CI
Dermatologist 1	11	347	0.860	0.784-0.936	44.0 (22/50)	34.8-49.3	92.0 (46/50)	82.8-97.3	9.036	2.570-34.814
Dermatologist 2*	9	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Dermatologist 3*	18	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
All dermatologists	11 (9-18)	347	0.860	0.784-0.936	44.0 (22/50)	34.8-49.3	92.0 (46/50)	82.8-97.3	9.036	2.570-34.814
Nurse 1	44	395	0.878	0.818-0.939	18.0 (9/50)	11.2-19.9	98.0 (49/50)	91.2-99.9	10.765	1.294-236.179
Nurse 2	21	593	0.896	0.833-0.959	44.0 (22/50)	35.9-45.9	98.0 (49/50)	89.9-99.9	38.500	5.012-808.216
All nurses	33 (21-44)	494 (395-593)	0.888	0.842-0.933	31.0 (31/100)	12.0-59.7	98.0 (98/100)	98.0-98.0	22.010	5.098-95.017
Resident 1	3	108	0.846	0.771-0.922	44.0 (22/50)	34.8-49.3	92.0 (46/50)	82.2-97.3	9.036	2.570-34.814
Resident 2	9	385	0.835	0.755-0.915	16.0 (8/50)	9.4-17.9	98.0 (49/50)	91.4-99.9	9.333	1.102-207.171
Resident 3	10	401	0.839	0.760-0.918	26.0 (13/50)	18.1-29.3	96.0 (48/50)	88.1-99.3	8.432	1.645-57.882
Resident 4**	4	282	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
All residents	7 (3-10)	334 (152-397)	0.834	0.788-0.880	28.7 (43/150)	15.5-46.9	95.3 (143/150)	90.4-97.8	8.210	3.554-18.963
Research physician 1	2	103	0.935	0.891-0.978	20.0 (10/50)	13.4-20.0	100 (50/50)	93.4-100	Inf	2.216-Inf
Research physician 2	10	539	0.863	0.791-0.935	42.0 (21/50)	33.5-45.3	96.0 (48/50)	87.5-99.3	17.379	3.522-116.087
Research physician 3	18	506	0.861	0.786-0.937	42.0 (21/50)	32.6-48.0	90.0 (45/50)	80.6-96.0	6.517	2.015-22.403
Research physician 4	12	385	0.904	0.845-0.963	22.0 (11/50)	14.8-23.9	98.0 (49/50)	90.8-99.9	13.821	1.709-298.770
All research physicians	11 (4-17)	446 (174-531)	0.888	0.856-0.921	31.5 (63/200)	20.9-44.4	96.0 (192/200)	88.8-98.6	11.037	5.122-23.779
Medical student 1	10	390	0.893	0.836-0.945	14.0 (7/50)	8.1-14.0	100 (50/50)	94.1-100	Inf	1.385-Inf
Medical student 2	11	387	0.827	0.748-0.905	8.0 (4/50)	3.1-9.9	98.0 (49/50)	93.1-99.9	4.261	0.421-103.968
Medical student 3	26	346	0.844	0.768-0.919	44.0 (22/50)	35.1-48.4	94.0 (47/50)	85.9-97.4	12.310	3.084-57.162
Medical student 4	12	374	0.732	0.640-0.823	20.0 (10/50)	12.6-23.3	96.0 (48/50)	88.6-99.3	6.000	1.129-42.278
Medical student 5	5	103	0.820	0.738-0.902	32.0 (16/50)	23.2-37.3	92.0 (46/50)	83.2-97.3	5.412	1.505-21.223
Medical student 6	20	456	0.867	0.796-0.938	62.0 (31/50)	52.2-68.6	88.0 (44/50)	78.2-94.6	11.965	3.908-38.487
All medical students	12 (9-22)	381 (285-407)	0.827	0.795-0.859	30.0 (90/300)	16.5-48.2	94.7 (283/300)	89.9-97.2	7.607	4.341-13.329
All trainees	11 (7-19)	385 (314-429)	**0.852**	0.833-0.870	**31.1** (249/800)	24.2-39.0	**95.4** (763/800)	93.2-96.9	**9.319**	6.487-13.388

Abbreviations: 95%CI; 95% confidence interval, AUC; area under the curve, DOR; diagnostic odds ratio, n/a; not applicable, Inf; infinite, IQR; interquartile range

* did not participate in diagnostic accuracy study because an acceptable error rate was not achieved and maintained during training

** did not participate in the diagnostic accuracy study, but achieved and maintained an acceptable error rate during training

Conclusions

With CUSUM-integrated e-learning, healthcare professionals can achieve and maintain an acceptable error rate in differentiating BCC from non-BCC lesions on OCT. Upon successful completion, novice assessors can accurately differentiate BCC from non-BCC whilst ensuring patient safety.

A-342

Dermoscopy of basal cell carcinoma explained by line-field confocal optical coherence tomography: preliminary results of a correlation study.

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Background
Basal cell carcinoma (BCC) is the most common type of skin cancer, demanding early and precise diagnosis for optimal treatment outcomes. Dermoscopy is the most established diagnostic technique for BCC diagnosis and management. Line-field confocal optical coherence tomography (LC-OCT) has emerged as a new imaging modality in this field and its most recent prototype includes an integrated dermoscopic camera ensuring a perfect correlation between dermoscopic and LC-OCT images. This study aims to investigate potential correlations between specific dermoscopic criteria and LC-OCT criteria in BCC lesions.

Methods
A total of 158 cases of BCC were included. Cases of BCC imaged with LC-OCT and integrated dermoscopy were consecutively enrolled in the study. The presence/absence of dermoscopic and LC-OCT criteria for BCC was assessed by three independent observers (in case of disagreement, a consensus between them was found).

Results
Preliminary data analysis has shown promising associations between dermoscopic criteria and LC-OCT findings in BCC, in particular: (i) arborizing vessels with dilated vessels in the dermis surrounding BCC lobules, (ii) blue-gray ovoid nests with large lobules; (iii) blue-gray globules with small lobules; (iv) spoke wheel areas and leaf-life areas have been associated with lobules appended to the epidermis (superficial BCC).
The final analysis will be presented during the congress in the form of a poster and/or an oral presentation.

Conclusions
In conclusion, associations between dermoscopic and LC-OCT might represent the gateway to better understand in vivo the histopathological correlates of BCC criteria. In the future, this could be paramount to increase the diagnostic performance and improve the non-invasive management of the disease.

A-363

Four years experience in Mohs Surgery

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Background
the objective of the presentation is to comment on the quadrennial experience in Mohs surgery carried out at the Hospital since the beginning of the service in January 2020. We will focus the presentation on the the data obtained, analyzing the trend throughout the four years of activity, commenting the type of pathology treated, comparing reconstructive techniques or combinations of techniques to repair the final defect.

Methods
From January 2020 to December 2023, the Hospital's Mohs Surgery service has performed a total number of 280 surgeries for the treatment of non-melanoma skin cancer: 75% for basal cell carcinoma, 21.7% for squamous cell carcinoma, and 3.3% for other tumors. Considering the cases treated, all were located in the head and neck district. Regarding the reconstruction of the final defect: 253 cases were reconstructed through the application of a single reconstructive technique: that is, 29 through direct closure, 13 through total skin graft, 8 through second intention, 203 through flap and 27 cases through a combination of multiple surgical techniques.

Results
the purpose of the presentation is to comment on the results obtained during the activity of the Mohs surgery service and, successively, to present the 3 most representative surgical cases that ended with a complex final defect and required an appropriate reconstructive approach, since by their complexity corresponded to a reconstructive challenge.

Conclusions
In Mohs surgery it is not possible to predict the entity of the final defect, especially when the technique is reserved for the most aggressive and invasive histological subtypes of skin cancer.
For this reason, the Mohs surgeon needs to master reconstructive techniques and adapt them to the resulting defect at the moment when, thanks to microscope observation, tumor-free margins have been assured. Once the tumor has been removed, the optimal result is to ensure that the reconstruction first ensures the restoration of the organ or the area involved from a functional point of view and at the same time that the reconstruction does not alter the macroscopic aesthetic appearance.

A-246

Histopathologic Correlation of Structures Seen in Super High Magnification Dermoscopy of Basal Cell Carcinoma

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Background

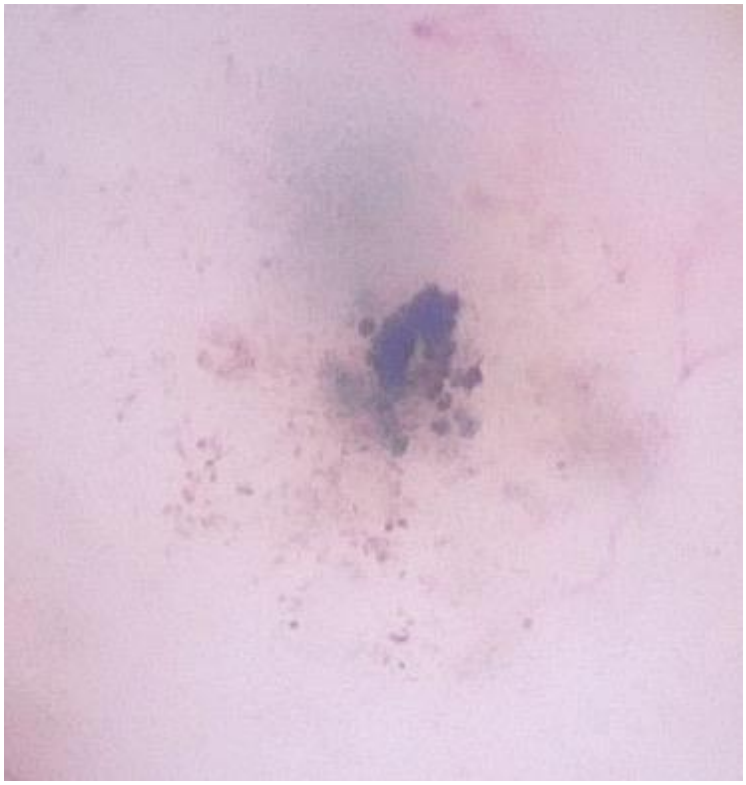
Basal cell carcinoma (BCC) is the most frequently diagnosed skin cancer. Super-high magnification dermoscopy (SHMD) is the new type of dermoscopy which allows us to observe lesions at magnifications of up to 400x. The aim of the study is to describe the concordance between SHMD and histopathological image in a patient with pigmented BCC.

Methods

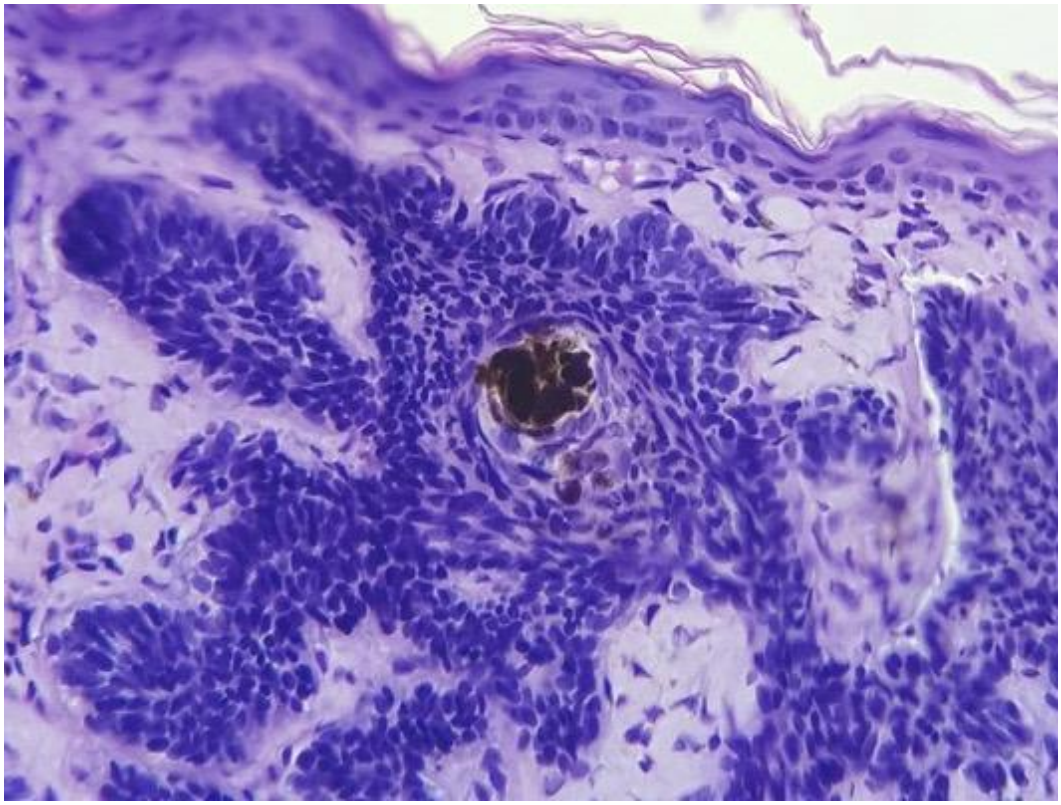
A 68-year-old man presented with the 6- mm tumor of the abdomen.
Dermoscopy (20x magnification) and SHMD (400x magnification) were performed with Medicam 1000 (FotoFinderSystemsGMBH) camera.

Results

Dermoscopy revealed ulceration in the center of the lesion, arborizing vessels and numerous blue-gray non-aggregated globules distributed throughout the whole lesion.
SHMD enabled visualization of the details invisible in standard dermoscopy and revealed the presence of blue-gray globules composed of blue-violet roundish and multi-shaped structures (Figure 1).



These structures correspond to nest of melanin-containing melanophages visible in the papillary dermis in histopathological examination of the lesion (Figure 2).



Conclusions

Correlation of the SHMD and histopathological images allows the identification of melanophages which form globules visible in BCC dermoscopy.

This method demonstrates that the use of SHMD adds novel insights to the dermoscopy of BCC

A-190

Imaging in Locally Advanced and Metastatic Basal Cell Carcinoma: Findings and Recommendations

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Background
Most basal cell carcinoma's (BCC) can be treated based on histology or clinical examination, but in both locally advanced (laBCC) and metastatic BCC (mBCC) radiologic imaging to determine suitable management might be required. Yet, a comprehensive guideline is missing. The objective of this study was to report onn findings and consequences of radiologic imaging in laBCC and mBCC, therefor attributing to evidence based recommendations on imaging strategies in this rare patient population.

Methods
A retrospective single center cohort study was conducted over a 32 year period to identify all laBCCs and mBCCs in our Cancer Center. Imaging information as well as basic patient-, tumour- and treatment characteristics were recorded from electronic patient files. Clinical outcomes were primary surgery radicality, local recurrence, metastasis and survival.

Results
Fifty-one patients were included. Thirty-four had laBCC, 5 of those patients developed subsequent metastasis. A total of 23 mBCC were included. Pre-operative locoregional imaging was performed in 45% of all patients and 65% of laBCC. MRI was the most used pre-operative imaging modality (70%), followed by ultrasound. Pre-operative maging showed relevant findings in 74% and changed management in 68%. When pre-operative imaging was performed, 79% of surgeries were radical versus 35% without imaging. Imaging for (re-)staging was performed in 78% of all patients. The most used modalities for this purpose were ultrasound and PET-CT, although a great variety of modality combinations was seen. (Re-)staging imaging was preceded by clinical symptoms in 33% of all patients; mostly palpable lymphadenopathy (89%). Of mBCC patients, 19 had local nodal-, 7 bone-, 5 distant nodal-, 4 subcutaneous- and 3 lung metastases. Interestingly, metastases were first found through clinical examination in 78%.

Conclusions
This study shows that pre-operative imaging in locally advanced BCC results in both management changes and a substantial increase of radical primary surgery. Therefore, pre-operative imaging looking at tissue involvement and resectability is advised for this high-risk BCC population. MRI scans are superior for evaluating soft tissue involvement, CT-scans for bone involvement. In follow-up, clinical symptoms often precede diagnosis of metastatic disease. Subsequently, complete re-staging using PET-CT is advised.

A-207

Interim analysis of the multinational, post-authorisation safety study (NISSO) to assess the long-term safety of sonidegib in patients with locally advanced basal cell carcinoma: Time to onset of adverse events

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Background

Following the pivotal Phase 2 trial BOLT (Basal Cell Carcinoma Outcomes with LDE225 Treatment), the Hedgehog inhibitor sonidegib was approved in the EU to treat locally advanced basal cell carcinoma (laBCC) in patients not amenable to surgery or radiotherapy. NISSO was designed to collect real-world safety data on the use of sonidegib in these patients.

Methods

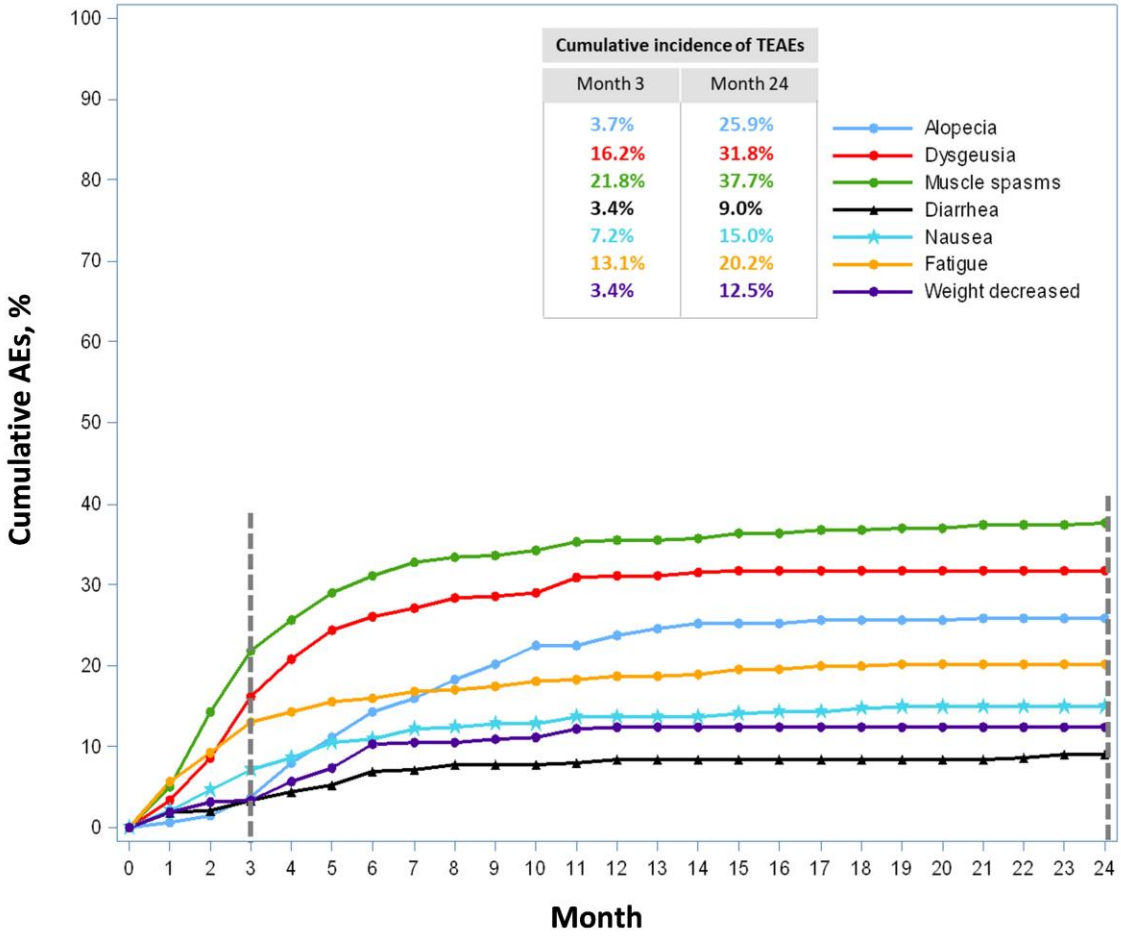
NISSO is a non-interventional, multinational, post-authorisation safety study (NCT04066504). Patients with laBCC were treated with sonidegib 200 mg orally once daily and followed for 3 years after enrolment. Dose modifications were allowed according to the local Prescribing Information.

Results

Between May 6, 2019, and March 15, 2022, 321 patients with laBCC were enrolled at 46 study sites in Germany, Italy, Spain, and Switzerland (data cut June 22, 2023). Treatment was ended in 239 (74.5%) patients and the main reasons were patient/guardian decision (n=69, 21.5%), physician decision (n=35, 10.9%), treatment success (n=40, 12.5%), disease progression (n=30, 9.3%), and toxicity (n=22, 6.9%). The median duration of sonidegib exposure was 8.8 months (interquartile range, 4.41–13.65 months). Overall, 284 (88.5%) patients had ≥1 treatment-emergent adverse event (TEAE). Most TEAEs were Grade ≤2 and the most common were muscle spasms (n=141, 43.9%), dysgeusia (n=119, 37.1%), and alopecia (n=98, 30.5%). After 3 months of treatment, the cumulative rates of muscle spasms, dysgeusia, and alopecia were 21.8%, 16.2%, and 3.7%, respectively (**Figure 1**). TEAEs led to treatment discontinuation in 59 (18.4%) patients, while 149 (46.4%) patients had at least 1 TEAE leading to dose reduction or interruption. Serious TEAEs were reported in 87 (27.1%) patients.

Conclusions

These results confirm the safety profile observed in the BOLT study, demonstrating that sonidegib treatment is manageable in a real-world setting. Most patients experienced the onset of common TEAEs after 3 months of treatment, and the cumulative incidence of muscle spasms, dysgeusia, and alopecia was lower compared to the BOLT study. The percentage of patients experiencing TEAEs requiring interruption or dose reduction was consistent with the BOLT study. Our study supports the use of sonidegib as a well-tolerated first-line treatment in patients with laBCC.



AE, adverse event; TEAE, treatment-emergent adverse event.

Figure 1. Cumulative onset of treatment-emergent adverse events

A-230

Management of muscle spasms induced by sonidegib in a 93-year-old patient with a multimodal gait disorder

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Background

Elderly patients aged 65 and above are eight times more likely to develop a locally advanced basal cell carcinoma (laBCC) than younger individuals[1]. However, elderly patients with comorbidities, extensive medication, or immobility are often not suitable for major surgeries[2]. In those cases, sonidegib is an excellent therapy option for elderly patients as it is not affected by concomitant medications and achieves at least a partial remission in more than 50% of cases[3,4]. Alongside taste and hair loss, muscle spasms are the most common adverse event during sonidegib therapy and occur in 50-60% of cases[5]. Especially in older patients who already suffer from immobility, muscle spasms can further impair the patients' mobility.

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[2] Van Coile L et al. J Geriatr Oncol. 2023.
[3] Dummer R et al. Br J Dermatol. 2020.
[4] Casey D et al. Clin Cancer Res. 2017.
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Methods

case report

Results

In November 2023 a 93-year-old patient with a laBCC of the nose presented in our outpatient department. Because of significant comorbidities such as rheumatoid arthritis, diabetes mellitus type two and chronic heart failure, this patient was not a candidate for surgery. Due to the location of the laBCC, radiation therapy was not a possible alternative. For this reason, we initiated therapy with sonidegib 200mg per os daily. In February 2023 the patient developed severe sonidegib-induced muscle spasms. Due to a pre-existing multimodal gait disorder, the muscle spasms strongly impaired the patient’s walking ability. However, the laBCC showed an excellent response. We reduced sonidegib to 200mg per os every other day. The muscle spasms significantly decreased after dose reduction. The patient is currently undergoing therapy and has shown complete remission as of today.

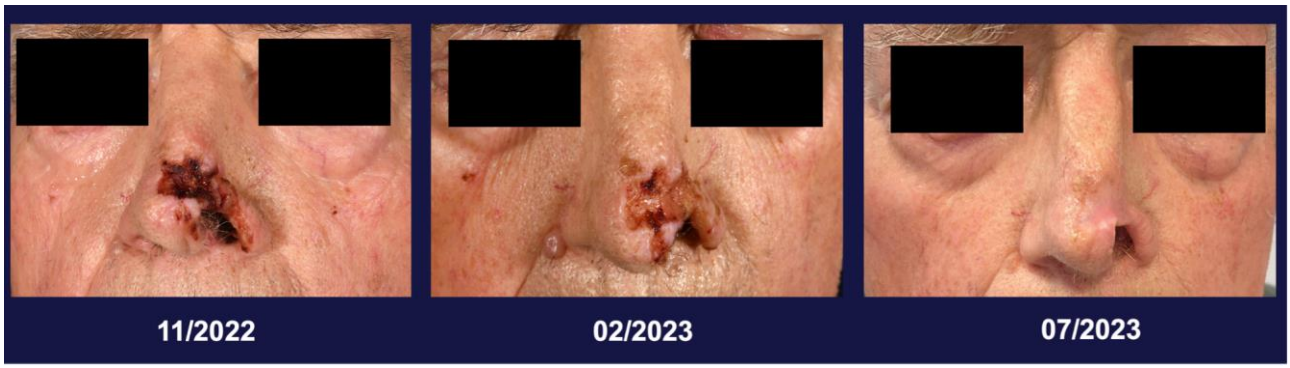

Image 1: Healing process of a a locally advanced basal cell carcinoma under sonidegib. Initially in November 2022, a deep ulcer appeared with destruction of the nasal cartilage. Over time this flattens out significantly until ultimately all that remains is a shiny plaque in July 2023.

Conclusions

In summary, there is a high medical need for systemic treatment alternatives like sonidegib in elderly patients not fit for extensive surgery. Sonidegib-induced muscle spasms are not a contraindication for patients with multimodal gait disorders. In our case, a reduced dosage does not affect the therapeutic outcome of sonidegib. Therefore, our case gives an example that sonidegib is feasible, safe and effective in very elderly patients.

A-365

Measuring health-related quality of life in patients with keratinocyte carcinoma: A multicenter cross-sectional study

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Background
Keratinocyte carcinoma (KC) constitutes 90% of all skin cancers and despite its relatively low mortality rate, it may affect patients' health-related quality of life (HRQoL). Studies examining the impact of KC on HRQoL are limited and are often relies on using generic measurement instruments. Such instruments lack sufficient validity in capturing the impact of KC on HRQoL. The objective of this study was to measure the impact of KC on HRQoL using generic instruments and a disease-specific questionnaire, while comparing these instruments in a Belgian/Dutch cross-sectional study.

Methods
HRQoL of KC patients was measured using the basal and squamous cell carcinoma quality of life (BaSQoL), a disease-specific questionnaire which contains of five subdomains (behavior, diagnosis and treatment, worries, appearance and other people). The EQ-5D-5L, visual analog scale (VAS), 15-dimensions (15D) and time trade-off (TTO) were used as generic instruments to measure HRQoL. Questionnaire scores were stratified by single vs. multiple KC, low vs. high comorbid and early vs. late surveyed patients. Generalized linear models assessed differences in mean HRQoL scores across KC groups, adjusting for inclusion center, age, sex, treatment, tumor location, comorbidities and time between diagnosis and survey. Significance level was set at $p \leq .005$ because of multiple testing.

Results
In total, 715 KC patients were included in this study. We found low to moderate BaSQoL scores and high utility scores, suggesting a minimal impact of KC on HRQoL. The impact on HRQoL was significantly higher in subdomain worries for patients with multiple KC compared to single KC ($p=.002$). Patients with multiple KC had a significantly worser health state measured with the EQ-5D-5L compared to patients with single KC ($p=.004$). No significant differences in HRQoL was observed in patients who were surveyed more closely to their diagnosis compared to later surveyed patients. Patients with more comorbidities demonstrated significant lower EQ-5D-5L, VAS and 15D scores compared to patients with lesser comorbidities, indicating a worser health state compared to patients with less comorbidities.

Conclusions
Findings suggest, both with disease-specific and generic instruments, a minimal impact of keratinocyte carcinoma on HRQoL. It is important to interpret these results with caution due to the cross-sectional nature of this study.

A-421

Neoadjuvant Vismodegib plus Mohs surgery for locally advanced periocular basal cell carcinoma. Real world scenario.

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Background
Eye sparing approaches in locally advanced periocular basal cell carcinoma (LAP-BCC) with neoadjuvant Vismodegib followed by Mohs surgery (NEOVISMO+MS) have demonstrated promising results.

Methods
Eighteen patients with LAP-BCC were considered for NEOVISMO+MS between 6/2014-6/2022. Two patients declined surgery after Vismodegib and were excluded from this analysis.
Patients received oral Vismodegib (150mg/daily) until maximal clinical response, progression, unacceptable toxicity or withdrawal.
Sex distribution was even. Mean age: 69.8 years(43-90). Mean size 21.3mm(10-35mm), inner canthus 12(66.7%). Histologic subtype: infiltrative 7, nodular 6, micro-nodular 3. Seven cases (43.7%) were previously treated, and 6(37.5%) had indication of orbital exenteration (EX). TNM staging: T2b 3, T2c 1, T3b 2, T3c 1, T4a 6, T4b 3.

Results
Mean administration of Vismodegib: 5.8 months(4-8). Results: complete clinical responses (CCR) 11(68.8%), partial responses (PR) 3(18.7%) , disease progression (PROG) 2(11.1)%.

MS confirmed complete histologic response (CHR) in 7/11(63.4%) CCRs.

Known follow-up: 100%, mean time 27.2 months(6-84). Five out of six (83.3%) patients that needed EX underwent eye sparing surgery.
We observed 1(5.6%) recurrence at 18 months, currently disease free after a second MS (29 months later).
Adverse effects were mild, only one patient suspended Vismodegib after 4 months (intolerable muscle cramps).

Conclusions
Large studies have shown that 31% of patients obtain a CCR after Vismodegib, and only 40% remain in CCR 3 years after drug suspension. Hence, Vismodegib alone is insufficient for cure.

Besides, a CCR should not be considered as a synonym of CHR. In this study only 63.4% of CCRs had a real CHR. MS allows to evaluate the real usefulness of the drug.

When treating a LAP-BCC the most important goal is ocular preservation. In this series, 5/6 patients that needed an EX, preserved the eye. In addition, the neoadjuvant approach allows better drug tolerance and reduces costs. Finally, preservation of normal tissue is critical to enable better functional and cosmetic outcomes.
One of the limitations of this study is the short period of drug administration.

A-349

New digital imaging technique for the follow-up of locally advanced basal cell carcinoma treated with systemic therapy

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Background
Locally advanced basal cell carcinoma (laBCC) include skin tumors invading local soft tissue and subcutaneous structures. Hedgehog pathway inhibitors (HHIs) represent the first-line therapy for laBCC, although the incidence of tumor resistance or recurrence. In this study we aimed to investigate the potential role of Line-field confocal optical coherence tomography (LC-OCT), a new non-invasive skin imaging tool, for the in-vivo detection of tumor persistence or recurrence in patients treated with HHIs.

Methods
Patients treated with HHIs for laBCC in the last 3 years (May 2020 - May 2023) who were performed LC-OCT exam during HHIs therapy once reached a clinical complete response or after its interruption.

Results
A total of 20 patients were included [16 (80%) males ,4 (20%) females, mean age 76 years (59 - 95)]. In 6 patients with a complete clinical response lasting for >12 months (4 patients) and for >6 months (2 patients), LC-OCT displays the absence of disease in 3 cases (50%), and BCC recurrence in 3 cases (50%), confirmed by histopathology (n = 1 nodular BCC, n = 2 micronodular BCCs).
In 14 patients either on treatment with HHIs or off treatment for < 3 months, LC-OCT showed no residual disease in 4 patients (28.6%), with no clinical relapse in the following 3 and 9-months. BCC persistence was found in 10 patients (71.4%): 4 patients underwent radical surgery after margin delineation by LC-OCT, with no recurrence at 6-months; 3 patients continued HHIs; 1 patient was treated with radiotherapy with complete clinical response and no recurrence at 3-months; 1 patient was treated with Imiquimod 5% cream with complete clinical response and no recurrence at 12-months; 1 patient refused surgery and discontinued therapy for adverse events.

Conclusions
LC-OCT may be a useful tool in the non-invasive follow-up of laBCC treated with HHIs. Integrating digital imaging in a such complex scenario may facilitate the assessment of complete response or disease recurrence, actively influencing physician decision-making.

A-431

Patient with metatypical metastatic Basal Cell Carcinoma treated with Vismodegib.

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Background

Introduction: Basal cell carcinoma (BCC) is a common type of skin cancer. Most of these tumors are mainly locally aggressive, but a deficient percentage of patients can develop distant metastases (estimated at 0.1%). Since exposure to ultraviolet radiation is the main factor in developing this type of cancer, most lesions are found in photo-exposed areas. Somatic mutations of PTCH1 were identified in over 70% of sporadic BCC. PTCH1 encodes a protein acting as a transmembrane receptor for the HH protein family, and vismodegib targets this mutation. Basosquamous cell carcinoma is a rare subtype of BCC that behaves aggressively. It is not clear how to treat patients with basosquamous metastatic melanoma [1]. We will present the report of a patient with metatypical metastatic BCC treated with vismodegib, who responded excellently[2].

Methods

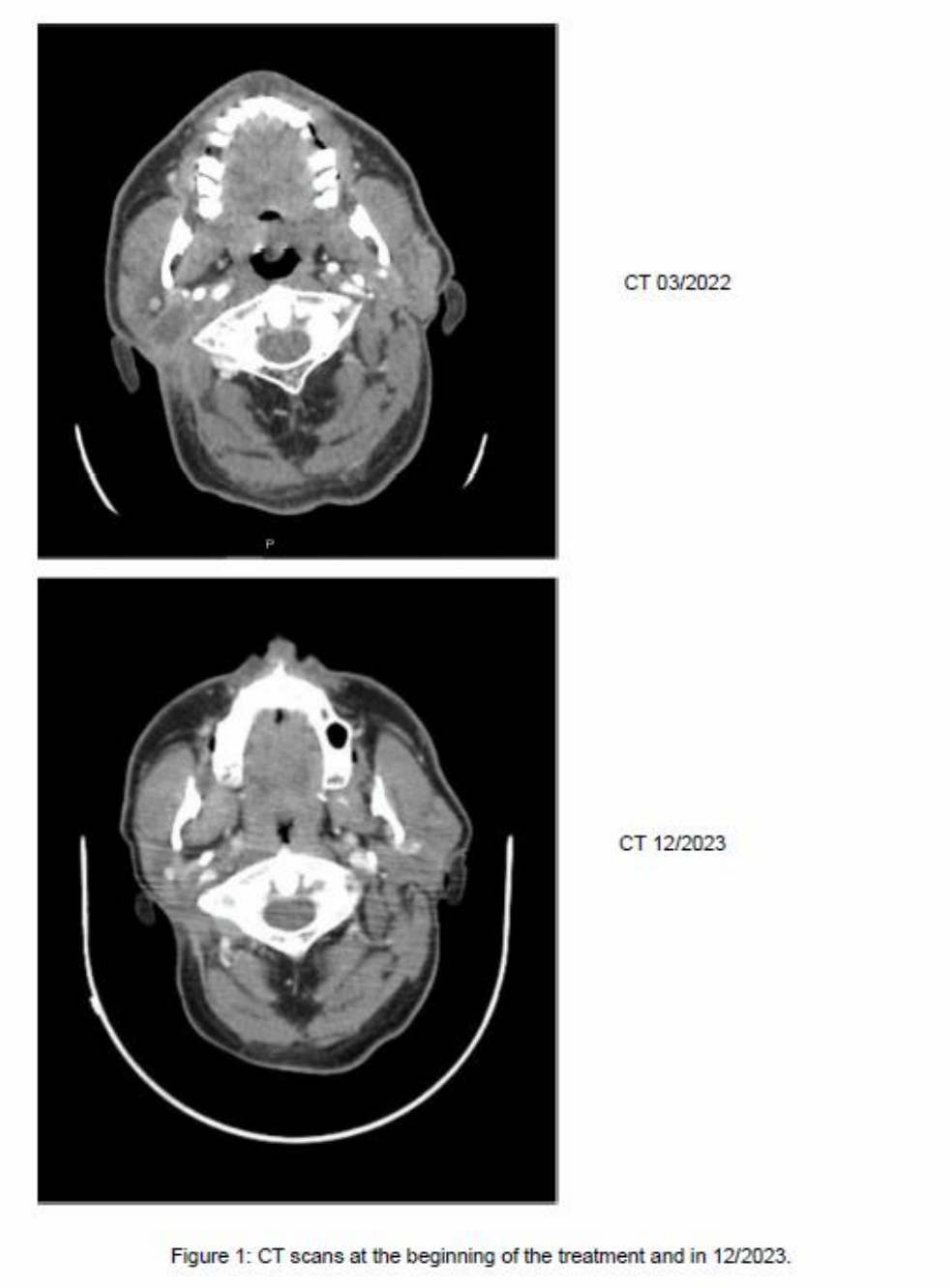

Figure 1: CT scans at the beginning of the treatment and in 12/2023.

CT scans at the beginning of the treatment and in 12/2023.

Case presentation:
This is a 56-year-old male patient with a diagnosis of metatypical retro auricular BCC with secondary lymph node involvement, resected in 2019. He also completed treatment with adjuvant radiotherapy. Then, he presented a local and pulmonary relapse in 2021, with a biopsy that showed squamous carcinoma. He started in April 2022 and received treatment with vismodegib 150 mg per day, with excellent response and tolerance until today.

Results
Discussion: We should offer systemic treatment in patients with locoregionally advanced or metastatic BCC who are not amenable to local treatment. In these cases, the first line of treatment is with inhibitors of the hedgehog pathway since it has been implicated in the proliferation and growth of these tumors. It needs to be clarified how to treat patients with basosquamous metastatic melanoma. Given the low percentage of patients with metastatic BCC, we have few studies in this population. A phase II study in which patients received vismodegib as the first line of treatment showed a progression-free survival (PFS) of 13 months. We did not know if this study included patients with basosquamous cell carcinomas. In the case of our patient, we have had 20 months of PFS[2].

Conclusions
Conclusion: We present the case of a patient with metastatic basosquamous carcinoma, treated in the Clinical Oncology Service of the Hospital de Clínicas, who was treated with a hedgehog pathway inhibitor as the first line in metastatic disease, with an excellent response and a more significant PFS compared to what was reported in the literature.
References:

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A-222

Patient-orientated evaluation of treatment of non-melanoma skin cancer with Rhenium-188 compared to surgery

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Background
Non-melanoma skin cancers (NMSC) are responsible for up to one-third of all human malignancies. Surgery is usually the treatment of choice, but patients often experience pain during the procedure. Treatment with topical rhenium-188 resin (RSCT) may be a valid and less painful alternative.

Methods
In this monocentric study 22 patients suffering from NMSC, who were treated with RSCT, surgery, or both (73%), were included. A questionnaire was used to assess patient's perceptions regarding side effects, aesthetic outcomes, wound care, fear of complications, and personal treatment preferences. Patient-reported outcomes were selected from a given list or rated on a scale from 0-10; the results for both treatments were compared.

Results
Patients were more afraid of complications before surgery than before RSCT (p=0.04). Treatment with RSCT caused significantly less pain on treatment day (mean 0.56) than surgery (mean 2.32) (0 no pain, 10 maximum pain) (p=0.02); 14 days after the procedure RSCT treated lesions were still significantly less painful (mean 0.89) than the operated lesions (mean 2.47) (p=0.02). On day 14 RSCT treatment caused also significantly less itching (mean 0.34) than surgery (mean 1.50). Most patients were very satisfied with the aesthetic outcome of both RSCT (mean 8.42) and surgery (mean 8.31) (p=0.89). In the case of a new NMCS the majority of patients, who experienced both treatments, would choose to be treated primarily with RSCT (44%) or would consider both options (31%).

Conclusions
The patient evaluated RSCT as less painful than surgery with a comparable aesthetic outcome.

A-121

Primary radiotherapy in older adults with basal cell carcinoma: results of the prospective, multicenter BATOA cohort study on treatment burden, short-term outcomes and a comparison with surgically treated patients

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Background

To optimize personalized care in older adults with basal cell carcinoma (BCC), data on treatment burden is needed. However, evidence regarding the (prediction of) treatment burden of radiotherapy (RT) in older patients with BCC is currently lacking. We aimed to evaluate the treatment burden in older adults treated with RT for BCC in the head and neck area, and compare this to surgically treated patients.

Methods

This study used data from the prospective, multicenter Basal Cell Carcinoma Treatment in Older Adults (BATOA) cohort. Patients aged ≥70 years and treated with primary RT or surgery for BCC in the head and neck area were included. Patient reported data on treatment burden (visual analog scale (VAS), 0-10 cm, higher scores indicate lower treatment burden) and cosmetic outcome ((VAS), 0-10 cm, higher scores indicate better cosmetic results) 2 to 4 months posttreatment and data on adverse events were collected. Univariate analyses using Student's t test and χ^2 test were performed.

Results

A total of 139 patients treated with RT in 7 centers were included and compared to 539 patients treated with surgery (Table 1). The treatment burden of RT was low (median VAS score of 8.9; interquartile range (IQR) 7.8-9.6), and cosmetic outcome was good (median VAS score of 9.4; IQR 8.7-9.8)(Table 2). Radiation dermatitis was seen in 119 patients (85.6%). Treatment burden of radiotherapy was slightly lower compared to the surgery group (median VAS score 8.6; IQR 7.3-9.4; P=0.001). Short-term cosmetic outcome was generally high in both treatment groups, though better in the RT group (median VAS of 9.4; (IQR 8.7-9.8) compared to the surgery group (median VAS 8.5; IQR 6.7-9.5; P<0.001).

Conclusions

RT is well tolerated in this cohort of older adults with BCC in the head and neck area. Although the treatment burden was found to be generally low in both treatment groups, it was slightly lower in patients treated with radiotherapy compared to surgery.

	Treated by RT (n=139)	Treated by surgery (n=539)	P value	95% CI (of the difference)
Patient characteristics				
Age[a] (years), Mean ± SD	81.8 ± 6.2	78.6 ± 5.8	0.338	-4.37 to -2.13
Sex, n (%)				
Male	67 (48.2)	304 (56.4)		
Female	72 (51.8)	235 (43.6)	<0.001	
History of keratinocyte cancer, n (%)	86 (77.5)	324 (60.7)	<0.001	
Previously treated with surgery, n (%)	78 (95.1)	312 (58.5)		
Previously treated with RT, n (%)	6 (5.9)	17 (3.2)		
Charlson Comorbidity Index, Median (IQR)	1 (0-2.25)	2 (0-3)	0.337	-0.52 to 0.674
Polypharmacy[b], n (%)	77 (61.6)	264 (50.1)	<0.001	
ADL dependent[c], n (%)	25 (20.0)	112 (21.1)	0.787	
iADL dependent[d], n (%)	58 (41.7)	222 (42.0)	0.330	
Tumor characteristics				
Previous treatment, n (%)				
No, primary tumor	127 (91.4)	467 (86.6)	0.132	
Yes, recurrent tumor	12 (8.6)	72 (13.4)		
Tumor location, n (%)				
Forehead	14 (10.1)	171 (31.7)		
Peri-ocular	4 (2.9)	34 (6.3)		
Cheek	3 (2.2)	66 (12.2)		
Nose	87 (62.6)	145 (26.9)		
Peri-oral	4 (2.9)	20 (3.7)		
Chin	1 (0.7)	5 (0.9)		
Ear	20 (14.4)	37 (6.9)		
Neck	3 (2.2)	40 (7.4)		
Scalp	3 (2.2)	21 (3.9)	<0.001	
BCC subtype, n (%)				
Mixed	36 (26.3)	156 (28.9)		
Nodular	45 (32.8)	206 (38.2)		
Micronodular	8 (5.8)	66 (12.2)		
Infiltrative	44 (32.1)	103 (19.1)		
Superficial	4 (2.9)	7 (1.3)		
Adenoid	0 (0.0)	1 (0.2)	0.008	
Maximum tumor diameter in mm, Median (IQR)	13 (8-20)	10 (7-15)	<0.001	-5.98 to -2.76
Treatment characteristics				
Type of surgery				
Mohs micrographic surgery	N/A	269 (54.9)		
Conventional excision	N/A	243 (45.1)	N/A	
Number of treatments (fractions) Median (IQR)	18 (10-18)	N/A	N/A	
Total dose (in Gray) Median (IQR)	54 (44-54)	N/A	N/A	
Type of RT, n (%)				
Conventional photons	10 (7.2)			
Low-energy photons	0 (0.0)			
Electrons	126 (90.6)			
Esteya	2 (1.4)			
Orthovoltage	1 (0.7)	N/A	N/A	
Total duration of the treatment period (days from date first and last visit) Median (IQR)	26 (17-30)	N/A	N/A	
Travel distance to treatment center (km) Median (IQR)	18.0 (9.0-26.3)	11.0 (6.0-17.0)	0.149	-7.65 to -2.70

[a] At the time of treatment.

[b] Defined as the chronic use of ≥5 medications with different anatomical therapeutic chemical (ATC3) codes.

[c] The Katz index of activities of daily living (ADL), comprising bathing, dressing, transferring, toileting, maintaining continence, and eating. Patients were considered ADL dependent if they were unable to perform ≥1 activity independently.

[d] Lawton and Brody index of instrumental ADL (iADL) comprising telephone use, grocery shopping, preparing meals, housekeeping, laundering, using transportation, taking medication, and managing finances. Patients were considered iADL dependent if they were unable to perform ≥1 activity independently.

Table 1: Patient-, tumor- and treatment characteristics of older adults (aged ≥70 years) treated for basal cell carcinoma in the head and neck area from the BATOA cohort, including a comparison between patients treated by primary radiotherapy vs. surgery.

	Treated by RT	Treated by surgery	P value	95% CI (of the difference)
Treatment burden (VAS, 0-10) Median (IQR)	8.9 (7.8-9.6)	8.6 (7.3-9.4)	0.001	-9.21 to -1.16
Cosmetic outcome (VAS, 0-10) Median (IQR)	9.4 (8.7-9.8)	8.5 (6.7-9.5)	<0.001	-14.2 to -6.49
Treatment experience, n (%):				
As expected	105 (76.1)	420 (80.2)	0.294	
Longer than expected	2 (1.4)	72 (13.7)	<0.001	
More painful than expected	2 (1.4)	55 (10.5)	<0.001	

Table 2. Experienced treatment burden in older adults (aged ≥70 years) treated with radiotherapy or surgery for basal cell carcinoma in the head and neck area.

A-159

Right-Sided Lateralisation of Basal Cell Carcinoma and Squamous Cell Carcinoma in a UK Cohort

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Background

Studies done in the US[1] and Germany[2] have found a higher prevalence of sun-exposure-related skin cancers on the left than the right. This has been suggested to be due to the driving side. To our knowledge, no UK studies have investigated this association. Right-sided lateralisation in the UK may strengthen the link between driving side and skin cancer occurrence.

The aim was to determine whether occurrence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) show an asymmetrical distribution (to left, right, or midline) in a UK cohort.

Methods

We reviewed records of patients with BCC or SCC confirmed by biopsy at Addenbrookes Hospital in 2018 and 2019 (5153 patients with BCC, 1728 patients with SCC). Patients with lesions located in face and scalp area were included. Lesions were classified as right, left, or midline.

Chi-squared test was used to determine whether there were significant differences in lesion prevalence at each location.

Results

There were 1053 facial/scalp SCCs and 3527 facial/scalp BCCs in 2018-2019, detailed in Figure 1.

Figure 1 – Number of facial/scalp BCC and SCC in 2018 and 2019 by side

lesion type	year	side of lesion			Total number of lesions	p value of Chi-square test comparing right, left, and midline	p value of Chi-square test comparing right and left
		right	left	midline			
BCC	2018	805	732	278	1815	<0.001*	0.063
	2019	719	681	312	1712	<0.001*	0.31
	2018-2019	1524	1413	590	3527	<0.001*	0.041*
SCC	2018	212	194	153	559	0.007*	0.372
	2019	227	191	76	494	<0.001*	0.078
	2018-2019	439	385	229	1053	<0.001*	0.06
BCC and SCC combined	2018	1017	926	431	2374	<0.001*	0.039*
	2019	946	872	388	2206	<0.001*	0.083
	2018-2019	1963	1798	819	4580	<0.001*	0.007*

Asterisks mark statistical significance: * p < 0.05

Figure 1: Number of facial/scalp BCC and SCC in 2018 and 2019 by side

For BCCs, there was a significant difference between lesion prevalence in right, left, and midline in 2018, 2019, and 2018-2019 ($p<0.001$). The highest occurrence side was the right with 44.4% of all BCCs in 2018, 42.0% in 2019, and 43.2% in 2018-2019.

For SCCs, there was a significant difference between the lesion prevalence in right, left, and midline in 2018, 2019, and 2018-2019 ($p<0.001$ in 2019 and 2018-2019, $p=0.007$ in 2018). The highest occurrence side was the right with 37.9% of all 2018 SCCs, 46.0% of all 2019 SCCs, and 41.2% of all SCCs in two years combined.

When comparing right and left-sided lesions only, there were significantly more right-sided BCCs in 2018-2019 (51.9% right, 48.1% left, $p=0.041$). For SCCs across two years, the difference was not significant, with $p = 0.06$ (53.3% right, 46.7% left). When combining BCCs and SCCs in 2018-2019, there were significantly more right-sided lesions than the left (52.2% right, 47.8% left, $p=0.007$).

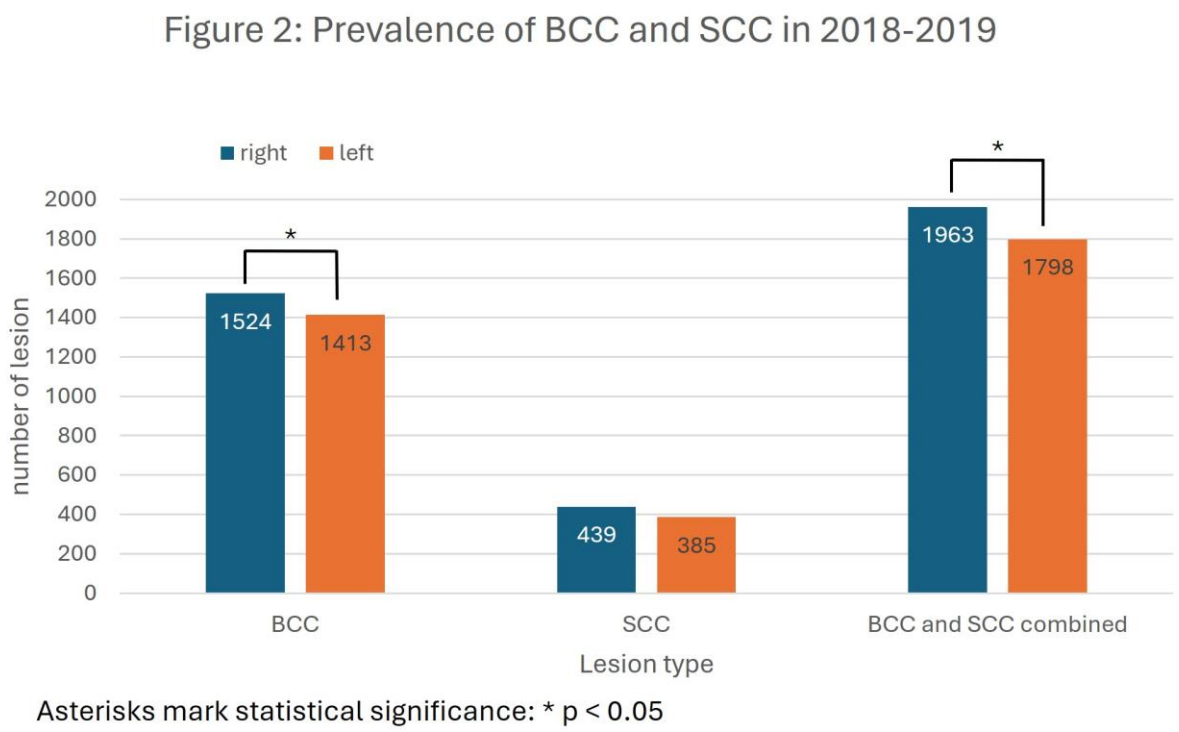

Figure 2: Prevalence of BCC and SCC in 2018-2019

Conclusions

SCCs and BCCs both showed highest occurrence on the right. In 2018-2019, prevalence of right-sided BCCs was higher than in the left. For SCCs, the same laterality was found but not statistically significant. This may be due to the smaller sample size, demonstrating the need for longer duration and larger sample research.

References:

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A-352

The use of High Frequency Ultrasound in Cutaneous Oncology Surgery

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Background
High Frequency Ultrasound is a safe, unexpensive and resolutive method of skin imaging in Dermatology.
The use of Ultrasound in the preoperative assessment of skin tumors allows optimizing surgical planning.

Methods
We studied 10 cases of Basal Cell Carcinoma prior to excisional surgery by Ultrasound and compare the Anatomopathological findings with the Ultrasound images.

Results
All 10 cases cases had an imagine-anatomopathological correlation regarding surgical planes.

Conclusions
Ultrasound was a good method for surgical planning, evaluation of affected surgical plans, and visualization of other important aspects for surgery such as local blood vascularization.
However, it is important to emphasize that these images are only suggestive and very dependent on the exam operator

A-213

Topical Rhenium-188 ionizing radiation therapy exerts high efficacy in curing non-melanoma skin cancer- Final study results

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Background
Nonmelanoma skin cancer (NMSC) is the most frequent malignancy. Surgical intervention is the common treatment but may lead to disappointing results; alternative treatment options are needed.

Methods
In this monocentric pilot study, topical 188Re resin was investigated as a treatment for invasive NMSC up to 3-mm thickness. Twenty-two patients with 40 histologically confirmed NMSCs with a median size of 1.25 cm2 (range, 0.04-16.8 cm2) and a median tumor thickness of 0.35 mm (range, 0.1-2.1 mm) were included. Patients were treated once with 188Re resin with a targeted dose of 50 Gy. The median applied activity was 111.4 MBq (range, 21.0-168.0 MBq), and the median treatment time was 89 minutes (range, 38-175 minutes). The response rate, adverse events, and cosmetic outcome were assessed at 14 days, 4 months, and 12 months.

Results
Response rate at 12 months was 97.5%, with 95% complete responses (clinically or histologically proven in case of clinical doubt). Most adverse events were reported at 14 days, with 20% itching and 12.5% mostly minor pain. Forty-nine percent of the lesions showed hypopigmentation only at 12 months. Forty-one percent of the lesions were graded as cosmetically superior to the expected result after surgery and 51.3% as comparable to successful surgery. The cosmetic outcome on the head and face was superior compared with the trunk and leg (P = 0.003).

Conclusions
188Re resin is a highly effective treatment for NMSC up to 3-mm thickness and a valid alternative to surgery, specifically for tumors located on sensitive areas such as nose or ear.

A-269

What is the quality-of-life impact of basal cell carcinoma in older patients? A multicentric cross-sectional study.

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Background
Basal cell carcinoma (BCC) is the most frequent malignant tumour worldwide and incidences are rising rapidly.(1,2) BCC mainly causes harm by invading surrounding tissues.(2) There is an important knowledge gap concerning the impact of BCC on the health-related quality of life (HrQoL) and limited data reported contradicting results.(3–5) Measuring HrQoL in BCC patients should be done using disease-specific questionnaires such as the Basal and Squamous cell carcinoma Quality of Life (BaSQoL) questionnaire.(6) This study assesses the BCC-related HrQoL and examines all patient, tumour and treatment characteristics to identify the most relevant factors. We focused on older BCC patients because of the often complex treatment decisions in this subgroup.

Methods
Patients ≥18 years with a history of BCC consulting four medical centers were asked to fill in the BaSQoL questionnaire, consisting of 5 subdomains. Multivariable analyses were done using a generalized additive model (GAM), incorporating non-linear functions.

Results
Four hundred BCC-patients with a median age of 66 were included. Mean BaSQoL subscores were 0.78 (SD 0.63) for 'behaviour', 1.01 (SD 0.73) for 'diagnosis&treatment', 0.90 (SD 0.73) for 'worries', 0.40 (SD 0.63) for 'appearance' and 1.20 (SD 0.75) for 'other people', illustrating the low/moderate impact of BCCs on the HrQoL. A GAM with subsequent ANOVA testing was done for all variables. In 4 out of 5 BaSQoL subdomains 'age' showed a significant correlation with the BaSQoL score ('behaviour' p=0.007; 'diagnosis & treatment' p=0.026; 'worries' p=0.003; 'appearance' p=0.008). Lower BaSQoL scores were seen in older patients, meaning less BCC-impact on their HrQoL. There was a clear non-linear correlation between the BaSQoL scores and the age (figure 1), demonstrating the impact of BCC on the HrQoL shows a rapid decrease starting around the age of 70.

Conclusions
This study is the first to illustrate the relation between the BCC-related HrQoL and the age of patients with the use of a disease-specific HrQoL instrument. We found a lower BaSQoL score in older adults, with a specific group of interest starting around the age of 70-75. This is an argument for a more conservative strategy for BCCs in these patients.

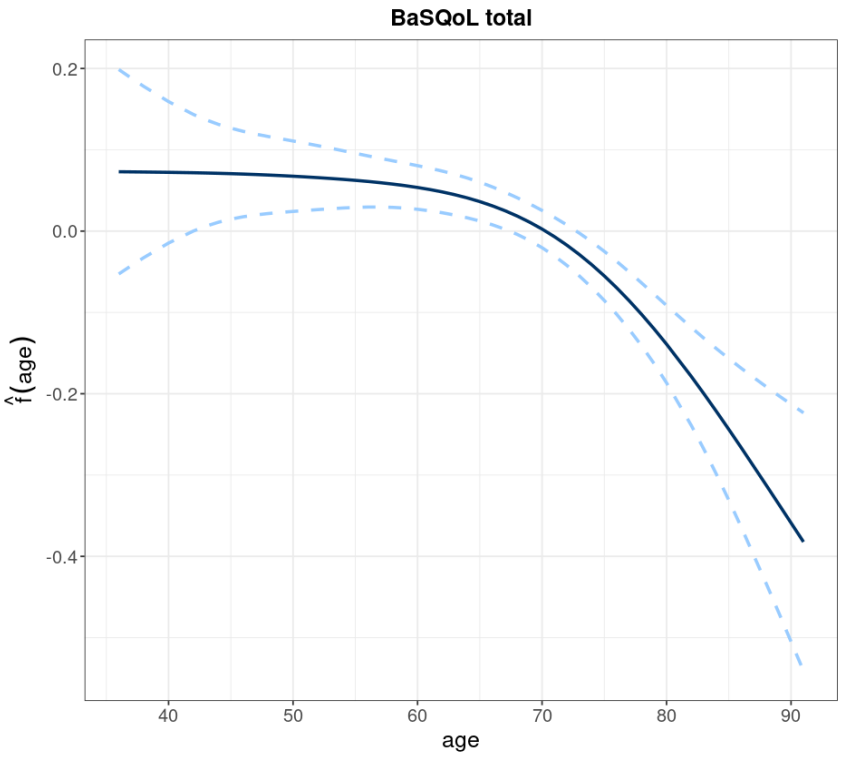

Figure 1. BaSQoL total score plotted in relation to the age of the patient.

Cutaneous sercoma

A-401

Incidence, local recurrence, metastasis, disease-specific survival, and overall survival in patients with cutaneous rhabdomyosarcoma: A nationwide cohort study of 24 patients

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Background
Cutaneous rhabdomyosarcoma (cRMS) is a very rare and aggressive type of mesenchymal derived tumour associated with a high risk of metastasis and death. The incidence, prognosis, and follow-up of patients with cRMS is unknown as the current knowledge is sparse and primarily based on case-reports. The purpose of this study is to describe the epidemiology of cRMS in terms of incidence, patient demographics, prognosis, and follow-up.

Methods
All patients with diagnosed cRMS in Denmark between 1982-2023 were identified in the Danish National Pathology Register. Risks of local recurrence, metastasis, and disease-specific survival were estimated with cumulative incidence functions with all-cause death considered a competing risk. Overall survival was estimated with the Kaplan-Meier method.

Results
A total of 24 patients with cRMS were included providing an incidence rate of 0.1468/1.000.000/year. The ages of diagnosed patients varied from 16,8 years to 90,8 years, and with a gender ratio with 37.5% (*n=9*) females and 62.5% (*n=15*) males. The RMS subtypes included 17 pleomorphic, 2 embryonal, 3 alveolar.

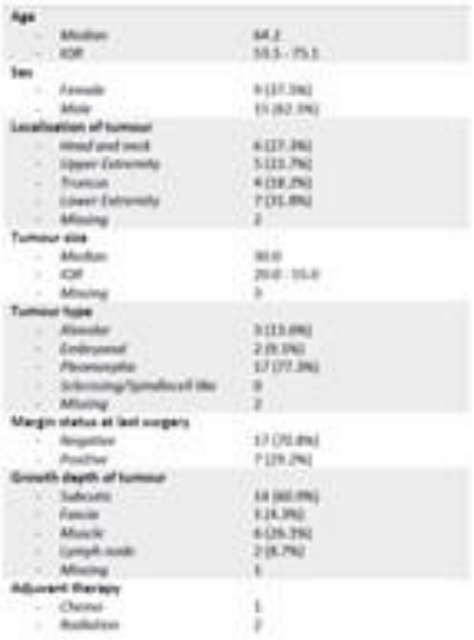

Table 1: Showing baseline characteristics of patient ages, sex, localisation of tumours, tumour sizes, tumour types, margin status at last surgery performed, growth depth of tumour and adjuvant therapy.

The used immunohistochemical markers for diagnosing cRMS were Myogenin (63%), MYOD1 (*21%*) and myoglobin (16%). Four patients experienced metastasis resulting in a 5-year risk of 24.4% (95%CI 3.5 - 45.3). Seven patients had metastases at the presentation of the diagnosis. Distant metastasis occurred in 17 patients (54%) and included the lungs, lymph nodes, brain, and GI-tract. Regional lymph node metastasis occurred in eight cases (26%) and local metastasis occurred in six cases (20%) including skin and bone invasion. Ten patients died from cRMS giving a 5-year disease specific survival of 56.2% (95%CI 35.1 - 76.8).

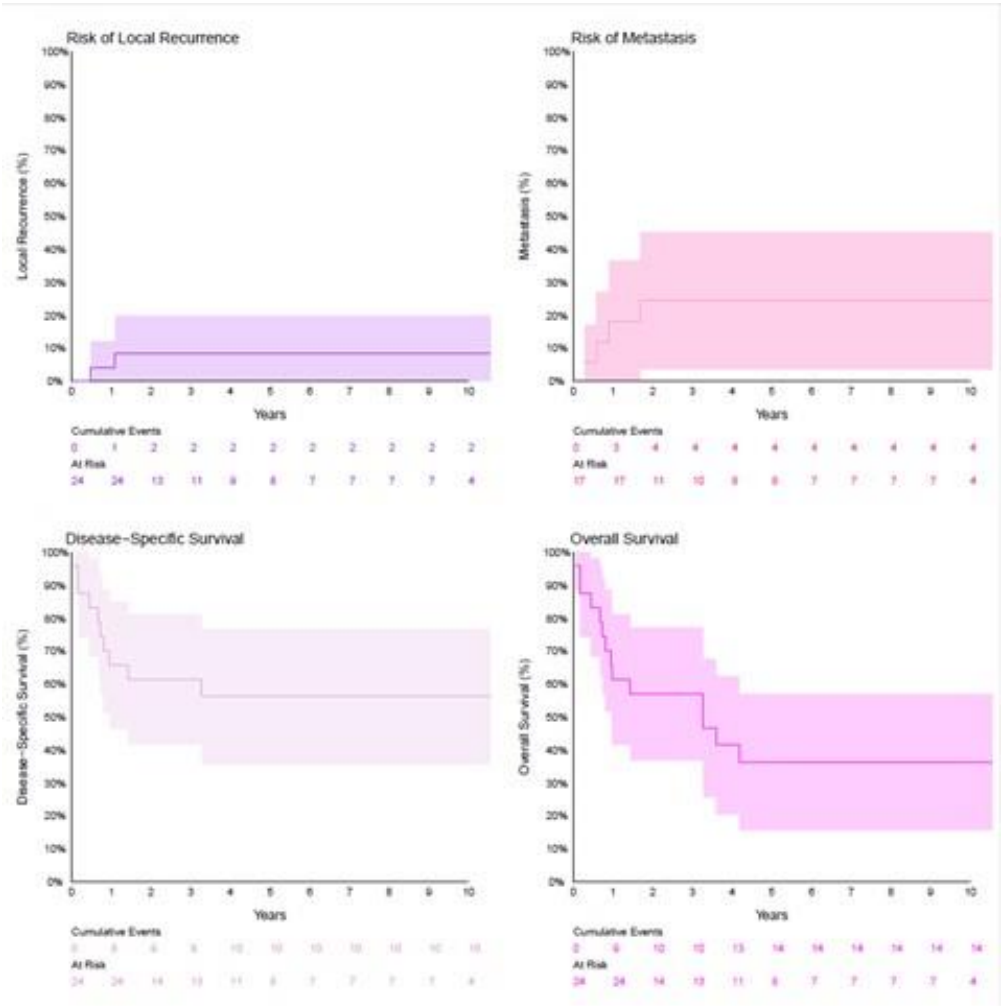

Figure 1: Cumulative incidences showing the risks of local recurrence (upper, left), metastasis (upper, right) and disease-specific survival (lower, left) and a Kaplan-Meier plot of overall survival (lower, right). The risk tables below the plots show cumulative events and the number of patients at risk each year up to ten years.

Conclusions

cRMS should be considered an aggressive cutaneous sarcoma with a high risk of metastasis and a low disease-specific survival. We propose that patients with cRMS should be followed with clinical visits and PET/CT every 4th month for three years followed by semi-annual visits the next two years. We suggest PET/CT as the distant metastasis localisations included both lungs, brain, viscera, and lymph nodes suggesting both hematogenous as well as lymphatic spread.

A-117

Cancers of the skin and mucous membranes in people living with HIV compared to the general population.

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Background
Despite the recent improvements in the clinical management of people living with immunodeficiency virus (PLWH), cancers still represent a serious issue. While it is already known that PLWH are at increased risk of squamous cell carcinoma of the anus, vulva, penis, and of the head-neck region, data about the risk of cutaneous and mucosal cancers in sites different from the anogenital/oropharyngeal ones are conflicting. This study aimed to assess the incidence and type of skin and visible mucosae cancers in a population of PLWH compared to the general population.

Methods
A cross-sectional analysis of consecutive PLWH referred to the Infectious Disease Unit at Policlinico Riuniti (Foggia, Italy) between July, 1st 2023, and December 31, 2023 was conducted. The presence of cancers through a full-body skin and visible mucosae examination was assessed by a board-certified dermatologist. All suspicious skin/mucosal lesions were surgically resected and evaluated by a pathologist for histological diagnosis.

Results
Thirthy-nine PLWH on antiretroviral therapy, of which 31 males (79%) with a mean age of 48.4 (+/-11.9) years, were collected. Phototype II was the most common (21 patients, 54%) and 23 patients (59%) reported sunburn in childhood/adolescence. Two patients (5%) had a family history of cutaneous melanoma and 7 (18%) had used photosensitizing drugs beyond 5 years. More than half of PLWH (51%) had a nevus count between 10 and 50 units whereas 9 patients (23%) had more than 50 units. These patients were compared to a matched series of 88 control patients (general population requiring a total skin examination for skin cancer screening) of which 4 (7%) were on immunosuppressive therapy. Forty-six (52%) control patients had a nevus count between 10 and 50 units and 16 patients (17%) had more than 50 units.
Only one of the PLWH (2%) presented a skin cancer, namely basal cell carcinoma, compared to 7 control patients (8%), of which 4 (4.5%) had basal cell carcinoma, 1 (1%) basosquamous carcinoma, 2 (2%) melanoma (p=0.24). Actinic keratosis was detected in 3 PLWH (8%) as compared to 10 (11%) controls (p=0.52).

Conclusions
The incidence of skin cancer in PLWH on antiretroviral therapy is not significantly different as compared to the general population. Skin cancer screening in PLWH should not be different from that of the general population.

A-330

Clinical features and treatment patterns of patients with classic Kaposi sarcoma in Greece.

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Background

Kaposi sarcoma (KS) is a multifocal malignancy originating from endothelial cells. The mainstay of therapy in advanced stage relies on liposomal doxorubicin (LD) during the last 25 years, with some additional chemotherapeutic drugs also available. Over the last few years, novel systemic therapies have emerged, based on the results of small phase I/II trials.

Given the rarity of the disease, there is a scarcity of prospective and comparative data on the efficacy of the different drugs. In addition, the optimal therapy sequence is yet to be defined. Therefore, we aimed to gather real-world data on clinical characteristics, treatment approaches and outcomes of systemic therapies in Greek patients with KS.

Methods

Medical records from classic KS patients treated with systemic therapies from 1999 to 2023 at 5 centers in Greece were retrospectively reviewed. End-points were overall response rate (ORR), treatment-free time and safety.

Results

In total, 81 patients with KS were identified (median age 75 years, range 42-91), including 64 males and 17 females. Seventy-four patients (91.4%) presented with cutaneous only involvement, six patients (7.4%) with both cutaneous and extra-cutaneous (oral, genital, gastrointestinal, nodal) involvement and one patient (1.2%) with genital only KS. Regarding skin involvement, the lower extremities were the most frequently affected part (n=74, 92.5%). The number of cutaneous lesions was 1-50 in 42 (51.9%), 50-100 in 24 (29.6%), >100 in 11 (13.6%) and not available in the remaining 4 patients. Twenty-six patients (32.1%) had received local therapies before the initiation of systemic therapy.

Patients received 1-14 (median 2) treatment lines and the different regimens are shown in table 1.

DRUGS	L1	L2	L3	L4	L5	L6	L7	L8	≥L9
LD	72	48	27	15	7	5	4	4	9
Doxorubicin	1								
Paclitaxel			1						
Bleomycin						1			
Vinblastine		1							
Thalidomide	1	1							
Pomalidomide			1						
Interferon	7		1						
Pembrolizumab		1	1						

Different regimens administered per line of systemic therapy.

In the first-line setting (L1), LD (n=72) yielded 28 complete responses and 36 partial responses, leading to an 88.9% ORR, versus 82.4% as ≥2nd-line therapy (n=119). Median treatment-free time was 7.6 (0-1387.7) and 13 (0-1374.9) months with L1 LD and L2 LD respectively.

The different regimens were in general well tolerated, with mainly grade 1-2 adverse events.

Conclusions

LD is the most common drug used in our KS population, as both initial and rechallenge therapy. With the limitation of a retrospective study design, this analysis shows that LD is very efficacious and safe. Prospective studies are needed to compare the different available regimes.

A-128

Evaluating the performance of a clinicopathological prognostic nomogram and utility of the 40-gene expression profile (40-GEP) test in refining risk of metastasis in high-risk cutaneous squamous cell carcinoma (HR-cSCC) patients

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Background
Risk stratification for cutaneous squamous cell carcinoma (cSCC) is challenging due to tumor heterogeneity associated with poor outcomes. Several tools exist, including clinical staging systems and 40-GEP testing. The 40-GEP test categorizes HR-cSCC tumors into three groups: Class 1-low, Class 2A-higher, and Class 2B-highest with event rates of <7%, 20%, and >50% biological risk of metastasis, respectively. The purpose of this study is to evaluate the performance of a cSCC nomogram published by Rentroia-Pacheco, et al (1) and test the additional prognostic value of the 40-GEP.

Methods
This retrospective cSCC cohort (n=760) of high (64.9% [493/760]) or very-high risk (35.1% [267/760]) NCCN tumors were categorized into 2 groups (low-risk group, LRG= 0-20%, n=737; high-risk group, HRG= ≥21%, n=23) by the nomogram, and compared to the results of 40-GEP testing. Kaplan-Meier (KM) curves were generated to determine 3-year metastasis-free survival (MFS).

Results
Overall MFS was 89.2% (95%CI:87.0-91.4%). Nomogram risk bins showed MFS rates of 90.2% (95%CI:88.1-92.4%) in the LRG and 56.5% (95%CI:39.5-80.9%) in the HRG. However, 88.5% (77/87) of all metastases were in tumors categorized as LRG. In the LRG, 40-GEP identified patients at increased risk of metastasis (Class 2A predicted risk: 39.1% (288/737), true metastases: 59.7% (46/77)); Class 2B predicted risk: 3.3% (24/737), true metastases: 10.4% (8/77)) with 3-year MFS rates of 84.4% (95% CI 80.3-88.7%) and 70.8% (95% CI 54.8-91.6%), for Class 2A and 2B respectively.

Conclusions
The nomogram classified 9 out of 10 tumors that metastasized as lower risk. However, the 40-GEP classified 70% of tumors missed by the nomogram as high-risk Class 2. These data demonstrate that 40-GEP improves risk stratification of NCCN high or very high-risk patients who were categorized as low-risk by this nomogram.
References:

[1] Rentroia-Pacheco B, Tokez S, Bramer EM, et al., (2023), Personalised decision making to predict absolute metastatic risk in cutaneous squamous cell carcinoma: development and validation of a clinico-pathological model, eClinicalMedicine, 63, https://pubmed.ncbi.nlm.nih.gov/37662519/

A-214

Evaluation of efficacy and tolerability of a repairing protective cream containing the postbiotic Aquaphilus Dolomiae extract G2 for onco-dermatological indications

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Background
Wound healing is a well-orchestrated series of biological events that comprises haemostasis, inflammation, proliferation and extracellular matrix remodelling. Improving and accelerating wound healing aims at reestablishing skin integrity while preventing abnormal scarring. The aim of the present study was to evaluate the immediate and long-lasting effects of a dermo-cosmetic formulation containing *Aquaphilus Dolomiae* ferment extract (ADE-G2) on various dermatologic clinical signs and symptoms in an oncological study population. Overall product effectiveness, tolerability, and user satisfaction were assessed.

Methods
We conducted a real-word, prospective, observational, non-interventional multi-center study in 7 countries (France, USA, Chile, Germany, Costa Rica, Czech Republic, Slovakia). Participants were instructed to use the study product containing ADE-G2, Cu/Zn complex and Avène Thermal Spring Water daily for 3 weeks according to their onco-dermatologist's advice. To evaluate effectiveness, objective and subjective dermatological clinical signs were assessed according to a 4-point Visual Analog Scale at inclusion and at the follow-up visit. Tolerability and user satisfaction were assessed using a questionnaire.

Results
189 subjects aged 3 to 90 and presenting with superficial skin impairment following oncological treatments (57.1% radiodermatitis grade 1, 33.3% post-surgical scars and 10.6% cutaneous side-effects due to chemotherapies/targeted therapies) were included.
The first application of the ADE-G2-based cream had an immediate relieving effect in 74% of subjects. Significant decreases from baseline were also found in subjective clinical symptom scores, with a mean decrease in total severity score of –24.1% at the first product application. Overall improvement in burning sensation was reported in 92.4% of subjects.
At study end, product tolerability was rated by the dermatologists as "very good" or "good" in 97.9% of subjects. 96.3% of subjects were "very satisfied" or "satisfied" with the product.

Conclusions
ADE-G2 has previously demonstrated *in vitro* stimulatory effects on keratinocytes migration and fibroblasts proliferation and accelerated the process of re-epithelization *in vivo* in a wounded skin model. This real-world international study confirms the interest of a repairing protective cream containing the ADE-G2 postbiotic in the treatment of superficial skin impairment or wound healing in an oncological patient population.

A-380

Multimodal skin imaging of a dermatofibrosarcoma protuberans using line-field confocal optical coherence tomography, ultra-high frequency ultrasound and reflectance confocal microscopy

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Background

Dermatofibrosarcoma protuberans (DFSP) is a rare, asymptomatic, and slow-growing tumor predominantly observed on the trunk of adults aged between 30 and 50 years (*Allen, Ahn, and Sangüeza 2019*). Management is primarily surgical, with local recurrences being common, while metastases are rare (*Lowe et al. 2017*). DFSP has been previously characterized using ultrasound (*Zou et al. 2021; Diago et al. 2021*), and two case reports have described DFSP utilizing reflectance confocal microscopy (RCM) (*Venturini et al. 2016; Acar et al. 2020*).

Methods

This case report introduces the novel application of line-field confocal optical coherence tomography (LC-OCT) in DFSP diagnosis. Our case report details a 35-year-old man presenting with a pinkish, slow-growing, and firm plaque between his scapulae. Skin imaging (employing ultra-high frequency ultrasound, RCM an LC-OCT) was performed.

Results

Ultra-high frequency ultrasound displayed a flat oval hypoechoic structure with tentacle-like projections in the dermis, estimating tumor depth at 9.9 mm. RCM exhibited a loss of the dermal-epidermal junction and a storiform pattern of dense hyperreflective collagen fibers containing hyporeflective fusiform cells. LC-OCT, in the vertical view, revealed a hyporeflective thin branched structure invading the dermis, while the horizontal view showed an altered dermal-epidermal junction and dermal collagen fibers densely organized in a storiform pattern. A skin biopsy confirmed the diagnosis of DFSP, leading to subsequent MRI and surgical excision with 3 cm margins

Conclusions

This case underscores the potential of non-invasive skin imaging in the initial diagnosis of DFSP and suggests its utility in assessing local recurrences. While RCM can give information at the cellular level to spot any local recurrence, imaging depth is limited to the upper dermis. (*Nawrocki et al. 2022*). The combined vertical and horizontal view, colocalized dermoscopy and imaging depth up to 500 µm position LC-OCT as a highly valuable non-invasive tool to assess initial suspicion of DFSP and potential local recurrence after surgery.

A-150

Optimizing Healing: Evaluating Ozone Therapy's Impact on Skin Cancer Surgery Reconstruction at the Amazon Head and Neck Surgery Center

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Background
This study investigates the effectiveness of ozone therapy in enhancing the healing process of grafts and flaps used in surgical reconstruction following skin cancer removal. The primary objective is to understand how ozone therapy accelerates tissue regeneration, thereby influencing the overall success of skin cancer surgery reconstruction. Additionally, the research aims to explore how ozone therapy can mitigate postoperative complications, contributing to more satisfactory outcomes in terms of both functionality and aesthetics. The study holds significance in expanding our understanding of ozone therapy applications in reconstructive surgery, particularly in the unique context of the Amazon Region.

Methods
The methodology involves a thorough evaluation of patients who underwent surgical transplants with grafts and flaps post-skin cancer resection. Specific inclusion criteria were applied to ensure relevance to the research objectives. A detailed assessment of patients' overall health and suitability for both skin cancer resection and subsequent ozone therapy was conducted before the surgical procedure. Ozone therapy was administered with careful consideration of dosage, duration, and frequency tailored to individual patient characteristics. Postoperative monitoring included regular evaluations of wound closure, tissue viability, and overall healing progression. Systematic data collection comprised quantitative and qualitative data on patient outcomes, satisfaction levels, and observed complications.

Results
Results indicated successful outcomes for several patients with ozone therapy application. In challenging cases, where grafts and flaps faced difficulties, ozone therapy, combined with standard postoperative protocols, consistently achieved a 100% recovery rate in a few sessions. Patients expressed high satisfaction levels, and the approach demonstrated notable cost-effectiveness. These findings highlight the broad applicability and success of ozone therapy in various cases at the Amazon Head and Neck Surgery Center.

Conclusions
In conclusion, the research emphasizes the crucial role of incorporating ozone therapy into graft and flap healing for skin cancer surgery reconstruction. The study aligns with the broader trend in medical research, advocating for innovative approaches to optimizing patient outcomes in reconstructive surgery

A-178

Stratified processing of skin lesions through deep learning

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Background
Skin cancer is rapidly increasing worldwide. Moreover, melanocytic lesions in particular show high internal heterogeneity in pigmentation and malignancy. Diagnostic accuracy and efficiency can be augmented through ex vivo dermoscopy with derm dotting. This encompasses marking of dermoscopically visible, diagnostical areas within excised skin tumours to process them in a targeted way and trace suspicious areas under the microscope. Automating ex vivo dermoscopical skin tumour classification can make the methodology accessible, cost-efficient and standardized for pathology labs. Therefore, we evaluated the feasibility of automating stratified, lesion-specific processing though deep learning.

Methods
Classification was evaluated on a dataset of 13729 images of skin tumours divided into 2, 3 and 7 classes. The first classification problem encompasses the general distinction between benign and malignant lesions; this makes it useful to increase attention of lab technicians in case of potential malignancy. The second classification deals with the division of skin biopsies into three main processing strategies. These strategies include (1) a basic protocol, bread loafing the skin tumour lesion; (2) a carcinoma protocol, raising attention to orientation and tracing of borders of carcinomatous lesions; and (3) a melanocytic protocol, raising awareness of the heterogeneity in pigment cell lesions requiring marking and tracing under the microscope. The third classification problem focuses on the distinction into one of seven main skin tumour classes, namely: seborrheic keratosis, dermatofibroma, haemangioma, naevus, melanoma, squamous cell carcinoma and basal cell carcinoma.

Results
Highest sensitivities were obtained with a ResNet CNN architecture, optimization through stochastic gradient descent, a learning rate of 0.001, a batch size of 32, pretraining and fine-tuning of all layers. In this case, overall sensitivity was 74% and class-specific sensitivities ranged from 50% to 88% depending on sample size and intra-class homogeneity. Classification of these lesions into their respective processing strategy reached a sensitivity of 84%. Furthermore, the network separated malignant tumours from benign tumours with a sensitivity of 87% and an AUROC of 0.9.

Conclusions
Our results indicate that ex vivo dermoscopical image classification of skin tumours is feasible, but could be further improved for practical applications.

A-216

Sun awareness and prevention in chemotherapy patients: a comparative study

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Background

Exposure to the sun, especially intense sunlight, poses increased health risks, especially for people undergoing chemotherapy. Our study assesses the awareness and use of public health recommendations for sun protection in chemotherapy patients, which is essential to minimise adverse effects and promote healing. Our aim was to determine whether undergoing chemotherapy leads to increased vigilance with regard to sun exposure, in particular the adoption of preventive behaviours such as avoiding sun exposure between 11am and 4 pm and the regular application of sunscreen.

Methods

From the ALL database (50,552 individuals from 20 countries), we identified 2,874 patients undergoing (or who had recently undergone) chemotherapy: the "exposed-population". A group of 6,034 individuals who were not recently exposed formed the "unexposed-population". Two key recommendations were prioritised: avoid exposure during peak hours and apply sunscreen every 2 hours.

Results

Fewer individuals in the exposed-population reported exposure between 11 am and 4 pm than in the unexposed-population [58.2% vs. 63.4%, P < 0.0001]. More people in the exposed population used sunscreen every 2 hours [42.5% vs. 27.9%, P < 0.0001] and were less likely not to use sunscreen [13.3% vs. 22.4%, P < 0.0001]. A higher percentage were aware of the recommendations [86% vs. 83%, P < 0.001]. Notably, more chemotherapy patients did not believe the prevention messages [9.96% vs. 3.20%, P < 0.0001]. No-significant-difference was found in sunscreen use for skin cancer prevention. The exposed-population was predominantly female and younger. Logistic regression confirmed "chemotherapy" as the most influential factor for sunscreen application (coefficient 0.6212), ahead of gender (coefficient 0.3712) and age (coefficient 0.0004). We find the same results for exposure during the peak hours (0.18 for chemotherapy, 0.04 for gender and 0.005 for age).

Main results of the analysis					
	Exposed Population		**Non-exposed Population**		
DEMOGRAPHICS	N	%	N	%	*P-value*
Identify as female	2006	69,80%	3757	62,26%	*4.146561051002515e-12*
Declare to be under 40	1841	64,06%	3071	50,89%	*2.1912510672802442e-31*
Report having dark skin (phototype IV, V and VI)	647	22,51%	1370	22,70%	*0.8604035061064447*
	N	%	N	%	*P-value*
DECLARE NOT TO HAVE BEEN EXPOSED TO THE SUN	425	14,79%	1177	19,51%	*5.9355504889566E-8*
TIME OF EXPOSURE REPORTED	2449		4857		
Before 11 am	1154	47,12%	2148	44,22%	*0.020159271012494234*
Between 11am and 4pm	1426	58,23%	3028	62,34%	*0.0007292742664513985*
After 4 pm	718	29,32%	1695	34,90%	*1.9273149616475695e-06*
	N	%	N	%	*P-value*
PREVALENCE OF THOSE HAVING HEARD OF THE RECOMMENDATION	2107	86,04%	4026	82,89%	*0.00062101012846366 91*
AMONG THOSE WHO SAY THEY EXPOSE THEMSELVES BETWEEN 11.00 AND 16.00, THE REASONS ARE	N	%	N	%	*P-value*
I didn't understand	121	8,49%	76	2,51%	*7.952271315989744e-16*
These are the most practical hours, given my activities.	528	37,03%	1030	34,02%	*0.6765976977201058*
These are the most pleasant hours of the day	327	22,93%	484	15,98%	*0.00014437872680229082*
These are the hours when I am available	515	36,12%	920	30,38%	*0.17201336941107354*
I don't believe in prevention messages	142	9,96%	97	3,20%	*1.5577827735027854e-16*
I don't know why I do it anyway	34	2,38%	97	3,20%	*0.05073466766175458*
I'm not worried because my skin tolerates the sun very well.	42	2,95%	73	2,41%	*0.6929966224505808*
DO YOU USE SUNSCREEN ?	N	%	N	%	
Yes, every two hours	1041	42,51%	1357	27,94%	*8.2685978467695 76e-36*
Yes, but irregularly or less often	1081	44,14%	2411	49,64%	*9.9924379 10871327e-06*
Not at all	327	13,35%	1089	22,42%	*2.8120552213649786e-20*
	2449		4857		
AMONG THOSE WHO USE SUNSCREEN EVERY 2 HOURS, THE MOTIVES ARE AS FOLLOWS	N	%	N	%	*P-value*
To avoid sunburn	1329	62,63%	2695	71,52%	*2.3111017657900167e-12*
To spend more time in the sun	600	28,28%	874	23,20%	*1.790028114757617e-05*
Because of a history of sunburn	575	27,10%	921	24,44%	*0.026719946018703353*
To protect against accelerated skin ageing	1103	51,98%	2171	57,62%	*3.2806149297055964e-05*
To protect against the risk of skin cancer	1021	48,11%	1811	48,06%	*0.9908679873070576*
AMONG THOSE WHO DO NOT USE SUNSCREEN, THE FOLLOWING REASONS ARE GIVEN	N	%	N	%	*P-value*
The products are too expensive	49	3,48%	107	3,06%	*0.5002735776832085*
I don't think about it	429	30,47%	896	25,60%	*0.0005825570164552504*
I don't see the point	523	37,14%	1356	38,74%	*0.31285973595648897*
It's too much trouble	268	19,03%	501	14,31%	*4.68244175926280 36e-05*
I was not aware of the recommendation	417	29,62%	994	28,40%	*0.4140294024834523*

Main results of the analysis

Conclusions

While chemotherapy patients are generally more vigilant about sun protection, a significant proportion remain sceptical about its effectiveness. This highlights the importance of personalised, repeated communication about the importance of sun protection, considering individual beliefs. Healthcare professionals need to step up their efforts to dispel myths and increase understanding of the benefits of sun protection, especially among those who are vulnerable due to aggressive treatments such as chemotherapy.

Cutaneous T- and B-cell lymphoma

A-348

Dermoscopic, Reflectance Confocal Microscopy and Line-field Optical Coherence Tomography features of Cutaneous Lymphomas

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Background
Primary cutaneous lymphomas (PCL) comprise a heterogeneous group of extra-nodal non-Hodgkin lymphomas arising from malignant clonal transformation of T lymphocytes (CTCL) or B lymphocytes (CBCL). The diagnosis of PCL can be a real challenge for clinicians, since they may mimic benign skin conditions. Although histopathology remains the gold standard for PCL diagnosis, multiple biopsies are often required because of their equivocal presentation. Recently, non-invasive diagnostic imaging modalities, including dermoscopy, Reflectance Confocal Microscopy (RCM) and Line-field Optical Coherence Tomography (LC-OCT), have been described as valuable tools to help clinicians rule out PCL diagnosis. On this background, the present study aims to evaluate dermoscopic, RCM and LC-OCT features of PCL and discuss the potential role of non-invasive skin imaging in PCL management.

Methods
Between December 2022 and January 2024, a total of 40 test sites of 18 patients with a histopathologically confirmed diagnosis of PCL were retrospectively analysed in the Dermatologic Clinic of the University of Siena, Italy. Predefined dermoscopic, LC-OCT, and RCM criteria were assessed, and their frequencies were calculated.

Results
The mean (SD) age of our cohort was 71 (12) years. CTCL represented 75 % of all cases, and the majority were Mycosis Fungoides (57.6%), followed by Sezary Syndrome (24.2%). Interestingly, epidermal lymphocytes, junctional lymphocytes and dermal lymphocytes were detected in 73.1%, 66.7% and 51.9% of CTCL cases, respectively, during LC-OCT evaluation. Similar percentages were observed in the RCM evaluation (72.2%, 55.6% and 61.1%, respectively). Overall, CBCL accounted for 25 % of test sites and they were predominantly nodules (90%), with 6 cases of primary cutaneous follicle center lymphoma and 4 of marginal zone B cell lympohma. At LC-OCT evaluation of CBCL, all lesions observed were characterized by the presence of telangiectasia, whereas a high prevalence of a medium reflective dermal infiltrate (80%) was detected. Considering dermoscopic features, CTCL lesions were mainly characterized by pinkish structureless areas (58.6%) and uniformly dotted vessels (35.7%), whereas 57.1% of CBCL cases presented orange-yellow structureless areas.

Conclusions
Although further studies are needed, the use of non-invasive imaging techniques appears promising for the diagnosis and management of PCL.

A-138

Insights on different erythroderma features in Sezary syndrome: a prospective validation study

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Background

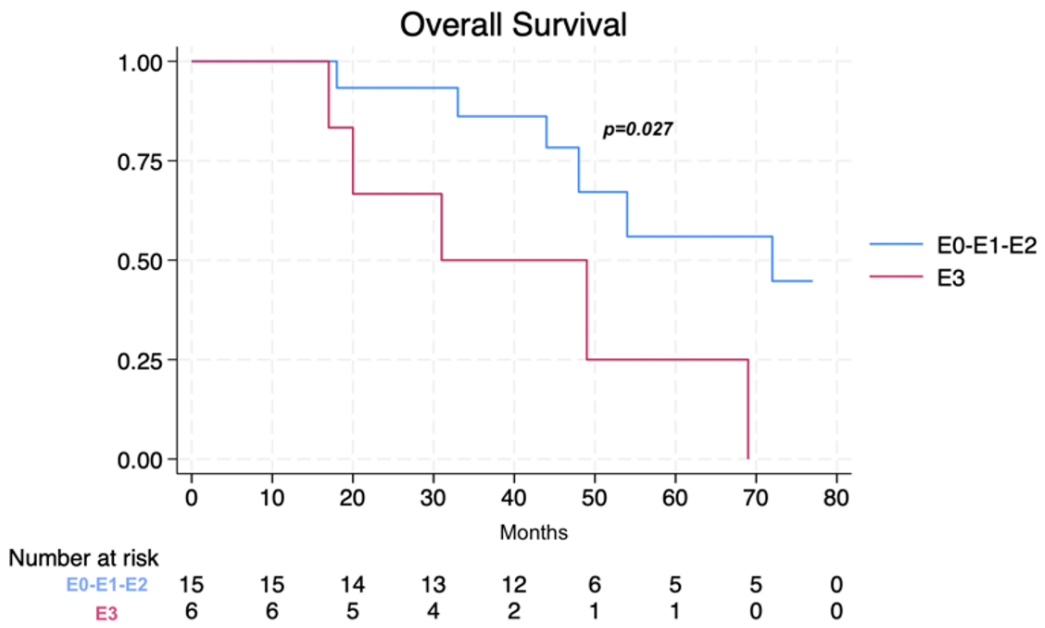
The current guidelines lack details on the potential variations in clinical features in Sézary syndrome (SS) patients. Recently, a clinical score has been proposed based on three main presentations of erythroderma, with potential prognostic value.[1]

Methods

Patients with Stage IV SS were prospectively treated and followed at a single-center university-based institution from January 1st, 2017, to November 2023. Patients were classified based on the recently proposed classification (E0 sub-erythroderma, E1 erythematous, E2 infiltrative, E3 melanoderma). Kaplan-Meier method and Cox regressions were employed to assess overall survival differences.

Results

After a median follow-up of 52 months, data on 21 stage IVA1 patients were available. The cohort displayed a male prevalence (66.7%), with a median age of 73 (range 28-88). Eighteen out of 21 patients (85.7%) had at least one other comorbidity, and 5/21 (23.8%) had a previous diagnosis of patch/plaque mycosis fungoides. Pruritus was present in 18 patients (85.7%). The median CD4+CD26-/CD7- count value at diagnosis was 3337 (range 100-14500). Four out of 21 patients (19.0%) showed large cell transformation. The mean total number of lines of therapies was 5 (range 2-9), with oral retinoids (85.7%), ECP (81.0%), and mogamulizumab (42.9%) being the most common. In the initial assessment, 12 patients were categorized as E0 (57.1%), 8 as E1 (38.1%), and 1 as E2 (4.8%). Over the follow-up period, 6 patients (28.6%) transitioned from sub-erythroderma (E0) to erythematous erythroderma (E1). Additionally, 6 patients (28.6%) developed melanoderma (E3), comprising 3 initially classified as E0 and the remaining 3 as E1. The sole E2 patient maintained consistent clinical features throughout the follow-up duration. According to the log-rank test, patients with melanoderma (E3) exhibited significantly inferior survival rates compared to non-melanodermic patients, with 48-month survival rates of 67.1% versus 25.0% (p=0.027). Cox regression analysis underscored the negative association between melanoderma (E3) and survival (3.72 HR, 95% CI 1.06-13.02, p=0.040), irrespective of other variables in the study.



Conclusions

Patients manifesting melanoderma (E3) demonstrate compromised overall survival, substantiating the adverse influence of melanoderma on prognosis. Despite the study's limited scale, the prospective data yield valuable insights applicable to clinical practice.
References:

[1] Roccuzzo G, Giordano S, Avallone G, et al. Sézary Syndrome: Different Erythroderma Morphological Features with Proposal for a Clinical Score System. Cells. 2022;11(3):333. Published 2022 Jan 20. doi:10.3390/cells11030333

A-113

Integrated transcriptomics reveals cellular and molecular interactions in pruritic cutaneous T-cell lymphoma

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Background

Intractable pruritus is a major factor reducing quality of life in patients with cutaneous T-cell lymphoma (CTCL). Traditional antipruritic medication shows little to no efficacy, partly due to a lack of knowledge about the underlying mechanism.
We investigate the transcriptional signature of the cutaneous microenvironment (CME) and in particular the keratinocytes to identify potential targets driving pruritus in CTCL.

Methods

Spatial and single-cell transcriptomic profiling was performed on pruritic and non-pruritic human CTCL skin samples.
Formalin-fixed paraffin embedded (FFPE) skin samples from patients with (n=3) and without (n=3) pruritus have been selected. For spatial transcriptomic analysis, immunofluorescent staining of keratinocytes (E-cadherin), subepidermal immune cells (CD45) and fibroblasts (Vimentin) (Figure1A) was used to determine respective regions of interests (ROIs) (n=96) and quantify >18'000 genes.
In a second cohort of CTCL skin samples with and without pruritus (2x n=5), multimodal single-cell sequencing has been performed to investigate transcriptome, surface proteome and T-cell receptor hyperexpansion.

Results

Spatial transcriptional profiling of key cell types within the CME revealed a pruritus-specific signature of epidermal keratinocytes. Gene set enrichment analysis confirmed enhanced sensory function ($p<0.001$) (Figure1B) in pruritic keratinocyte subpopulation. Within the immune compartment, pruritic and non-pruritic skin had a divergent cell-type composition ($p=0.01$) (Figure1C), driven by a significantly increased fraction of CD4 memory cells in pruritic CTCL skin ($p<0.01$) (Figure1D).
Additional single-cell profiling identified a distinct keratinocyte cluster expressing sensory receptors known for interleukin-mediated signaling (e.g. OSMR, IL4R). Further, malignant and non-malignant CD4 T-cells differed in the expression pattern of cytokines and interleukins (e.g. IL4).
Intercellular communication networks within the CME highlighted interleukin- mediated signaling between immune-cells and specific keratinocyte populations as major interaction paths (e.g. IL4/IL4R). Potential druggable receptor targets were primarily expressed in the CME, but not by T-cells.

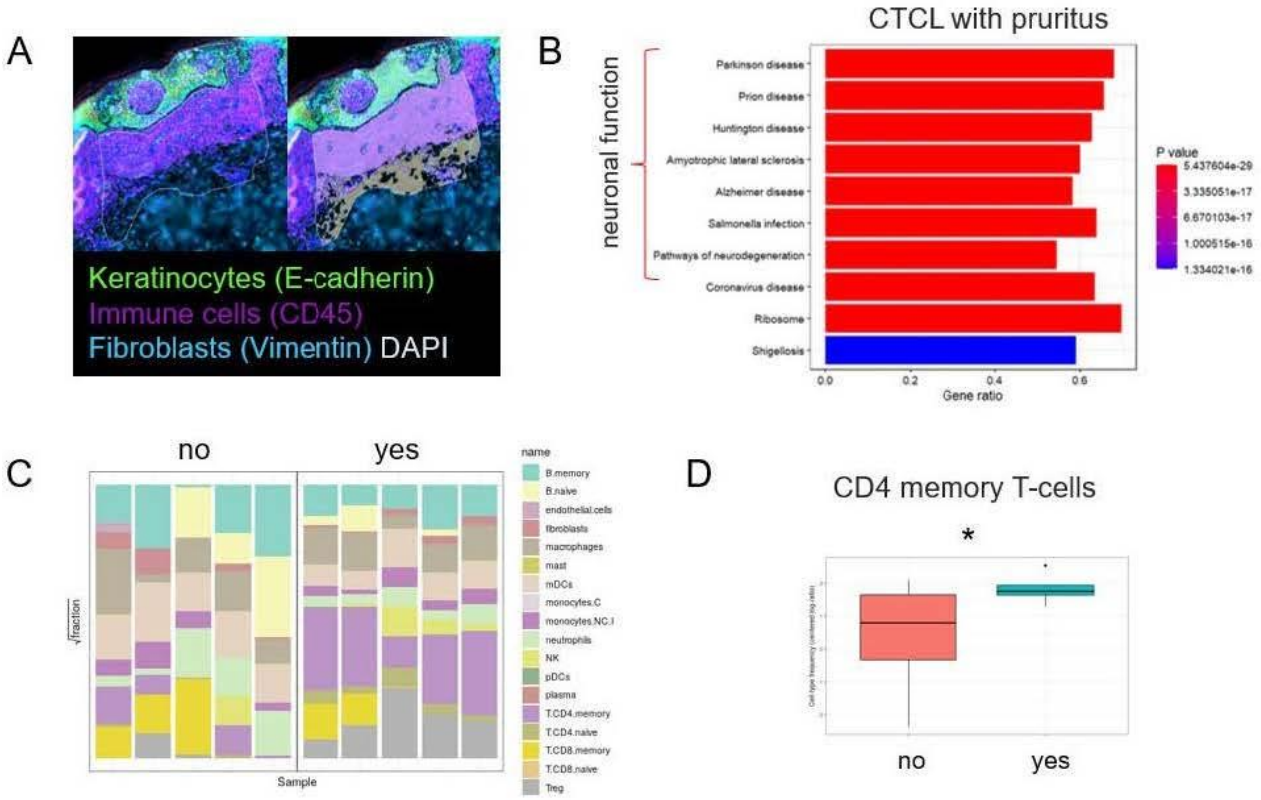

Figure1 (A) Immunofluorescent staining for selection of ROIs (B) Top upregulated pathways in pruritic versus non-pruritic keratinocytes. (C) Cellular composition of immune segment. (D) Fractional upregulation of CD4 memory T-cells in pruritic CD45 compartment.

Conclusions

Our results highlight the contribution of the keratinocyte-immune crosstalk to pruritic sensation and the sensory function of keratinocytes. Different expression patterns of sensory receptors within the CME could guide safe repurposing of targeted antipruritic medications.

A-361

Leg lymphoma not leg type lymphoma

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Background
Introduction: Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (PCAECTCL) is a rare and provisional entity, characterized by a CD8+ cytotoxic T cells proliferation, an aggressive clinical behaviour and bad prognosis. In cases where PCAECTCL doesn't show its characteristic immunophenotype, clinicopathological correlation becomes essential.

Methods
Clinical report: A 79 man consulted because of a painful left knee lesion that had appeared 4 months ago. He didn't have constitutional syndrome. Physical examination showed a big tumoral subcutaneous infiltrated mass with purplish patched erythema on its surface which occupied all the outside of his left knee. An incisional biopsy was performed due to the clinical suspicion of primary cutaneous diffuse large B-cell lymphoma, leg type. Bacterial, mycobacterial, and fungal cults were performed too. Histological findings showed a neoplastic diffuse proliferation pattern with marked epidermotropism, spongiosis and positive expression of the cytotoxic markers TIA1, perforin, TCR-B and CD2 although CD8 was negative. The clinicopathological correlation allowed us to reach the PCAECTCL diagnose. The extension studies didn't find marrow bone invasion nor visceral affectation so a polychemotherapy scheme treatment with minni-CHOP was started.

Results
Discussion: The PCAECTCL represents less than a 1% of all T cutaneous cell lymphoma and it usually presents as eruptive tumoral nodules with ulcerated and necrotic centre. It's characterized by a rapid progression and the visceral affectation is common when it's diagnosed. The histology is very variable and the immunochemistry can be positive for beta-F1, CD3, CD8, granzyme B, perforin and TIA 1. PCAECTL diagnosis is based in the combination of clinical, histological and immunophenotype findings and the differential diagnosis between other entities like the primary cutaneous acral CD8 t-cell lymphoma, lymphomatoid papulosis or the panniculitic T-cell lymphoma must be done. Its treatment its based on polychemotherapy scheme, using drugs that are indicated for peripheric T-cell lymphomas. However the response to treatment is variable, the estimated survival is two years.

Conclusions
Conclusion: We present a leg PCAECTCL case with CD8 negative immunophenotype, highlighting the need of an optimal clinicopathological correlation for reaching the diagnose of these entities that have been recently described.

A-133

Updates on CTCL diagnostic and therapeutic trends amidst the COVID-19 pandemic: insights from a referral center

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Background

The COVID-19 pandemic disrupted healthcare priorities, affecting the diagnosis and treatment of various medical conditions, including skin cancers. This study aimed to investigate the impact of the pandemic on the incidence rates, clinical characteristics, and treatments of cutaneous T-cell lymphomas (CTCL) patients at a tertiary referral center.

Methods

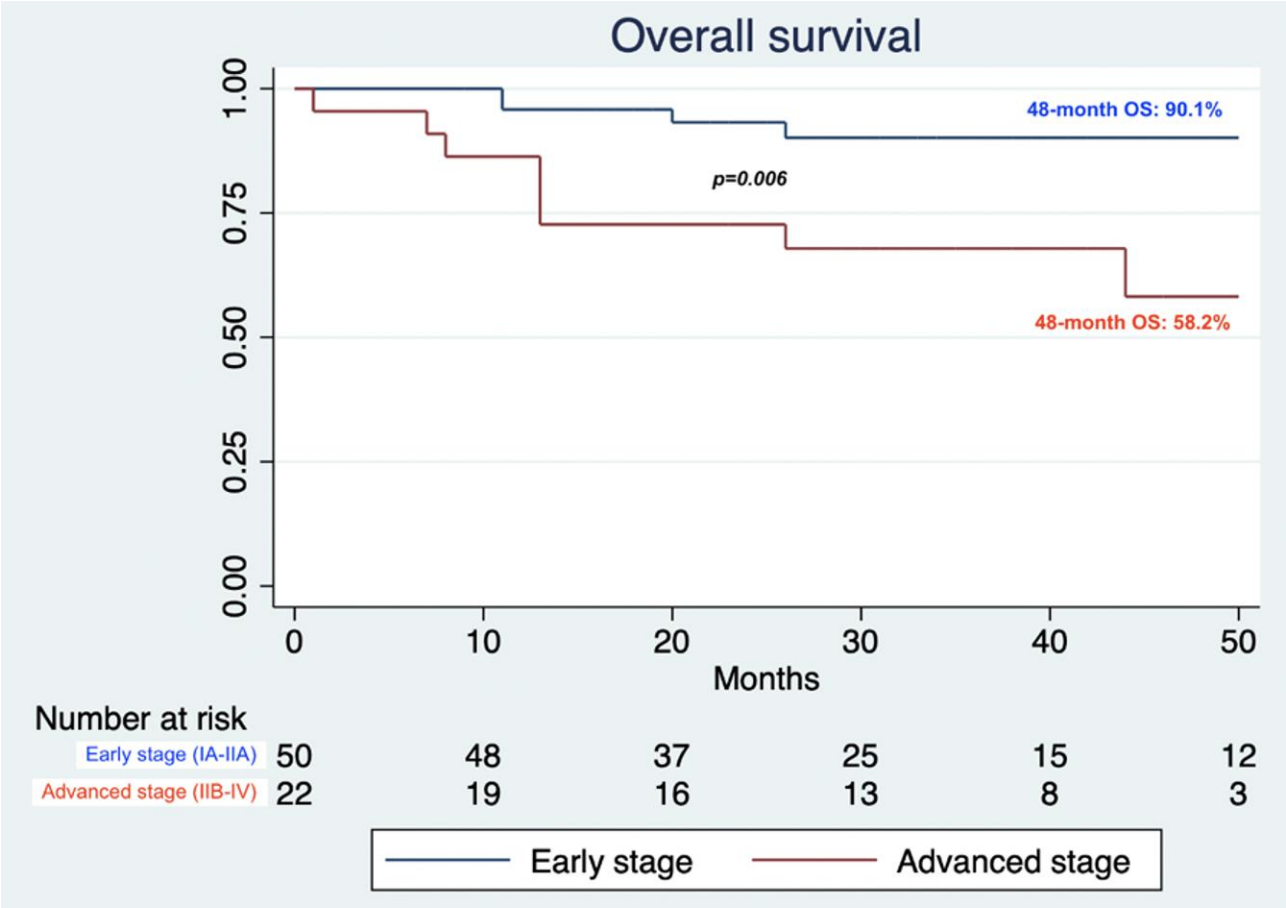
Clinical data from CTCL patients attending our dermatologic clinic between January 2020 and December 2022 were collected. Patients meeting specific criteria were included, and their data were compared to a pre-pandemic cohort from 2019 (n=247). [1]Mann-Whitney, Chi-squared, and Fisher's exact tests were used to analyze continuous and paired nominal data, respectively. Kaplan Meier curves and Cox regressions were used to identify factors related to survival in the subgroups of early (IA-IIA) and advanced (IIB-IV) stages.

Results

During 2020-2022, 72 new cases of CTCL were evaluated.

	Pre-pandemic Cohort	2020-2022 Cohort	*p-value*
CTCL patients, n	247	72	-
Male, n (%)	95 (38.5%)	47 (65.3%)	***<0.001***
Female, n (%)	152 (61.5%)	25 (34.7%)	***<0.001***
Age (years), median (range)	58.0 (44.5-67)	67.2 (20.0-92.0)	*0.060*
Diagnostic delay (months), median (range)	13.5 (4-38.5)	32.6 (0.0-314.0)	***0.043***
Pruritus as most relevant symptom, n (%)	65 (26.3%)	53 (73.6%)	***<0.001***
Follow up (months), median (range)	60.1 (36-108)	17.5 (8-44)	***0.021***
CTCL types according to 2018 WHO-EORTC, n (%)			
- MF	186 (75.3%)	57 (79.2%)	*0.458*
- FMF	22 (11.8%)	9 (15.8%)	*0.432*
- SS	11 (4.5%)	7 (9.7%)	*0.697*
- Primary cutaneous CD30+ LPD: LyP	19 (7.7%)	2 (2.8%)	*0.139*
- Primary cutaneous CD30+ LPD: C-ALCL	18 (7.3%)	5 (6.9%)	*0.921*
- Primary cutaneous CD4+ small/medium T-cell	11 (4.5%)	1 (1.4%)	*0.391*
- CD8+ AECTCL	2 (0.8%)	0 (0%)	*1*
Stage at diagnosis for MF-SS, n (%)	197	64	-
- IA	106 (53.8%)	24 (37.5%)	*0.784*
- IB	58 (29.4%)	18 (28.1%)	*0.840*
- IIA	6 (3%)	6 (9.4%)	***0.041***
- IIB	12 (6.1%)	9 (14.1%)	***0.042***
- III	6 (3%)	1 (1.5%)	*0.523*
- IV	6 (3%)	6 (9.4%)	***0.041***
B score at diagnosis, n (%)	105	39	-
- B0	69 (53.8%)	23 (59%)	*0.454*
- B1	26 (24.8%)	7 (18%)	*0.388*
- B2	10 (9.5%)	9 (23%)	***0.033***
Complete response achieved, n (%)	150 (60.1%)	30 (41.6%)	***0.004***
Progression, n (%)	29 (14.7%)	11 (17.2%)	*0.092*
Other dermatologic cancers, n (%)	38 (15.4%)	5 (6.9%)	*0.065*
Other non-dermatologic cancers, n (%)	50 (20.2%)	14 (19.4%)	*0.882*
Treatments	247	72	
- Topical steroids	162 (65.6%)	58 (80.6%)	***0.016***
- Phototherapy	124 (50.2%)	23 (31.9%)	***0.001***
- Localized RT	41 (17.0%)	4 (5.6%)	***0.018***
- TSEBI	11 (4.5%)	3 (4.2%)	*0.917*
- Methotrexate	26 (10.5%)	9 (12.5%)	*0.637*
- Bexarotene	36 (14.6%)	13 (18.1%)	*0.471*
- Other retinoids	44 (17.8%)	19 (26.4%)	*0.108*
- ECP	16 (6.5%)	5 (6.9%)	*0.889*
- Interferon	22 (8.9%)	1 (1.4%)	***0.030***
- Chemotherapy	15 (6.0%)	3 (4.2%)	*0.538*
- Atezolizumab	2 (0.8%)	0 (0%)	*1*
- Mogamulizumab	1 (0.4%)	9 (12.5%)	***<0.001***
- Brentuximab-vedotin	8 (3.2%)	11 (15.3%)	***<0.001***
- Surgery	10 (4.0%)	0 (0%)	*0.124*

Compared to the pre-pandemic, notable changes were observed in terms of prolonged median diagnostic delay (32.6 *vs* 13.5 months, *p*=0.043) and shifts in stage at diagnosis, with an increase in the advanced stages (*p*=0.013), in both tumoral (*p*=0.042) and leukemic forms (Stage IV *p*=0.041, B2 *p*=0.033).[2] Moreover, a higher incidence of symptomatic cases with pruritus at the time of first evaluation was registered (*p*<0.001). As for treatment approaches, a greater proportion of patients received systemic agents such as anti-CD30 brentuximab-vedotin and anti-CCR4 mogamulizumab (15.3% *vs* 3.2% and 12.5% *vs* 0.4%, *p*<0.001).[2] Conversely, there was a decline in the use of traditional treatments, such radiation therapy (*p*=0.016), phototherapy (*p*=0.001), and peg-interferon-alpha-2a (*p*=0.030). The percentage of patients achieving a complete response dropped from 60.1% in the pre-COVID cohort to 41.6% in the 2020-2022 cohort (p=0.004). At data cut-off, 48-month OS rates of 90.1% and 58.2% (*p*=0.006) were registered in the early and advanced stage subsets of patients, respectively.



At Cox regression, the presence of other non-dermatological cancers (HR 4.47, 95% CI 1.44-13.90, *p*=0.010), advanced stage (HR 4.51, 95% CI 1.37-15.11, *p*=0.014), and disease progression (HR 6.34, 95% CI 2.00-20.16, *p*=0.002) were negatively associated with survival.

Conclusions

The pandemic led to significant shifts in the diagnosis and treatment of CTCL patients, with a higher incidence of advanced symptomatic cases, a decline in traditional therapies, and an increased use of systemic agents.

References:

[1] 10.Macagno N, Mastorino L, Rubatto M, et al. Primary cutaneous lymphoma patients seen at a referral dermatological centre in 1 year: A single-centre observational retrospective cohort study of the diagnoses and staging, comorbidities and associated symptoms, treatment performed and clinical course. J Eur Acad Dermatol Venereol. 2022;36(12):2388-2392. doi:10.1111/jdv.18469

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Melanoma – Epidemiology and diagnostics

A-265

Phenocopies in melanoma families with germline mutations in CDKN2A are associated to MC1R polymorphisms and high total body nevus count

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Background
5 to 10% of all cutaneous melanomas develop in melanoma families with an autosomal dominant inheritance pattern with incomplete penetrance. The first gene associated with melanoma susceptibility was cyclin dependent kinase inhibitor 2A (*CDKN2A*). Between 5 and 20% of melanoma families have *CDKN2A* germline mutations.
Within melanoma families with germline mutated *CDKN2A*, some members do not carry the mutation but develop melanoma, these cases are called phenocopies.
The aim of the study is to analyze the characteristics of phenocopies within melanoma families with germline mutations in *CDKN2A*.

Methods
A retrospective cohort study was conducted. All the phenocopies in the context of melanoma families with germline mutations in *CDKN2A*, from 2010 to 2023, were included. We analyzed the basal clinical characteristics, phenotype, and studied the following melanoma susceptibility genes: *CDK4* (exon 2), *MC1R, MITF* (exon 9), *BAP1, POT1, ACD, TERF2IP, TERT* promoter and include the opportunistic testing of *BRCA1, BRCA2, MLH1, MSH2, MSH6.*

Results
In the period of the study 9 phenocopies were identified. Women were predominant (66%) and the median age at diagnosis of cutaneous melanoma was 33 years.
Concerning the phenotype, all the patients were Caucasians and most had high total body nevus count. *MC1R* polymorphisms were found in 100% of the phenocopies with no other genetic mutations identified.

Conclusions
The fact that there are phenocopies within melanoma families with *CDKN2A* mutations, shows that the known mutation is not the only factor that led to the development of melanoma, but that there are other aspects related such as fair skin, high total body nevus count and *MC1R* polymorphisms, among others. Due to the multifactorial etiology, in the case of a family member with a negative genetic test, the risk of developing melanoma should not be underestimated. Clinical follow-up, total body photography and digital dermoscopy should be carried out, according to individual risk factors, for the early detection of melanoma.

A-340

Level of satisfaction with treatment and clinical care at the Skin Cancer Unit in patients with cutaneous melanoma - A single specialist referral centre analysis.

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Background

In recent years, it has become clear in clinical practice that treatment outcomes and low complication rates are not the only important factors in the overall analysis of medical care. The degree of patient satisfaction with the diagnostic and therapeutic procedures implemented is one of the most important quality criteria and indicators. For this reason, at the Melanoma Unit, Patient-Reported Outcome Measures (PROMs) have become a very important issue. The aim of this study was to evaluate an innovative Medical Care Quality Improvement Programme related to satisfaction levels in a group of patients with a diagnosis of melanoma, treated at a single specialist centre.

Methods

The study was based on the development and subsequent analysis of the results of a dedicated Melanoma Unit questionnaire, which was offered to all melanoma patients treated at the Lower Silesian Centre for Oncology, Pulmonology and Haematology (LSOPAHC) in Wrocław.

Results

A total of 432 patients diagnosed with melanoma between May 2020 and February 2023 participated in the study, of whom 221 (51.2%) were women. The study was able to obtain results for the four relevant aspects identified in the basic assumptions of the developed survey and questionnaire, namely: 1) Infrastructure and organisation of treatment; 2) Quality of medical care; 3) Extent of information provided to patients; and 4) Summary of satisfaction with the Medical Care Quality Improvement Programme.

Conclusions

The detailed questions in the survey provided concrete data indicating both the strengths and weaknesses of the care provided to patients included in the new healthcare quality improvement programme. The results, as well as the design of the patient satisfaction assessment, can provide important guidance for other skin cancer departments. However, an important limitation of this study is that it is based solely on a questionnaire-based assessment conducted at a single centre.

A-278

ANALYSIS OF GLOBAL Skin-Cancer Epidemiology and Correlation with Dermatologist Density and Population Risk Factors

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Background
Melanoma and Non-Melanoma Skin Cancers (NMSC), such as Squamous Cell Carcinoma (SCC), Basal carcinoma (BCC), and Merkel Cell Carcinoma (MCC), pose a global health burden. This study assesses global skin cancer epidemiology, emphasizing incidence, mortality, risk profiles, and dermatologist density's impact.

Methods
Using WHO IARC data, we analyzed skin cancer epidemiology, focusing on its global spread and the relationship between dermatologist density and mortality-to-incidence ratios. By mapping these ratios against dermatologist density, we created an efficiency indicator for melanoma management. We studied skin cancer Relative Risks (RR) in immunocompromised, genodermatosis (albinism, xeroderma pigmentosum (XP)), elderly, outdoor workers, indoor tanners, and skin colors.

Results
In 2020, global melanoma incidence was 324,635, resulting in 57,043 deaths. Europe bears the heaviest burden with 150k cases and 26,360 deaths. Africa had the highest mortality-to-incidence ratio (0.25 vs 0.026 for Europe). Key 'at risk' populations: elderly (RR: 8.5), organ transplant recipients (RR: 8), fair skin (RR: 5.7), and XP (RR: 2000). Outdoor workers face a higher risk of NMSC compared to Melanoma. NMSC, despite lower mortality likelihood, led to 63,731 deaths in 2020 due to significantly higher incidence. Africa registered 11,281 deaths from skin cancer despite the relatively low prevalence. Dermatologist densities varied widely from 0.33 per 100k in Pakistan to 15.15 in Greece. Mapping dermatologist density against mortality-to-incidence ratios revealed various interesting profiles of countries.

Conclusions
Our findings emphasize the need for enhanced melanoma awareness, early detection, and patient education, especially in vulnerable populations and countries with high mortality-to-incidence ratios. The involvement of other healthcare professionals, education on photoprotection and early access to healthcare professionals for at-risk groups are crucial for improving survival. NMSC require improved surveillance through national registries.

A-445

Analysis of the long-term survival of patients with thin melanomas using comprehensive, population-based Australian data.

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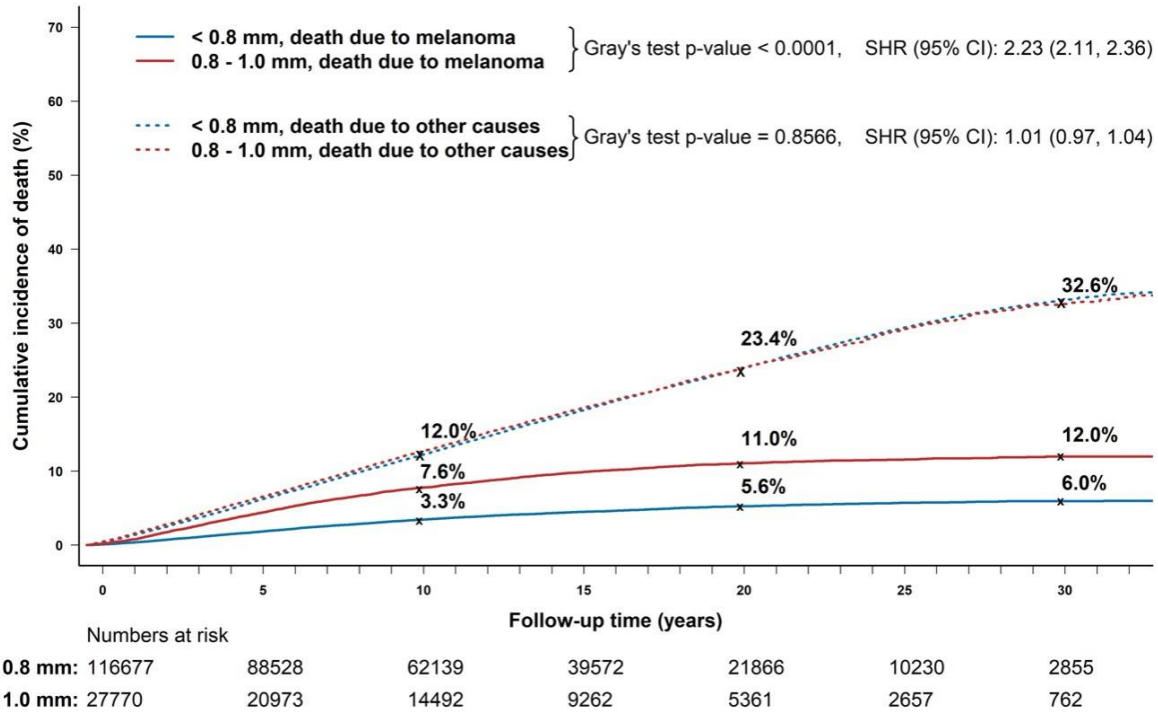
Background
The five-year survival of patients with thin melanomas (<=1mm in Breslow thickness) is generally considered to be good. However, the majority of melanomas are thin and around half of all melanoma deaths occur within this subgroup, many of them well beyond five years following diagnosis. These late outcomes are poorly documented in the literature. This study therefore evaluated the long-term survival of patients with thin melanomas and the competing risks of death from other causes.

Methods
Data were obtained from the eight Australian state and territory cancer registries and the linked National Death Index for all patients aged ≥18 years diagnosed between 1982 and 2014 with an invasive primary cutaneous melanoma ≤1.0mm in Breslow thickness. Information collected included age at diagnosis, Breslow thickness,sex, primary tumour site, date of diagnosis, date and cause of death. Analysis was performed using multivariable competing-risks regression for both melanoma-specific mortality and non-melanoma mortality. Subgroup analyses were performed, stratified according to age and Breslow thickness.

Results
For the 144,447 patients with thin melanomas the median duration of follow-up was 15 years. The overall 20-year crude melanoma mortality rate was 6.3% (6.0% for tumors <0.8mm, 12.0% for tumors 0.8-1.0mm). The 20-year melanoma-specific survival rates were 91.9% for the whole cohort, 94.2% for tumors <0.8mm, and 87.8% for tumors 0.8-1.0mm. On multivariable analysis tumour thickness 0.8-1.0mm was significantly associated with a greater absolute risk of melanoma death (HR 2.23, p<0.001), compared to thickness <0.8mm.



Cumulative incidence of melanoma and non-melanoma deaths over time following primary melanoma diagnosis adjusted for competing risks.

The 10-year overall risks of melanoma versus non-melanoma death were 4.1% v 11.8%, respectively. However, for patients with thin melanomas who were aged ≤50 years at diagnosis, the risk of melanoma death was greater than the risk of non-melanoma death.

Conclusions

The overall survival of patients with thin melanomas is good, however, late recurrences leading to death may occur up to 30 years after diagnosis. Furthermore, increasing Breslow thickness within this tumour thickness category is associated with poorer prognosis, particularly for those with melanomas ≥0.8mm. Whilst the risk of dying from other causes is much greater than from melanoma in older patients, this is not the case for younger patients.

A-279

Assessment of facial pigmented lesions using Line-field Confocal Optical Coherence Tomography and its correlation with Reflectance Confocal Microscopy and histopathology

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Background

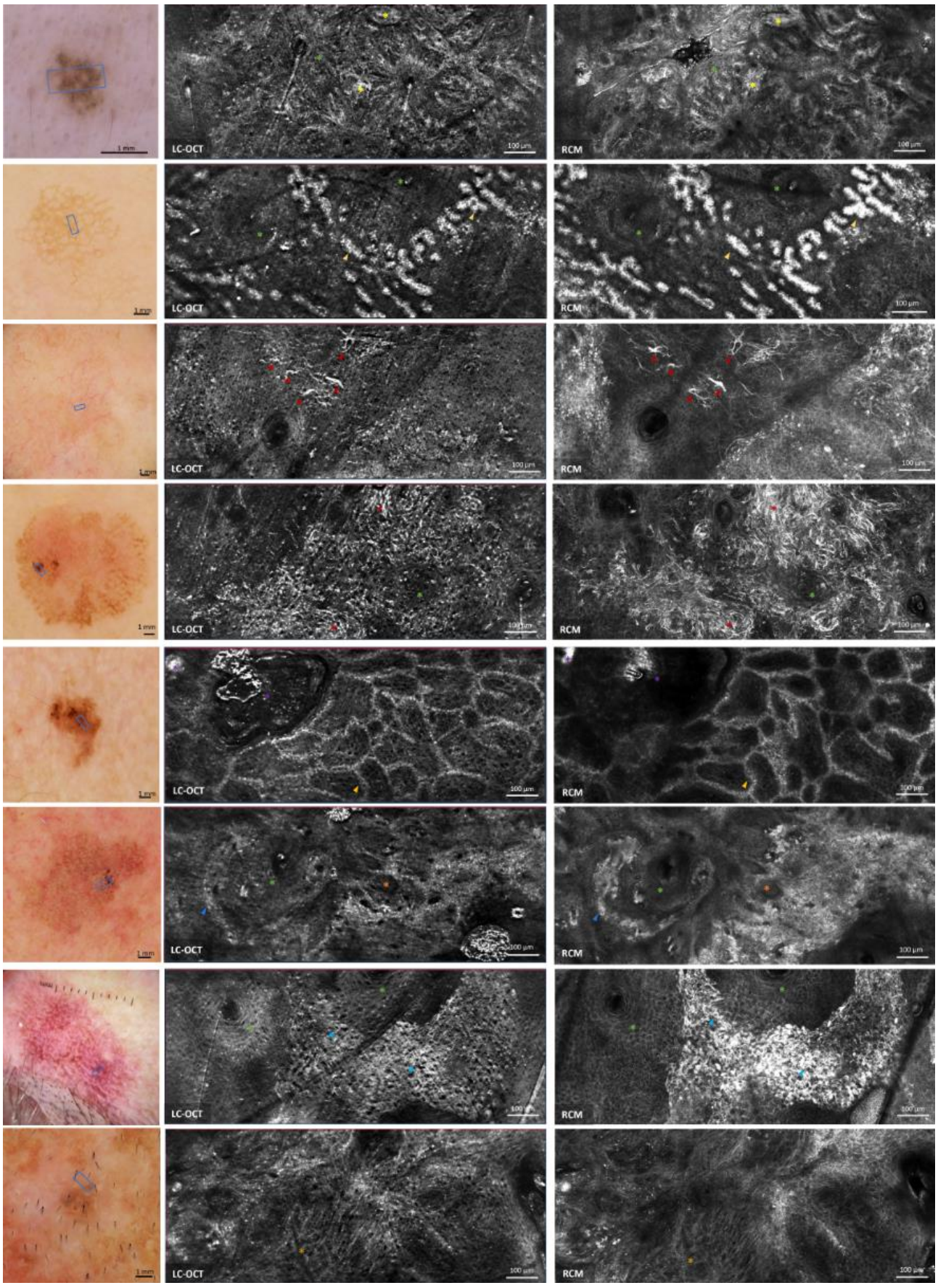
The accurate diagnosis of facial pigmented lesions is crucial due to their potential for malignancy and significant cosmetic concerns. This study aims to evaluate the effectiveness of line-field confocal optical coherence tomography (LC-OCT) in the morphological assessment of facial pigmented lesions and its correlation with reflectance confocal microscopy (RCM), thereby enhancing diagnostic accuracy and management strategies.

Methods

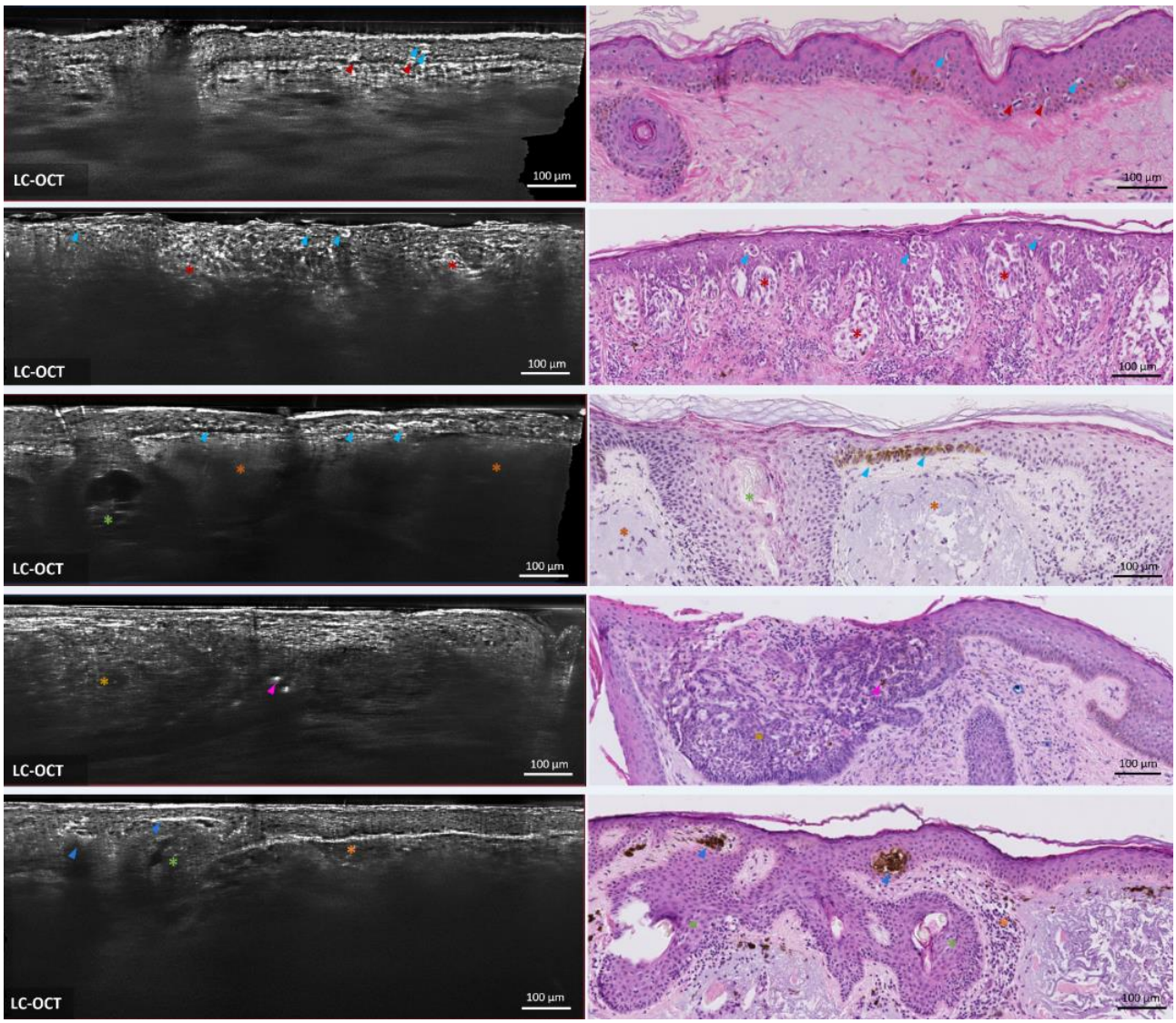
Adult patients with clinically equivocal facial and scalp pigmented lesions were prospectively assessed using LC-OCT and RCM. Lesions included seborrheic keratosis, lichen-planus like keratosis, pigmented actinic keratosis, pigmented compound nevus, lentigo maligna, and invasive melanoma, with solar lentigo as a comparative entity. Images were analyzed for morphologic criteria and diagnostic performance, correlating LC-OCT findings with RCM and histopathological outcomes where applicable.

Results

LC-OCT demonstrated high-resolution, tridimensional images that closely correlated with RCM findings, providing valuable insights into the micro-architectural and cytological aspects of lesions.



For instance, solar lentigo revealed a regular honeycomb pattern and elongated rete ridges on both LC-OCT and RCM, while lentigo maligna and invasive melanoma presented atypical dendritic cells in the epidermis with follicular involvement. LC-OCT's vertical and tridimensional imaging capabilities offered enhanced visualization of the lesions' architecture and depth, providing easily-recognizable histopathology-like features.



Conclusions

LC-OCT, with its ability to generate high-resolution, tridimensional images, complements RCM in the assessment of facial pigmented lesions, potentially offering enhanced diagnostic accuracy and potential for better management decisions. The technology's depth penetration and visualization capabilities highlight its value in dermatological practice, particularly for lesions where detailed architectural analysis is essential. This study underscores the utility of LC-OCT in the evolving landscape of dermatological imaging, warranting further research to establish its role in clinical practice.

A-393

Assessment of performance in clinical risk prediction tools for cutaneous melanoma in the UK population

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Background

Clinical prediction tools utilise patient data to estimate risk for patient outcomes, such as disease specific survival, recurrence, and metastasis. Whilst not a new idea, recent focus on artificial intelligence techniques such as machine learning, has drawn attention to the power of large datasets and the potential to impact individualised decision-making and prognostic staging of disease. We assess such tools available for use in cutaneous melanoma.

Methods

A review of the literature was conducted to identify clinical prediction tools for patients diagnosed with cutaneous melanoma focusing on reported assessment of performance. A dataset of patients who underwent a sentinel lymph node biopsy (SLNB) procedure at a regional melanoma centre in the United Kingdom (n = 1466) was utilised to externally validate two models designed to estimate the probability of a positive SLNB. These models were selected due to recent publication, ease of access for the clinician user and availability of model parameters.

Model discrimination was determined using the area under the receiver operating characteristics curve (AUC under ROC) and calibration by calibration plot with calculated intercept and coefficient of a regression model of outcome on the model's linear predictor.

Results

Twenty-eight tools were identified. Nineteen describe conducting internal validation and fourteen an external validation. Validation results relating to discriminative performance outnumbered those summarising calibration by a ratio of >3:1.

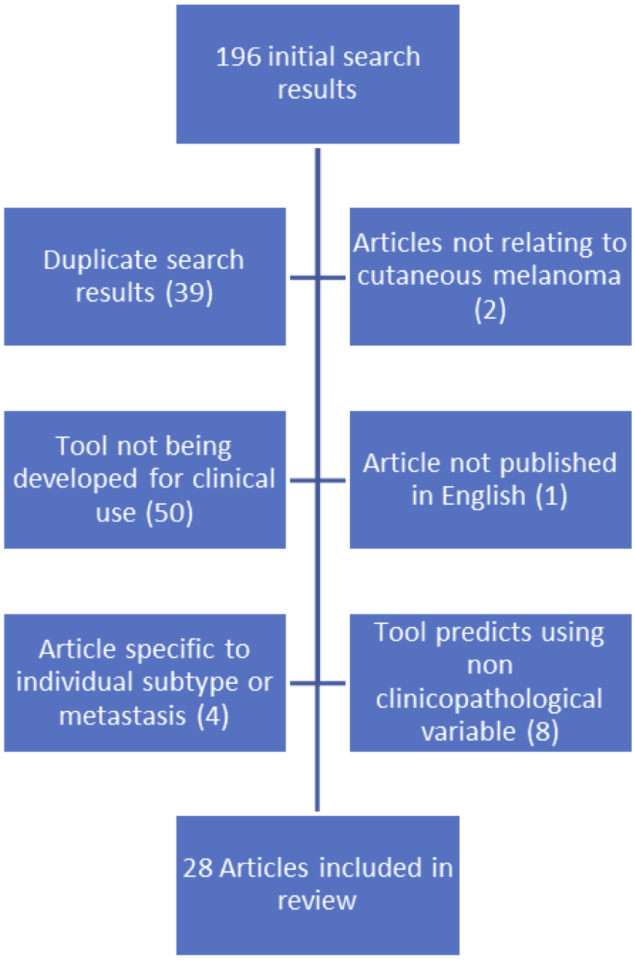

Figure 1 - Article search and filtering process

External validation analysis of models by Lo et al [lo] and Friedman et al [fr] resulted in AUC values of 67.6 (63.8-71.6) and 75.9 (64.9-84.6) respectively, with calibration assessment displayed in Fig 2.

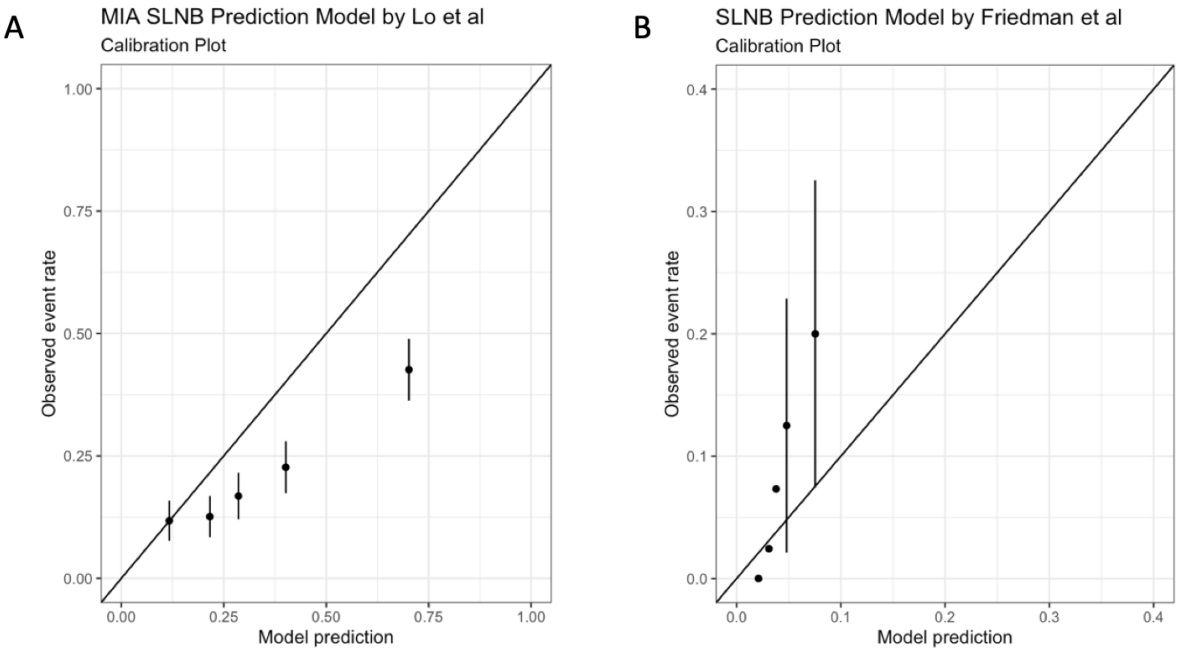

Figure 2 - Calibration Plot for (A) MIA SLNB Prediction Model by Lo et al and (B) Thin melanoma (0.5-1.0mm Breslow) SLNB prediction model Friedman et al

Conclusions

This work highlights variation in reporting of validation statistics alongside clinical prediction models. Of those tools examined, discriminative performance of models is often presented without assessment of calibration. <50% included details of an external validation and often with little training population characteristic information provided.

Our specific analysis of both discrimination and calibration for two recent models identified suboptimal calibration for our referral population. Further analysis comparing the populations identifies significant differences in both patient and disease characteristics.

Together this highlights the importance of model validation, thorough assessment of performance in an appropriate patient population before application in clinical practice.

References:

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[lo] Lo et al, (2020), Improved Risk Prediction Calculator for Sentinel Node Positivity in Patients with Melanoma: The Melanoma Institute Australia Nomogram, Journal of Clinical Oncology, 2719-2727

A-433

Assessment of the impact of a dermoscopy training associated with an artificial intelligence on general practitioner residents

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Background
Confronted with issues regarding the medical demography and the constant tension on the primary care system with a significant lack of health professionals throughout the territory, general practitioners are increasingly challenged by the need to carry out skin cancer screening and prevention themselves. However, even with dermoscopy as the keystone of skin cancer screening, many general practitioners are not trained in how to use dermoscopy in primary care. We therefore wished to evaluate the impact on the diagnostic accuracy after two training sessions, using the two-step algorithm associated with the use of an artificial intelligence on general practicians residents.

Methods
A before-and-after interventional study was conducted to assess the impact of the two training procedures. General practitioner residents from two universities were invited to participate in our study by completing three online tests before and after each training. Then, a further test was carried out at a one-month interval from the date of the participant's last training session. Each online test was composed of 51 cases: assessing the diagnostic accuracy, the determination of the nature of the lesion, the ability to offer a therapeutic strategy, and the level of confidence for each case.

Results
Forty-one general practitioner residents completed all four tests. We found a significant improvement in their mean score for diagnostic accuracy after each training procedure. The 1st test took place before any training had taken place and showed a mean score of -4.71 out of 51; this compared to 6.72 out of 51 in the 2nd test, which was carried out after the first training procedure; and 25.6 out of 51 for the 3rd test, which took place after the second training session. These differences were each statistically significant (paired Wilcoxon: p-value < 0.001). The results of the 4th test allowed us to demonstrate a significantly persistent improvement on the average score at one month after the last training session, and that the score was particularly improved with the use of the artificial intelligence analysis (mean score = 27.18).

Conclusions
These results confirmed that dermoscopy training combined with an artificial intelligence considerably improves the diagnostic accuracy and the management of pigmented lesions. Encouraging universities to propose that general practician residents undergo training in dermoscopy could significantly improve skin cancer screening and therefore improuve skin cancer survival.

A-235

Augmented intelligence using 2D and 3D total body photography for melanoma screening: Patient and dermatologist perspectives in real-world application

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Background
Augmented intelligence (AuI), the synergistic combination of human and artificial intelligence (AI), has great potential to revolutionize early melanoma detection. Before clinical implementation, novel AI-based technologies should be critically evaluated in a real-world setting. We aimed to investigate the perspectives of both patients and dermatologists after experiencing skin cancer screening by human, artificial, and augmented intelligence.

Methods
At the University Hospital Basel, a prospective comparative cohort study included 205 patients (at high-risk for melanoma, with resected or metastatic disease) and 8 dermatologists. After skin cancer screening by a dermatologist, 2D and 3D total body photography (TBP) was performed. Digital dermatoscopes were used to image any clinically suspicious and all melanocytic skin lesions ≥3 mm. Dermoscopic images were classified by convolutional neural networks (CNNs) of 2D/3D TBP systems. Excisions were based on melanoma suspicion before and/or after AuI, or if study-specific CNN melanoma risk scores were elevated. Subsequently, all participants completed questionnaires about their experience, including patients' safety perception quantification following different examinations (subjective safety score (SSS): 0-10).

Results
Most patients believed that AI could improve diagnostic performance (95.5%, n=192/201). Skin cancer screening by AuI was preferred by 83.4% of patients compared to an AI- or dermatologist-only examination (3D-TBP: 61.3%; 2D-TBP: 22.1%, n=199). In terms of SSS, AuI elicited a significantly higher perception of safety than a screening by AI (mean-SSS (mSSS): 9.5 vs. 7.7, p<0.0001) or a dermatologist alone (mSSS: 9.5 vs. 9.1, p=0.001). Most dermatologists expressed high confidence in the results of AI examinations (3D-TBP: 90.2%; 2D-TBP: 96.1%, n=205). In 68.3% of screenings (n=140/205), dermatologists felt their diagnostic accuracy improved by additional AI evaluation. However, only 1.5% of dermatologists trusted a benign CNN classification more than their personal suspicion of malignancy (n=3/205). Particularly beginners (<2 years' dermoscopic experience) found AI helpful in facilitating their clinical work (61.8%, n=94/152) in comparison to experts (>5 years' dermoscopic experience; 20.9%, n=9/43).

Conclusions
Patients already prefer AuI-based skin cancer screening with 3D-TBP. Despite high confidence in AI assessment, clinical decision-making by dermatologists remains mostly based on personal judgement.

A-344

Breslow thickness depends significantly on the individual suspecting melanoma: the importance of guaranteeing access to a dermatologist.

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Background

The incidence of primary cutaneous melanoma (PCM) is rapidly increasing, posing a significant public health concern. Prognosis is heavily influenced by Breslow thickness; hence, early detection of suspicious lesions is imperative. This study aims to compare the Breslow thickness of primary tumors based on the individual detecting the melanoma (patient, relative, general practitioner, dermatologist, or other medical specialists).

Methods

An observational, descriptive, multicentre, and retrospective study was conducted in the seven health areas of Galicia, a region located in northwest Spain with a population of 2.695.645 inhabitants in 2021, predominantly comprising a white population . Newly diagnosed PCM cases during 2021 and 2022 were included. Data were retrieved from the Galician Melanoma Registry, encompassing demographic, epidemiological, clinical, histological, and genetic variables. The study received approval from the reference ethics committee.

Results

A total of 928 PCMs were included. Among them, 596 were females and 332 were males, with a mean age of 65.2 years (minimum 14; maximum 105). Our study affirms that there is a statistically significant variation in mean Breslow thickness depending on the individual detecting the melanoma: it is higher in melanomas detected by relatives or patients than in those detected by a dermatologist ($p<0.05$). Melanomas detected by other medical specialists exhibit higher Breslow thickness compared to those detected by family doctors ($p<0.05$). In the in situ melanoma group, the proportion diagnosed by dermatologists is significantly higher than for other groups ($p<0.05$).

Conclusions

Dermatologists unquestionably detect melanomas with the lowest Breslow thickness. However, given the structure of the Spanish national health system, these specialists evaluate only a small percentage of the general population. It is crucial not only to ensure that general practitioners are well-trained in identifying pigmented lesions suggestive of malignancy but also that they have expedited referral pathways to dermatologists for assessing patients with suspected melanoma. In addition, educational campaigns should be conducted to raise melanoma awareness in the general population, particularly targeting high-risk individuals.

A-146

Changes in the pigmentation of melanocytic nevi associated with the use of self-tanners: a diagnostic challenge in patients at risk of melanoma

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Background

Certain patients advised to avoid sun exposure, opt for self-tanning products, considered safe. However, these products can induce changes in pigmented lesions, mimicking melanomas.

Methods

Case: We present the case of a 48-year-old woman, Fitzpatrick skin type III, with over 200 nevi, a history of blistering sunburns in childhood, intense recreational sun exposure, and regular use of UVA tanning booths. She was diagnosed with superficial spreading melanoma on the right chest excised in 2017 (Breslow thickness 2mm, 4 mitoses/field, negative sentinel node biopsy and staging studies). In June 2022, dermoscopic changes were observed in numerous pigmented lesions (appearance of yellowish-brown globules, peppering, and size reduction). She denied history of recent laser treatment or sun exposure but confirmed the use of self-tanners continuously for years. Subsequently, the disappearance of some pigmented globules was noted in areas where no self-tanner was applied, with persistence of regression in some lesions, without other suggestive changes of melanoma.

Results

Discussion: Dermoscopic changes in pigmented lesions secondary to the use of self-tanners have been sparsely described in the literature, primarily manifesting as the appearance of yellowish-brown spots of varying sizes or follicular pigmentation resembling "comedo-like" structures. Our patient used two self-tanning products containing dihydroxyacetone, a compound that temporarily stains the skin and fades over time. However, some of these dermoscopic changes did not resolve despite discontinuation of the self-tanner, and some nevi partially or completely regressed. In vitro, dihydroxyacetone can induce cytotoxicity and apoptosis in melanocytes and keratinocytes, in a dose- and time-dependent manner. This could explain the regression of some pigmented lesions, although its biological effect remains uncertain. Nevertheless, these changes may complicate the monitoring of melanoma patients, leading to unnecessary biopsies.

Conclusions

Given the increasing use of self-tanners, it is imperative to understand their biological effects and study in depth the dermoscopic changes in pigmented lesions.

A-302

Characterization of 10 cutaneous tumors with ex vivo LC-OCT: A novel tool in dermato-oncological surgery with margin control?

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Background
Currently, we have numerous imaging techniques for skin evaluation, such as *in vivo* and *ex vivo* reflectance confocal microscopy (RCM), optical coherence tomography (OCT), and Line-field Confocal OCT (LC-OCT). With LC-OCT technology, a vertical image similar to histology, a horizontal image similar to RCM, and a three-dimensional image can be obtained. A new prototype that allows obtaining *ex vivo* images with LC-OCT has been developed. This not only facilitates a more comprehensive understanding of the histology of cutaneous tumors but also holds promise for advancing surgical margin detection in the future.
The aim of this project is to evaluate the quality of images obtained with *ex vivo* LC-OCT in different cutaneous tumors, describe the morphological characteristics of the evaluated lesions and correlate them with dermoscopy, *in vivo* RCM, *in vivo* LC-OCT and histology.

Methods
We prospectively evaluated patients with diverse cutaneous tumors between June 2022 and July 2023, with the following inclusion criteria: ≥18 years and a cutaneous tumor on the trunk and limbs. We collected clinical, dermoscopic, RCM, *in vivo* LC-OCT, *ex vivo* LC-OCT, and histopathological images of different types of cutaneous tumors.

Results
In total, 10 cutaneous tumors from 10 patients were evaluated using this new technology: 3 melanomas, 2 seborrheic keratoses, 2 basal cell carcinomas, and 3 melanocytic nevi.

Conclusions
For the first time, we have been able to visualize excised cutaneous tumors in three dimensions. The images obtained are equivalent to those acquired with *in vivo* devices. We have appreciated cellular resolution and conducted cellular correlation with confocal microscopy, *in vivo* LC-OCT, and histology. These promising results may initiate further investigations into the assessment of this technology in dermato-oncological surgery with margin control.

A-360

Cost-of-illness of skin cancer: A systematic review

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Background
Skin cancer's rising incidence demands understanding of its economic impact. However, it remains unclear what the main cost drivers are in skin cancer. Current understanding is fragmented because of the various methodological approaches applied in skin cancer cost-of-illness studies.This study systematically reviews melanoma and keratinocyte carcinoma cost-of-illness studies to provide an overview of the applied methodological approaches and to identify the main cost drivers.

Methods
This systematic review was conducted adhering to the 2020 PRISMA guidelines. PubMed, Embase and Web of Science were searched from December 2022 until August 2023 using a search strategy with entry term related to the concepts skin cancer and cost-of-illness. The records were screened on title and abstract and subsequently on full text against predetermined eligibility criteria. A nine-item checklist adapted for cost-of-illness studies was used to assess the methodological quality of the articles.

Results
This review included a total of 45 studies, together evaluating more than half a million patients. The majority of the studies (n=36) focused on melanoma skin cancer, a few (n=3) focused on keratinocyte carcinomas and six studies examined both. Direct costs were estimated in all studies, while indirect costs were only estimated in nine studies. Considerable heterogeneity was observed across studies, mainly due to disparities in study population, methodological approaches, included cost categories and differences in healthcare systems. In melanoma skin cancer, both direct and indirect costs increased with progressing tumor stage. In advanced stage melanoma, systemic therapy emerged as the main cost driver. In contrast, for keratinocyte carcinoma no obvious cost drivers were identified.

Conclusions
A homogeneous skin cancer cost-of-illness study design would be beneficial to enhance between-studies comparability, identification of cost drivers and support evidence-based decision-making for skin cancer.

A-244

Developing a patient-informed conceptual model of advanced and metastatic melanoma

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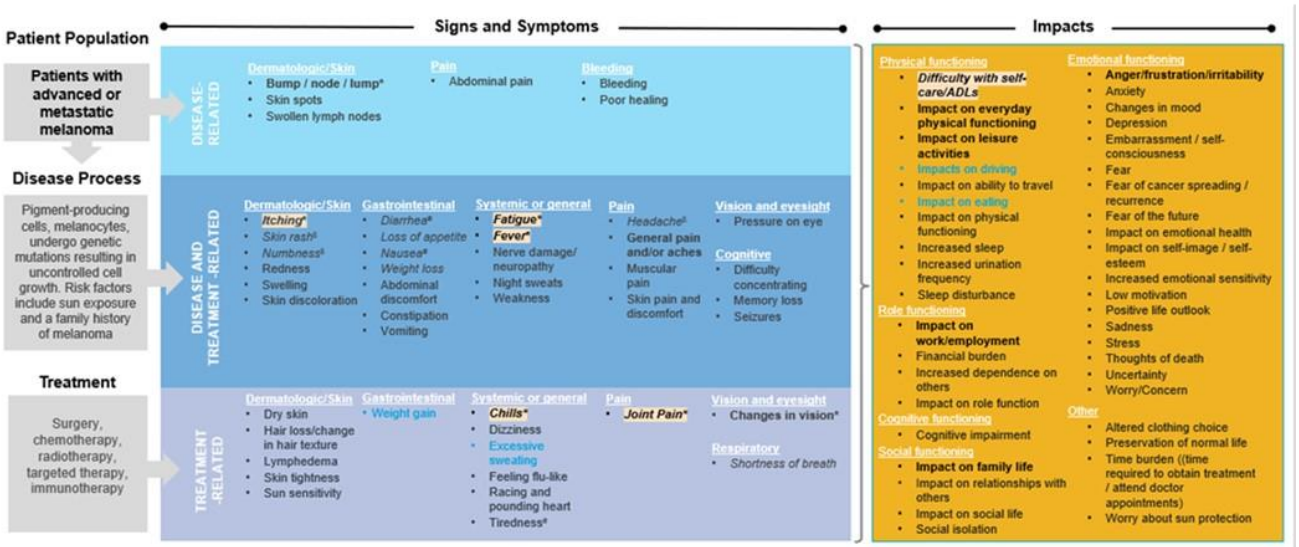
Background
Patients with advanced or metastatic melanoma experience symptoms that negatively affect their Health-Related Quality-of-Life. To our knowledge, there is no existing conceptual model (CM) consisting of relevant signs, symptoms, and impacts among patients with this condition. Our objective was to gain deeper understanding of the patient experience with advanced or metastatic melanoma, as reported by patients or observed by clinicians, which was then used to develop a patient-centered comprehensive CM.

Methods
A targeted literature review and clinician interviews were conducted to develop a preliminary CM and inform semi-structured interviews with US participants treated for advanced or metastatic melanoma in the preceding 24 months. Interviews were analyzed to identify concepts to update a final CM of the patient experience.

Results
Ten articles and five blogs were used to develop the preliminary CM. Concepts from this model were subsequently probed in interviews with three clinicians, identifying 15 priority symptoms and 1 priority impact.

Sign / Symptom	Number of clinicians mentioning (N=3)	Disease-related, treatment-related, or both
Itching	3	Both
Nausea	3	Both
Pain	3	Both
Headache	3	Both
Fatigue	3	Both
Numbness	3	Both
Loss of appetite	3	Both
Weight loss	3	Both
Changes in vision	3	Treatment-related
Diarrhea	3	Treatment-related
Difficulty breathing	3	Both
Fever	3	Both
Skin rash	3	Both
Joint Pain	2	Both
Chills	2	Treatment-related
Impact	**Number of clinicians mentioning (N=3)**	**Disease-related, treatment-related, or both**
Difficulty with self-care/ADLs	3	NA

To refine this CM, 8 participants with advanced melanoma and 12 with metastatic melanoma were interviewed, revealing 70 symptoms and 47 impacts. Results from the interviews highlighted fatigue, general pain, bump, node, or lump, fever, joint pain, changes in vision, chills, and itching as the most frequent and bothersome symptoms to patients. Most symptoms presented similarly between advanced and metastatic melanoma; however, joint pain and headache were more frequent in those with advanced disease, while fever, tiredness, and diarrhea were more frequently experienced by patients with metastatic disease. Two symptoms (excessive sweating and weight gain) and 2 impacts (difficulty with driving and with eating) were added to the final CM, while 14 symptoms and 9 impacts were removed due to low frequency.



Bolded concepts were mentioned by ≥50% of patients (≥10 patients), with a bothersomeness/disturbance rating of ≥5; *Italicized concepts* were mentioned by 3 clinicians or perceived by 2/3 clinicians as most impactful; Highlighted concepts were mentioned by ≥50% of patients (≥10 patients), with a bothersomeness/disturbance rating of ≥5 AND mentioned by 3 clinicians or perceived by 2/3 clinicians as most impactful; **Concepts in blue** were not previously included in the CM and were endorsed by ≥5 patients *salient symptom across the entire sample (stage III and stage IV); §salient symptom across sample with metastatic disease (stage IV); ‡salient symptom across sample with advanced disease (stage III)

Conclusions

Patients with advanced and metastatic melanoma exhibit a high amount of disease- and treatment- related symptoms that impact Quality-of-Life. This research provides a comprehensive description of the signs, symptoms, and impacts experienced by patients with advanced or metastatic melanoma, allowing the development of the first CM of this disease. Additionally, the concepts considered important by clinicians were endorsed by participants and can guide the selection of adequate assessments to incorporate the patient voice in future clinical trials.

A-160

Diagnosis of vulvar pigmented lesions with confocal microscopy

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Background

The diagnosis and management of vulvar-pigmented lesions (VPLs) still represent a challenging entity for dermatologists. Benign vulvar melanosis (BVM) account for the vast majority of the pigmented lesions of the female genital area, however, they must be differentiated from the rare but aggressive form of vulvar melanoma (VM). Indeed, VM represents only 1-3% of female melanoma but it is associated with a very poor long-term prognosis.
Dermoscopic features of vulvar-pigmented lesions might help in differential diagnosis, but they are frequently inconclusive, requiring histological exam through incisional or excisional biopsies. However, considering the sensitivity of the genital area, surgical procedures are associated with great discomfort to the patients, leading to psychological and aesthetic damage.
For these reasons, reflectance confocal microscopy (RCM) might help in doubtful cases to avoid unnecessary surgical interventions.
In this context, we performed a prospective study on VPLs, comparing clinical and dermoscopic characteristics with RCM parameters.
The final aim of our work was to create a diagnostic algorithm to help dermatologists and other clinicians in VPLs management.

Methods

We acquired baseline and follow-up clinical, dermoscopic and RCM pictures of 128 VPLs in 112 female patients.
We classified the lesions based on the following dermoscopic patterns: structureless, cobblestone, reticular, globular, ringed, parallel, and combined (2 o more patterns within the same lesions).
Then we performed handheld 3000 RCM acquisitions and we sub-divided the VPLs into three major categories: rimmed, non-rimmed with dendritic cells, and rimmed with dendritic cells. We completed the work with incisional/excisional histological examination of doubtful cases.

Results

Our study found 90 BVMs, 28 moles, 8 atypical melanocytic nevi of genital type (AMNGT), and 2 melanoma.
Considering our acquisitions, we proposed a diagnostic algorithm:
1. Rimmed melanosis (73%) no need of follow-up
2. Rimmed + dendritic cells at the dermo-epidermal junction melanosis (20%): follow-up
3. Non rimmed + chaotic dendritic proliferation melanosis (7%): short time follow-up/biopsy
4. Non rimmed + chaotic dendritic proliferation + round cells: suggestive for melanoma (excision)

Conclusions

In conclusion, our work proposes a new RCM-based algorithm for the management of VPLs. Further studies are needed to confirm our preliminary work.

A-191

Diagnostic criteria for melanocytic lesions in LC-OCT

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Background

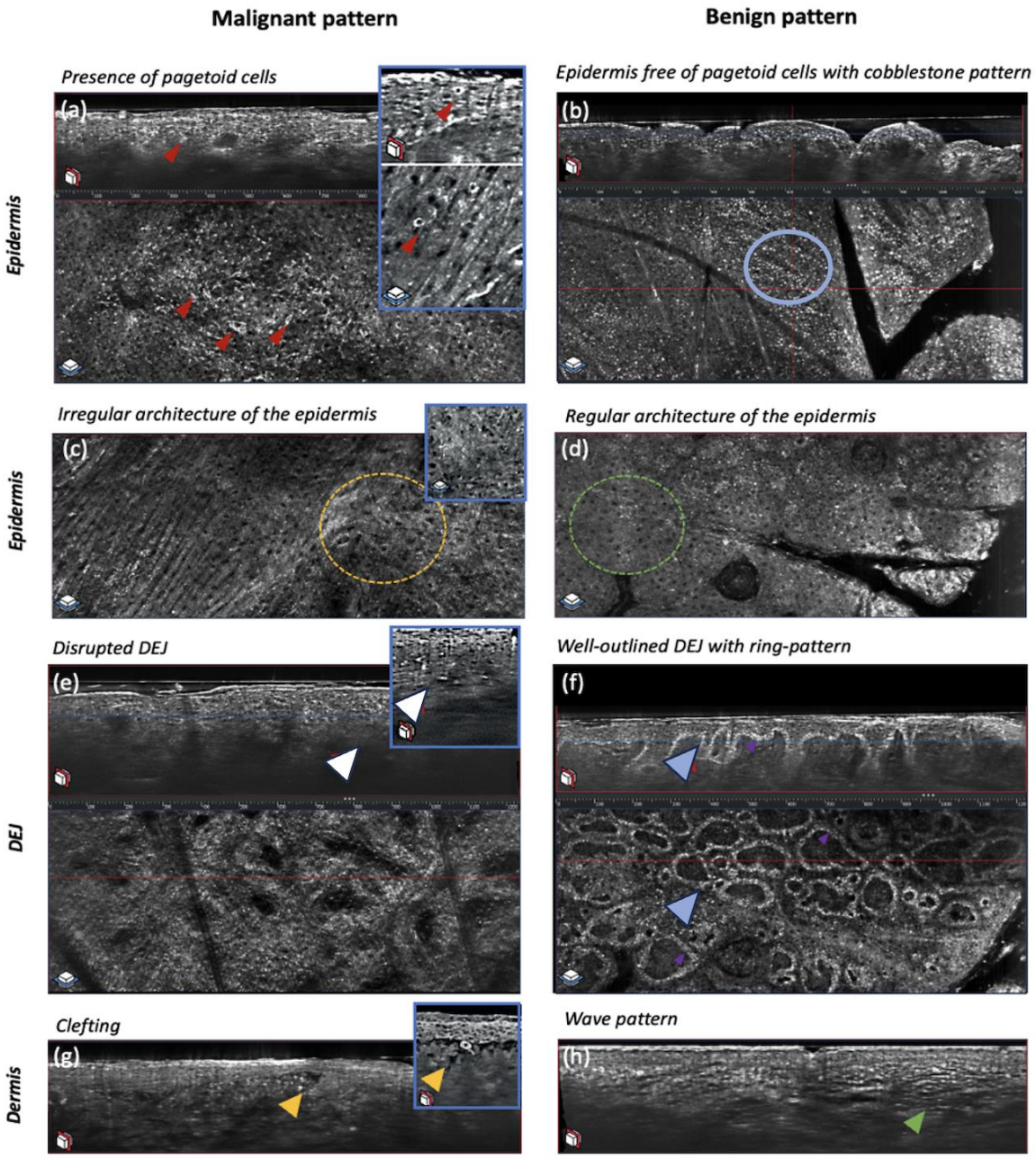
Line-field confocal optical coherence tomography (LC-OCT) is an emerging diagnostic tool with imaging depth reaching ~400 µm and a novel 3-dimensional (3D) cube providing cellular resolution. As far as we are aware, there are only a limited number of papers that have reported diagnostic criteria for melanocytic lesions using this technique, and none of them have been multicentric.

Our aim was to establish the diagnostic criteria for melanocytic lesions using LC-OCT and identify the most significant architectural and cytologic features associated with malignancy.

Methods

A retrospective evaluation of 80 consecutive melanocytic lesions from a prospective multicentric dataset spanning three European centers was conducted. We excluded facial, acral, and mucosal lesions from the study. Dermoscopic and LC-OCT images were evaluated by a consensus of four observers. Multivariate logistic regression with backward elimination was employed, and an artificial intelligence tree model was developed to determine the most relevant criteria for distinguishing nevus from melanoma. The two methods were compared for their performance.

Results



Main diagnostic benign and malignant diagnostic criteria

The main melanoma diagnostic criteria include detecting >10 pagetoid cells in 3D acquisition, irregular 3D epidermal architecture, disrupted dermo-epidermal junction (DEJ), and clefting. Significant risk factors based on both analysis: irregular 3D epidermal architecture, >10 pagetoid cells, dendritic cells at DEJ without underlying inflammation. Novel malignancy criteria in vertical view: DEJ disruption and clefting around atypical melanocyte nests. Exclusive melanoma features: epidermal nests, epidermal consumption, dense dermal nests with atypia. Protective features in the absence of any malignancy indicators: DEJ ring pattern, cobblestone, elongated rete-ridges (vertical), well-defined DEJ, and wave pattern (vertical). Figure 1. Table 1a and 1b.

Table 1. Descriptive statistics

	Criteria	Nevi (N=46)	Melanoma (N=34)	PPV	NPV	OR (95% CI)	p-value
ARCHITECTURAL CRITERIA							
Stratum corneum	Parakeratosis	1 (2.2)	3 (8.8)	75.0%	59.2%	4.28 (0.33 - 233)	0.31
	Erosion/disruption of the stratum corneum	0 (0.0)	1 (2.9)	100.0%	58.2%	Inf (0.03 - Inf)	0.43
	Hyperkeratosis	6 (13.0)	10 (29.4)	62.5%	62.5%	2.74 (0.79 - 10.4)	0.12
	Pigment ascension into the SC	2 (4.3)	2 (5.9)	50.0%	57.9%	1.37 (0.09 - 19.8)	1
Epidermis – Horizontal view	Irregular honeycomb pattern	3 (6.5)	19 (55.9)	86.4%	74.1%	17.4 (4.28 - 105)	< **0.001**
	Cobblestone pattern	26 (56.5)	11 (32.4)	29.7%	46.5%	0.37 (0.13 - 1.02)	0.06
	DEJ ring pattern	24 (52.2)	8 (23.5)	25.0%	45.8%	0.29 (0.09 - 0.82)	**0.02**
	DEJ meshwork pattern	14 (30.4)	14 (41.2)	50.0%	61.5%	1.59 (0.57 - 4.47)	0.45
	Cerebriform structures	0 (0.0)	2 (5.9)	100.0%	59.0%	Inf (0.26 - Inf)	0.18
Epidermis – 3D architecture	Irregular 3D epidermis architecture	6 (13.0)	26 (76.5)	81.3%	83.3%	20.5 (5.97 - 83.0)	< **0.001**
	Nest of cells in the epidermis	0 (0.0)	7 (20.6)	100.0%	63.0%	Inf (2.21 - Inf)	**0.002**
	Small nest of pagetoid cells within epidermis	0 (0.0)	5 (14.7)	100.0%	61.3%	Inf (1.33 - Inf)	**0.01**
	Big nest of pagetoid cells within epidermis	0 (0.0)	5 (14.7)	100.0%	61.3%	Inf (1.33 - Inf)	**0.01**
	Clefting around epidermal nest	0 (0.0)	5 (14.7)	100.0%	61.3%	Inf (1.33 - Inf)	**0.01**
	Consumption of the epidermis	0 (0.0)	7 (20.6)	100.0%	63.0%	Inf (2.21 - Inf)	**0.002**
	Atrophic epidermis	12 (26.1)	3 (8.8)	20.0%	52.3%	0.28 (0.05 - 1.17)	0.08
	Hypertrophic epidermis	2 (4.3)	11 (32.4)	84.6%	65.7%	10.2 (1.99 - 103)	**0.001**
Dermoepidermal junction	Disrupted DEJ 3D	17 (37.0)	30 (88.2)	63.8%	87.9%	12.4 (3.52 - 56.6)	< **0.001**
	Elongated rete-ridge	40 (87.0)	22 (64.7)	35.5%	33.3%	0.28 (0.08 - 0.94)	**0.04**
	Bridging nest 3D (junctional nest)	37 (80.4)	22 (64.7)	37.3%	42.9%	0.45 (0.14 - 1.38)	0.19
	Irregular distribution of rete ridges 3D and papillae: top	18 (40.0)	25 (83.3)	58.1%	75.7%	7.29 (2.20 - 29.0)	**0.005**
	Irregular distribution of rete ridges 3D and papillae: bottom	23 (51.1)	27 (90.0)	54.0%	76.7%	8.37 (2.12 - 49.3)	**0.01**
Dermis	Dermal nests	10 (21.7)	18 (52.9)	64.3%	69.2%	3.97 (1.39 - 12.1)	**0.008**
	Dense dermal nests	8 (17.4)	12 (35.3)	60.0%	63.3%	2.56 (0.81 – 8.45)	0.12
	Sparse dermal nests	3 (6.5)	14 (41.2)	82.4%	68.3%	9.72 (2.35 – 58.7)	< **0.001**
	Irregular shape of the dermal nests	2 (4.3)	13 (38.2)	86.7%	67.7%	13.2 (2.63 - 131)	< **0.001**

Descriptive statistics

Conclusions

A series of diagnostic criteria for the identification of melanocytic lesions with LC-OCT have been established. Validation of these criteria in clinical practice through future studies is essential to further establish their utility.[Ref1][Ref02]

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A-370

Early detection of skin cancer: a nurse-initiated consultation to improve dermatology access.

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Background

According to the World Health Organization (WHO), one in three cancers diagnosed is a skin cancer (1), and the incidence is expected to further rise in Europe by 2040 (2). WHO acknowledges the relevance of early diagnosis programmes to reduce the proportion of patients with late-stage skin cancer diagnoses, with improved healthcare accessibility as a key component (3). Currently, dermatologists have long waiting lists, and general practitioners do not always feel comfortable evaluating skin lesions. Considering the anticipated rise in skin cancers, safeguarding timely diagnosis and treatment poses a significant challenge. To address this challenge, we implemented a nurse-initiated one-spot-check consultation to increase dermatology capacity and accessibility.

Methods

The Dermatology Department of University Hospital Ghent offered nurse-initiated early-access consultations to adult patients with concerns about specific lesions meeting predefined criteria. To optimise these consultations, nurses received training on skin tumours and basic dermoscopy and gained expertise through clinical apprenticeship, close guidance and feedback. A dedicated patient file tab was developed to streamline operations and reduce administrative workload. During these consultations, nurses performed patient assessments, clinical and dermoscopic examinations, lesion imaging, completed patient files, and executed necessary management actions. The diagnosis and management strategy were established under the supervision of a dermatologist. Before dermatologist supervision, nurses assessed the skin lesions as high or low risk for cancer. These assessments were compared with the dermatologist's final diagnosis to evaluate the nurses' diagnostic accuracy.

Results

From April 2021 until April 2023, 1183 patients received a nurse-initiated one-spot-check consultation, yielding a 10% detection rate of skin cancer. 179 lesions were included to determine the nurses' diagnostic accuracy. The results revealed a sensitivity range of 73 to 81% and a specificity range of 88 to 90%, illustrating the variability in diagnostic accuracy associated with nurse experience.

Conclusions

Preliminary findings suggest that nurses, with appropriate education and training, can acquire competence in differentiating benign and malignant skin lesions. Implementing nurse-initiated consultations in the department has increased operational capacity, improving early access to dermatological advice for individuals with suspicious skin lesions.

A-423

Epidemiological indicators of melanoma in the Republic of Uzbekistan

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Background

Relevance. Despite the introduction of modern diagnostic and treatment methods into medicine, morbidity and mortality from malignant tumors remain high, and this represents a problem of social significance. They continue to develop and in recent years have become one of the main causes of death and disability in developing countries, leading to significant losses of the working population.

Methods

Materials and methods. In this study, based on statistical data from the report form 7SSV of the Ministry of Health of the Republic of Uzbekistan for 2020-2022, cases of primary melanoma disease were studied. The male to female incidence ratio was 1.3:1.

Results

Results. In the republic, the intensive incidence rate of melanoma was 0.4 in 2015-2019, 0.3 in 2020, and 0.4 in 2021-2022. In absolute numbers: 132 in 2015, 130 in 2016, 132 in 2017, 124 in 2018, 147 in 2019, 105 in 2020, 85 in 2021 and 128 in 2022. When studying by stages of the disease, the frequency of detection of late stages (III and IV) was 40.1% in 2015, 58.8% in 2016, 35.6% in 2017, 31 in 2018 .5%, in 2019 - 25.1%, in 2020 - 35.3%, in 2021 - 33.8%, and in 2022 this figure was 36.0%. The 5-year survival rate is 38.3% in 2015, 37.6% in 2016, 40.1% in 2017, 36.8% in 2018, 31.3% in 2019, 32. 1% in 2020, 34 in 2021, 6%, and in 2022 this figure was 34.5%, and this was revealed in the statistics.

Conclusions

Conclusions. Based on statistical data, it can be said that the incidence rate of melanoma in Uzbekistan varies from year to year: it can be seen that the incidence rate in 2015 decreased by 4% (per 100,000 population) by 2022. The late stage detection rate decreased from 40.1% to 36% due to tumor heterogeneity. The decrease in five-year survival of patients with melanoma (from 38.3% to 34.5%) is partly proportional to the heterogeneity of this disease and, therefore, the complexity of the treatment method.

A-141

Estimating Occupational Exposure to Ultraviolet Radiation Using the Canadian Occupation Exposure Matrix (CANJEM) in a Nationwide Cohort of French Adults

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Background
In Europe, 14.5 million workers are exposed to significant levels of ultraviolet radiation (UVR), increasing their risk of non-melanoma skin cancer. This issue has not received sufficient recognition or research, particularly in France. Our objective was to estimate the occupational exposure to UVR in a large sample of French adults.

Methods
Constances, a French nationwide population-based cohort initiated in 2012, includes a random sample of adults aged 18-69 years. Lifetime occupational histories were available in 98,895 participants. Their jobs were classified using PCS 2003 for occupations and NAF 2008 for industries and were linked to the Canadian occupation-exposure matrix (CANJEM), enabling the generation of UVR exposure histories for 93,009 participants (94.0 %).
Workers were considered as exposed to UVR if, during their whole career, they held for at least 1 year at least one UVR-exposed occupation (using 15% and 25% probability thresholds).

Results
Among the 93,009 studied participants, 54.2% were men, and the mean age was 49.2 years. Using a ≥15% probability threshold, 8.13% (95% confidence interval (CI) [7.95-8.31]) were exposed to UVR. With a ≥25% exposure probability threshold, 3.39% (95% CI [3.28-3.52]) were exposed to UVR.
For individuals with a probability threshold≥15%, 58.23% were blue-collar workers, primarily men (84.24%), while most women were clerical and related workers (63.23%). The top five professions in this group were sociocultural and leisure animators (24.96%, mostly women), skilled masons (5.73%, all men), gardeners (3.93%, mainly men), directors of sociocultural and leisure centers (3.74%, gender-balanced), and market gardening or horticultural workers (3.64%, balanced gender).
For those with a probability threshold ≥25%, 85.95% were blue-collar workers of both genders. The top five professions in this group were gardeners (9.49%, mostly men), market gardening or horticultural workers (8.50 %, mixed gender), viticulture/fruit tree cultivation workers (7.78%, balanced gender), agricultural/forestry workers (7.65%, mostly men), and qualified welders (7.30%, mainly men).

Conclusions
This study estimated combined solar and artificial UVR radiation exposure among French workers using the Canjem matrix. Future research will investigate associations with skin cancers and eye diseases (cataracts, age-related macular degeneration) and explore the use of the Carex matrix for solar exposure alone.

A-134

Gamification of Dermoscopy Education Using a Smartphone Mobile Platform: A Pilot Study

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Background
Dermoscopy is a non-invasive method of examining skin lesions under high magnification, gradually replacing the need for invasive biopsies. Training is required to gain clinical competency. Gamification employs game-like elements to enhance education engagement and is an engaging means of delivering medical education. We sought to use gamification and a mobile-based platform to deliver dermoscopy education to physicians.

Methods
We developed SKIN@GoPRIME, an interactive smartphone platform. 30 physician participants were randomly assigned to watch an online dermoscopy lecture or to use SKIN@GoPRIME. 28 participants completed pre- and post-learning quizzes and provided feedback on SKIN@GoPRIME.

Results
Users of SKIN@GoPRIME demonstrated a significant 1.71-point mean score improvement ($p = 0.0018$). Compared to family medicine physicians, internal medicine physicians had a greater mean score improvement after using SKIN@GoPRIME (2.14 vs. 1.29, $p = 0.35$). Based on feedback, 83% felt that SKIN@GoPRIME can be used to acquire the applied competencies required for their job scope.

Conclusions
SKIN@GoPRIME, a novel learning tool developed with the principles of gamification, effectively delivers dermoscopy education. Larger studies are required to further validate the effectiveness of gamified learning techniques in dermoscopy education. Future studies should involve the optimization of SKIN@GoPRIME to more effectively deliver dermoscopy education.

A-287

Incidence Of Skin Melanoma And Mortality From It Among The Population Of The Republic Of Belarus (epidemiological data from a 30-year study)

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Background

Aim of the research: Analysis of the dynamics of morbidity and mortality from skin melanoma over the past 30 years in the Republic of Belarus (1993-2022).

Methods

Official annual statistical data from the Belarusian Cancer Registry were used, which formed the basis for data on new cases of malignant neoplasms.

Results

The primary incidence of skin melanoma in the Republic of Belarus over 30 years (from 1993 to 2022) has increased among the urban population by 3.7 times - from 3.1 to 11.5 per 100,000 population; and among the rural population by 3.9 times – from 2.8 to 10.9 per 100,000 population. Urban residents are at greater risk of developing primary skin melanoma compared to rural residents, namely 1.8 times (1993-2002); 1.7 times (2003-2012) and 1.5 times (2013-2022). Over the past 30 years, the incidence of new cases of cutaneous melanoma has increased with age, starting in the 15-19 age group. The peak incidence in 1993-2012 was in the age group of 80-84 years, and in 2013-2022 it shifted to the age group of 75-79 years. Among the urban population, women are more often to develop melanoma than men aged from 20 to 39 years (4.3 cases versus 2.5 cases per 100,000 population, respectively, $p<0.001$) and aged from 40 to 64 years (12.6 cases versus 8 .4 cases per 100,000 population, respectively, $p<0.001$); and at the age of over 65 years, men more often to develop melanoma than women (32.3 cases versus 26.4 cases per 100,000 population, respectively, $p<0.001$. In rural areas, women are more often to develop melanoma than men in all age groups, such as those aged from 20 to 39 years (2.4 cases versus 1.4 cases per 100,000 population, respectively, $p<0.001$); aged 40 to 64 years (7.6 cases versus 5.5 cases per 100,000 population, respectively, $p<0.001$; over the age of 65 years (14.0 cases versus 12.6 cases per 100,000 population, respectively, $p<0.001$.Compared to 1993-2002,1-year mortality decreased significantly by 29% (2003-2012) and 47% (2013-2022).

Conclusions

Over the past 30 years, the primary incidence of skin melanoma in the Republic of Belarus has increased in 3.7 times. At the same time, there has been a decrease in one-year mortality from this cancer pathology. Considering these circumstances, improving the early diagnosis of malignant skin tumors in the Republic of Belarus remains relevant.

A-169

Is melanoma a death sentence in Black Africans? A three-year institutional study from a resource limited setting

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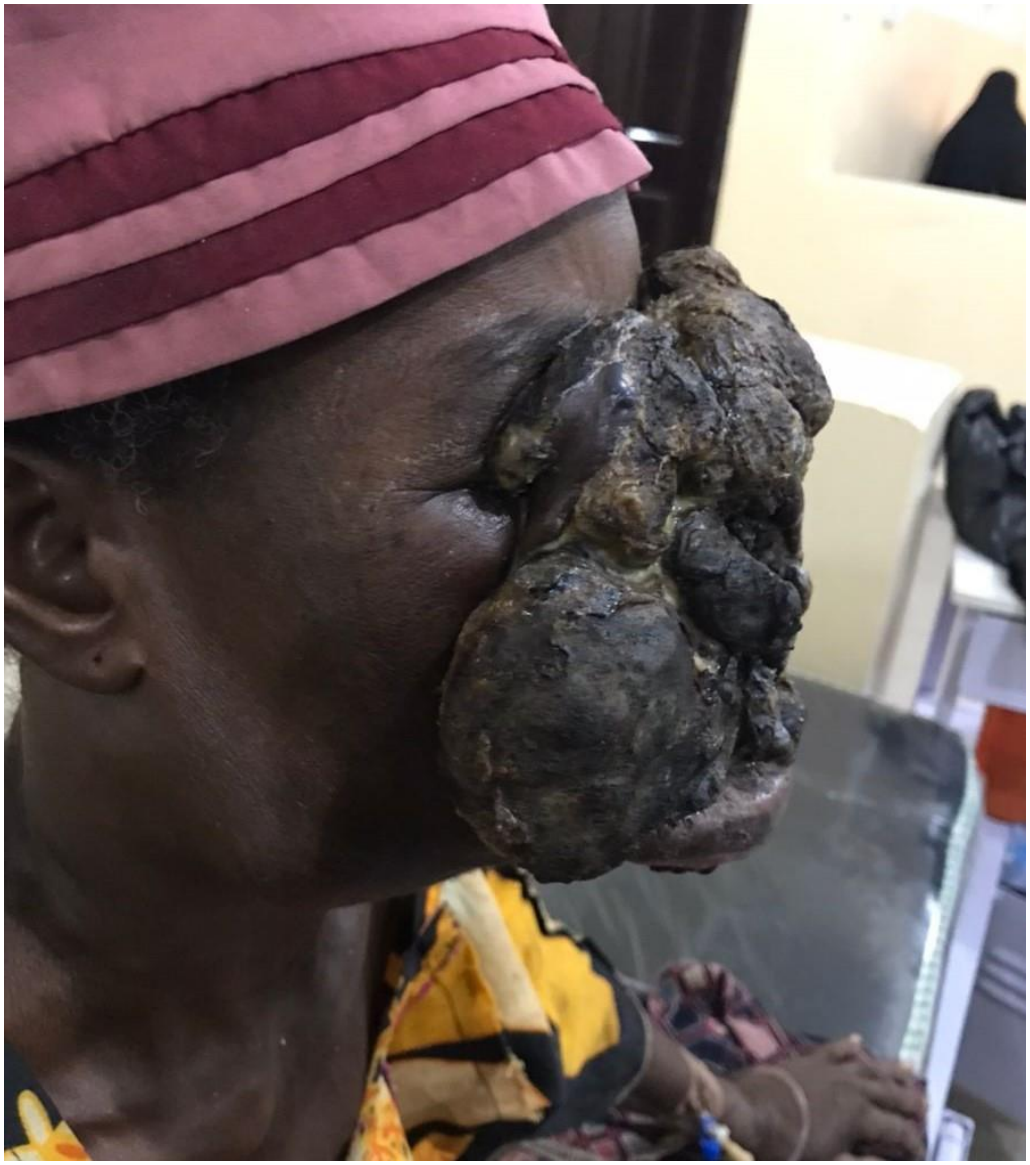
Background
Melanoma is a malignant skin cancer that arises from melanocytes. Melanocytes are cells in the body responsible for giving the skin its brown or tanned appearance. Melanoma risk has long been associated with skin, hair, and eye coloration. Generally, people with darker skin have a lower risk of developing skin cancer because the darker eumelanin serves as a better UV protection.

Methods
This is a three year (2021-2023) retrospective study of melanoma diagnosed in the Department with the source of study material been the Departmental bench registers where patients' biodata was extracted.

Results



Advanced facial melanoma with metastasis to the lymph nodes in a 50 year old woman

Advanced facial melanoma with metastasis to the lymph nodes in a 50 year old woman

A total of 57 cases were seen during the study period with a mean age of 52.63±12.85. The male female ratio was 1:1.7. Acral lentiginous melanoma (ALM) constituted 45 (78.9%), Ocular 6 (10.5%), Nodular Melanoma 5 (8.8%), Mucosal (1.8%). The commonest site was the foot 45 (78.9%). Eighteen (31.6%) and 4 (7.0%) cases presented with stage III and IV respectively. Fifteen (26.3%) cases had lymph node metastasis while 3 (5.3%) had brain metastasis. All patients had chemotherapy with almost half of the patients 22 (38.6%) dead within two years of treatment

Conclusions

Melanoma in our settings presents on the foot with advanced disease, it is associated with recurrence and distant metastasis with overall high mortality. This can be attributed to late presentation, lack of access to targeted, immunotherapy and other advance treatment modalities which have contributed to this dismal outcome.

A-446

Long-term survival of melanoma patients according to primary tumour thickness – an Australian population-based study

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Background

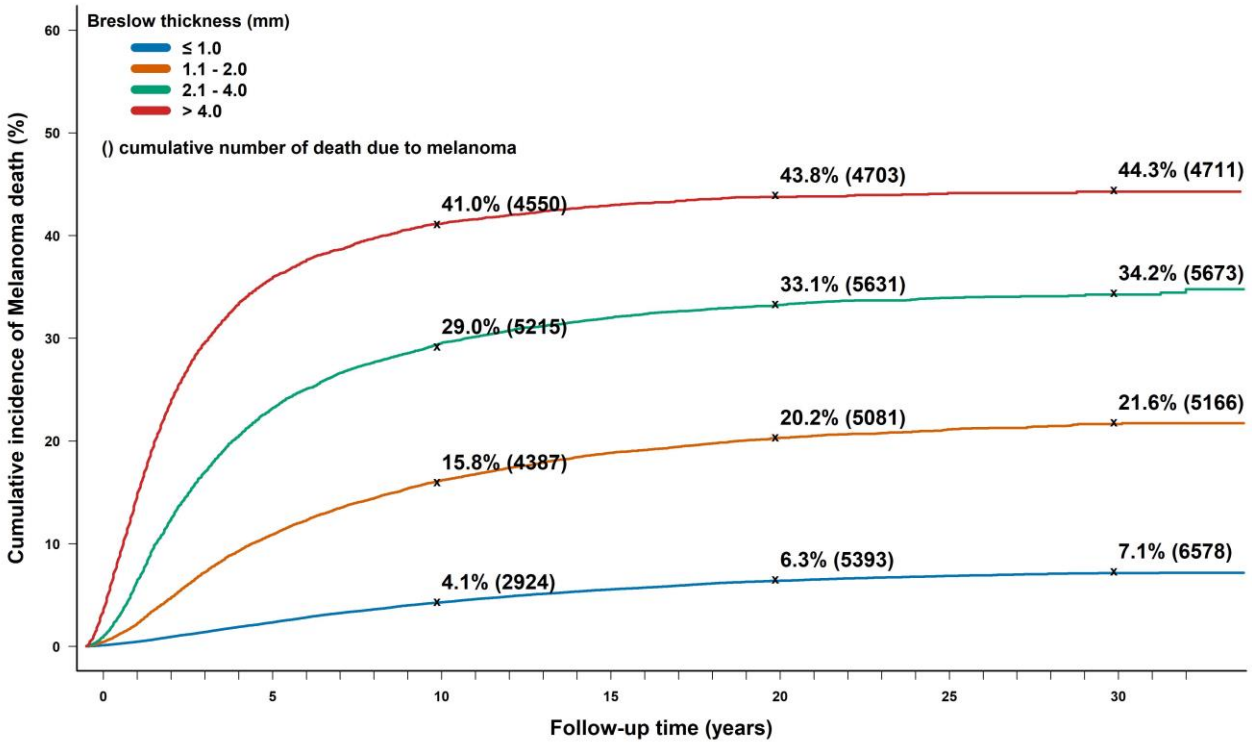
For most patients with newly-diagnosed melanomas their disease is localised (AJCC Stage-I and II) and they can be given an estimate of their risk of dying of melanoma based on the Breslow thickness of the primary tumour provided in the pathology report. This study sought to investigate the impact of T category on long-term survival by examining its effect on the incidence of both melanoma-related and non-melanoma-related death in a large population-based dataset.

Methods

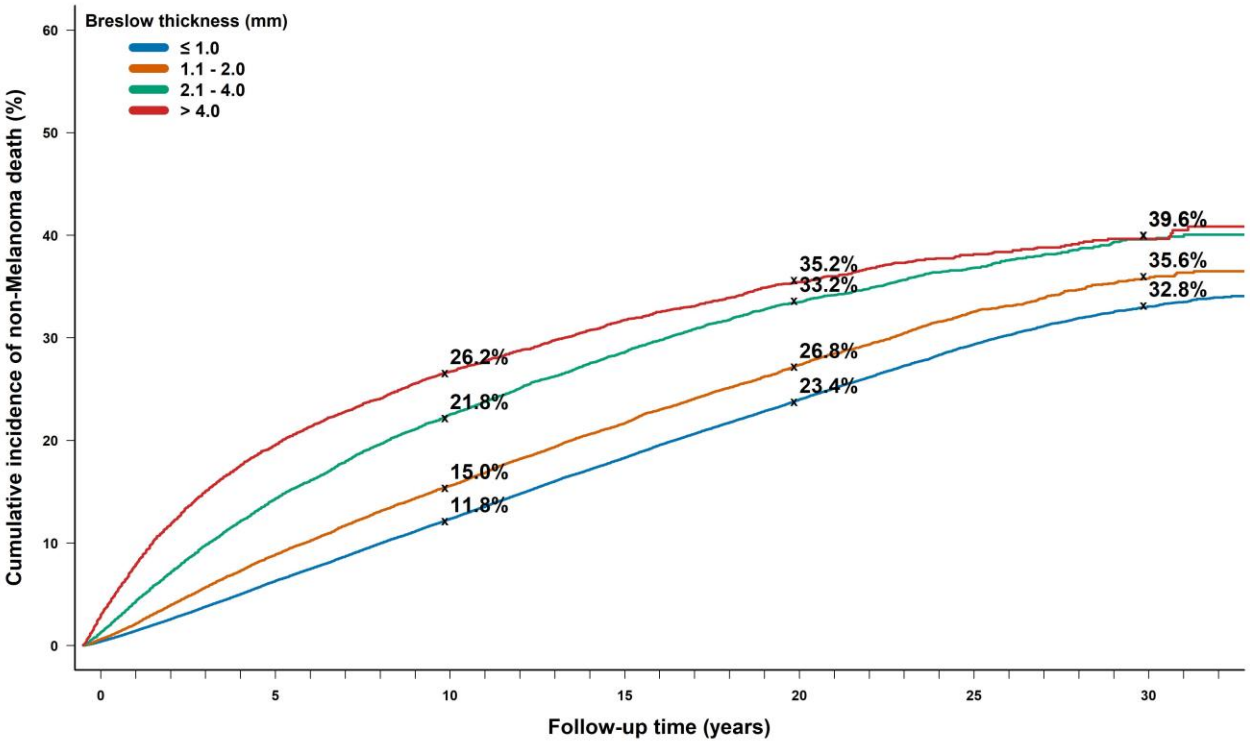
Data were analysed for 210,042 patients diagnosed with invasive cutaneous melanoma (from 1982-2014). The information was obtained from all eight Australian state and territory cancer registries, to which reporting of every cancer diagnosis is mandatory, and from the National Death Index. Melanoma-specific survival (MSS) and overall survival (OS) stratified by T category were determined using the Kaplan-Meier method and the rates at 10, 20 and 30 years were calculated. Proportional hazard models were used to quantify the relative risk differences between T categories adjusted for age, sex and body site. For each T category and at each follow-up time point, the rates of deaths due to melanoma and non-melanoma causes were determined using the cumulative incidence functions.

Results

The MSS and OS rates for each T category at follow-up times of 10, 20 and 30 years are shown in Figures 1 and 2. Patients with a T1 melanoma (Breslow thickness ≤1.0mm) by 10 years post-diagnosis had a risk of dying from their melanoma of 4.1% and a risk of dying from a non-melanoma cause of 11.8%; after 30 years their risk of death due to melanoma was 7.1% and their risk of death from another cause 32.8%. For T2 melanomas (1.1-2mm in thickness) the risks of melanoma death and non-melanoma death after 10 years were 15.8% and 15%, respectively, for T3 melanomas (2.1-4mm) 29.0% and 21.8%, and for T4 melanomas (>4mm) 41.0% and 26.2%.



Cumulative incidence of melanoma deaths over time following primary melanoma diagnosis.



Cumulative incidence of non-melanoma deaths over time following primary melanoma diagnosis.

Conclusions

This analysis of population-based Australian data provides reliable estimates of 10, 20 and 30-year risks of death due to melanoma and other causes according to thickness categories, which will be useful to both clinicians and patients.

A-105

Loss of AMBRA1 expression in the tumour endothelium as a potential biomarker to identify AJCC stage I/II melanomas at high risk of metastasis.

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Background
Loss of epidermal AMBRA1 and Loricrin (AMBLor) overlying AJCC stage I/II primary melanomas has recently been validated as a prognostic biomarker[1]. However, while loss of AMBLor identifies low risk tumour subsets, a need for a robust biomarker able to identify early-stage melanomas at risk of metastasis remains. To this aim, our pilot data shows loss of epidermal AMBRA1 overlying primary melanomas is also associated with loss of expression in the surrounding tumour endothelium, suggesting endothelial AMBRA1 (eAMBRA1) expression may define high-risk tumour subsets. To evaluate this potential, the aim of the present study was to evaluate the immunohistochemical expression of eAMBRA1 in a cohort of primary melanomas with loss of epidermal AMBLor and corelate expression levels with clinical outcome over 5 years.

Methods
Automated immunohistochemical analysis of eAMBRA1 expression was evaluated in a cohort of FFPE tissue derived from 47 AJCC stage I/II melanomas (23 metastatic/24 non-metastatic) with loss of epidermal AMBLor. eAMBRA1 expression was determined by positive pixel count using Aperio ImageScope software and normalised to vessel area.

Results
Data revealed an increased proportion of intra/peri-tumoural vessels with low eAMBRA1 expression (in which AMBRA1 expression was decreased by more than 55% compared to the average AMBRA1 vessel score throughout the tissue section) in melanomas that developed metastasis; reduced eAMBRA1 expression was observed in 21.5% of vessels in tumours that developed metastasis compared to 9.9% in non-metastatic tumours ($p < 0.004$). Grouping patients according to whether the percentage of intra/peri-tumoural vessels with reduced eAMBRA1 expression was lower than or at least 9.4% (determined by ROC analysis), Kaplan Meier analysis revealed a significantly reduced 5-year recurrence-free survival for those patients with melanomas with ≥ 9.4% vessels with reduced eAMBRA1 expression (logrank HR 18.32, 95% CI 8.1-41.6, $p < 0.001$). Conversely no difference in the proportion of vessels with low eAMBRA1 expression was observed between normal skin, primary melanomas with maintained epidermal AMBLor or tumours with loss of AMBLor that did not metastasise.

Conclusions
Collectively, these data suggest the increased proportion of vessels in the melanoma microenvironment with reduced eAMBRA1 expression as a novel putative biomarker to identify and aid the stratification of early AJCC stage I/II melanomas at risk of metastasis.

[1] Ewen at al. *Brit J Dermatol* 2023 in press

A-345

Melanoma Diagnostic Accuracy in a Total Body Photography System with an AI Dermoscopy App

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Background

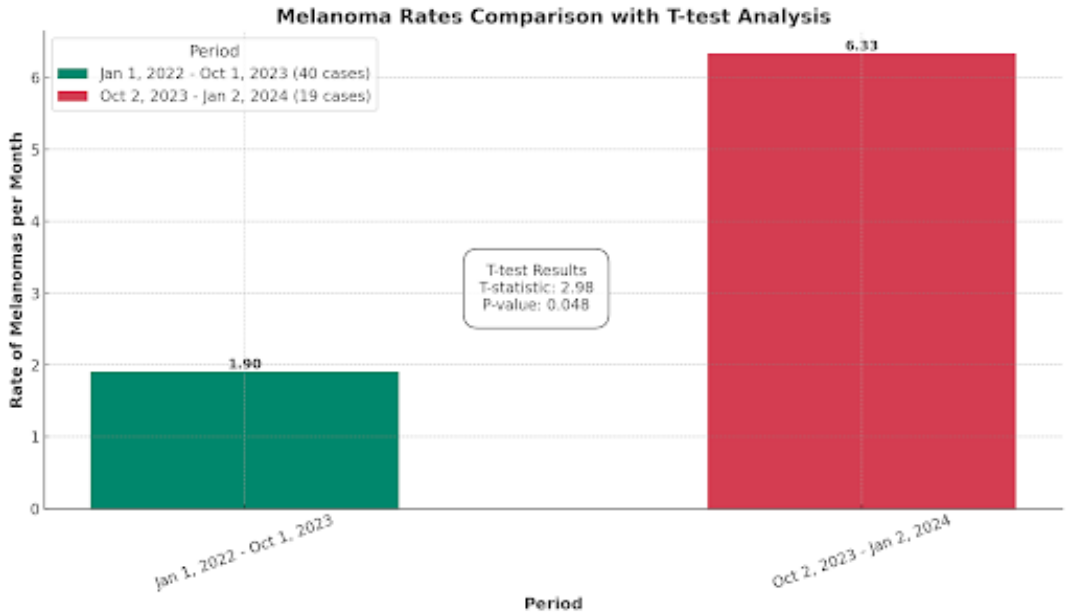
A total body photography system, Melanoscan, is augmented by a rapid bedside SQL query of AI classified images on an Android app. This study evaluates the impact of adding the SQL query to melanoma detection and surveillance. Employing deep learning for lesion segmentation and classification, we explore the efficacy of real-time SQL queries in a melanoma screening inside a specialized skin cancer center.

Methods

Utilizing the Melanoscan App's skin cancer risk query function, we access a database of 155,000+ dermatoscopy images. AI algorithms, including ResNet and EfficientNet for segmentation and various CNN architectures for classification, helped identify lesions at increased melanoma risk among patients attending the clinic. We analyze melanoma detection rates before and after integrating this function (January 1, 2022 - October 1, 2023, vs. October 2, 2023 - January 2, 2024), using statistical methods to assess these AI models' effectiveness. We evaluated NNT within 2023 to assess the effect of biopsy numbers on outcomes.

Results

Implementing the Companion App's query function led to a substantial rise in melanoma detection—40 cases in the 21 months before vs. 19 in the 3 months after. This marked improvement (t-statistic of 2.98, p-value of 0.048) showcases the AI integration's success in early melanoma detection



melanoma detection rates before and after integrating the AI risk Query (January 1, 2022 - October 1, 2023, vs. October 2, 2023 - January 2, 2024)

. Adding skin vs. background segmentation and multi-view Melanoscan image feature generation enhanced spot detection accuracy. The NNT improved from 3.57 in the first three quarters of 2023 to 2.22 in the last quarter, indicating increased detection efficiency. However, the observed difference was not statistically significant (p-value of 0.146), suggesting potential variability. a detailed examination of melanoma detection efficiencies and operational improvements from January to December 2023 is presented in the accompanying table. Notably, the fourth quarter showcases significant advancements following the intervention

2023 Quarter	Melanoscans M	Dermoscopy D	D/M	App Queries	MEL Score Avg
1	733	2824	3.85		0.113
2	713	2938	4.10		0.127
3	757	3209	4.25		0.117
4	624	3257	5.22	531	0.122
2023 Period	Biopsies	Melanomas	NNT	p-value	
1st 3 Quarters	50	14	3.57	0.146	
Last Quarter	40	18	2.22	0.146	

2023 Melanoscan and App System Usage and Number Needed to Treat

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Conclusions

Integrating the Melanoscan™ system with an AI-driven skin cancer risk query function significantly improved melanoma detection rates. Incorporating deep learning for lesion analysis highlights AI's essential role in advancing dermatological oncology toward more personalized and precise care. Despite the NNT improvement indicating enhanced detection efficiency, the need for further research to solidify these findings and explore broader clinical and public health applications remains critical. [PMID19723475][PMID30624234]

References:

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[PMID30624234] Hagerty, Jason; Stanley, Joe; Almubarak, Haidar; Lama, Norsang; Kasmi, Reda; Guo, Peng; Drugge, Rhett; Rabinovitz, Harold; Olivero, Margaret; Stoecker, William V, (2019), Deep Learning and Handcrafted Method Fusion: Higher Diagnostic Accuracy for Melanoma Dermoscopy Images, IEEE, IEEE journal of biomedical and health informatics, http://dx.doi.org/10.1109/JBHI.2019.2891049, 2024-02-15

A-334

Melanoma in Children, Adolescents, and Young Adults: The Spanish Cohort of the MELCAYA Consortium

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Background

Melanoma in children, adolescents, and young adults (CAYA) is critically understudied, leading to suboptimal diagnostic accuracy and treatment approaches. The MELCAYA consortium targets this gap by focusing on the unique epidemiology, progression, and treatment responses of melanoma in CAYA compared to adults. Through integrating European cohorts, employing omics for risk factor identification, developing AI-based diagnostic tools, and validating non-invasive detection methods, MELCAYA aims to enhance melanoma management in this demographic, underscoring the need for tailored research and clinical strategies.

Methods

This study characterizes patients with melanoma before the age of 30, diagnosed between 1977 and 2022 and registered in the Catalunya Network of Melanoma Centers (XXMM). It includes 403 cases confirmed clinically and histopathologically by the Dermatology Service at Hospital Clínic of Barcelona, Spain.

Results

Our CAYA cohort showed a mean age at diagnosis of 24.4 years (SD 4.8), with 9.9% of patients diagnosed <18 years. Females represented 61.3% of the cohort. No significant age differences at diagnosis were found between genders. In our cohort analysis, the <18 years group demonstrated a lower frequency of superficial spreading melanoma subtypes compared to the ≥18 group. Additionally, the younger group exhibited a higher frequency of tumors at stages III-IV (p=0.01). No statistical differences were observed regarding sex, eye color, hair color, skin phototype, or Breslow thickness. We noticed that CAYA patients carried at least one red hair color variant in *MC1R* gene in a higher proportion than general Spanish population (35% vs. 20%).

Conclusions

These differences underscore the importance of developing age-specific clinical guidelines and emphasize the need to integrate novel therapeutic approaches tailored to the CAYA population. The MELCAYA consortium will drive a strategic shift towards personalized medicine in CAYA melanoma care, highlighting the significance of leveraging genetic insights, specific guidelines, and targeted intervention strategies to improve prognosis and treatment outcomes.

A-311

Melanoma Prognosis and Associated Risk Factors: A Retrospective Cohort Study Using Semantic Map Analysis

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Background
By using semantic map analysis, this study aimed to visualize a more comprehensive understanding of the associations among epidemiological and clinicopathological characteristics of patients with primary cutaneous MM, which critically affect disease-free survival (DFS) and melanoma-related overall survival (MROS).

Methods
This single-centre retrospective study included all consecutive cases of single, primary, localized, histopathological confirmed cutaneous MM tumours that were diagnosed between February 1990 and July 2014 and followed up until July 2021 at the Department of Dermatology, University Hospital of Bern, Switzerland. A total of 1,110 melanoma patients (median follow-up 10.6 years) were included. Associations among patients' demographics, clinical characteristics and survival were explored using semantic map analysis (1–4). This is a data-mining algorithm that is able to find and display the most important associations between different variables, taking into account the effect of other covariates in the system.

Results
The analysis revealed a clustering of variables around 2 main hubs: Breslow thickness < 1 mm and ≥ 4 mm. Factors connected with high melanoma thickness were: older age, positive sentinel lymph node biopsy findings, presence of ulceration, nodular melanoma type, and light skin phototype. Both disease-free and melanoma-related overall survival were in this cluster and connected with positive sentinel lymph node biopsy and Breslow ≥ 4 mm. Patients with Breslow between 1 and 3.9 mm were also in this cluster and linked with negative sentinel lymph node biopsy, nodular melanoma and safety distance > 10 mm.

Conclusions
This semantic analysis confirmed the close link between Breslow thickness, age, sentinel lymph node biopsy findings, skin type, melanoma subtype and prognosis, and provides prognostic information useful for the further stratification and management of patients with melanoma.

A-390

Nationwide study of the treatment options of lentigo maligna and recurrence rates in the Netherlands

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Background
The treatment of lentigo maligna (LM) can be challenging in elderly patients and in delicate facial areas. Previous studies showed that 10% of LM were upgraded to LMM after surgery. [1] This nationwide cohort study aims to identify the choice and frequency of diagnostic and treatment modalities in LM patients in the Netherlands and to investigate the rate of upgrade to LMM after LM surgery and recurrences after treatment.

Methods
To investigate the diagnostic modalities to diagnose LM and upgrade into LMM after surgery, data were retrieved from PALGA (nationwide pathology registry) registered in 2020. To investigate the treatment modalities of LM, data were retrieved from the Netherlands Cancer Registry between 2013-2016. In order to investigate the recurrences after the treatment modalities, all LM from 2013 until 11-6-2021 were retrieved from PALGA.

Results
In 2020, 1422 patients were diagnosed with a primary LM in the Netherlands, mostly the diagnose was made by biopsy (61%) and conventional excision (37%). Half of the patients were treated with surgery and 14% was upgraded into LMM/melanoma after surgery.

	N (%)	Surgical treatment	No surgery or histological evaluation
Total of primary LM	1422 (100)	713 (50.1)	709 (49.9)
LM after surgery	-	612 (85.8)	-
LMM after surgery	-	101 (14.2)	-
Diagnostic modality			
Biopsy	864 (60.8)	633 (88.8)	231 (32.6)
Excision	527 (37.1)	67 (9.4)	460 (64.9)
Shave/ curettage	14 (1)	7 (1)	7 (1)
Breuninger	12 (0.8)	5 (0.7)	7 (1)
Other	5 (0.4)	1 (0.1)	4 (0.6)

Characteristics and diagnostic modalities of LM in the Netherlands between 1st January and 31st December 2020 and upgrade after surgery.
Between 2013-2016, there were 3587 primary LM cases and most of these patients were treated with conventional excision (80%) and less with staged excision (2%), laser or radiotherapy (1%), or local immunotherapy (3%). With a follow up until 11-6-2021 there were 432 recurrences.

Conclusions
First choice of diagnostic modality in LM patients in the Netherlands is a biopsy. In this nationwide database there was an upgrade of histological proven LM into LMM/melanoma after surgery in 14% of the cases. This should be taken into account when choosing treatment modalities, especially when considering non-surgical treatment modalities. Most LM patients were treated with conventional excision, conform the dutch melanoma guideline. The high number of recurrences shows us the complexity of choosing the right treatment in LM and searching for balance between histological clearance and mutilating surgery in delicate areas.
References:

[1] J Zoutendijk, et al, (2022), Clinical findings are not helpful in detecting lentigo maligna melanoma in patients with biopsy-proven lentigo maligna, J Eur Acad Dermatol Venereol , Rotterdam, 2325-2330, Dec;36(12), https://doi.org/10.1111/jdv.18346, ErasmusMC

A-106

New designed, non-invasive diagnostic tools for the diagnosis of oral mucosal lesions.

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Background
Diagnosis of pigmented and non pigmented lesions involving the oral mucosa are complicated because of limited access to the oral cavity with tools like dermoscopy or other methods usually applied for the evaluation of lesions involving skin and outer part of the oral cavity as lips and external cheeks. Confocal microscopy has been demonstrated to have a singnificant impact in the diangosis of skin and genital lesions. Adapted tools are needed in order to covoer the umeet needs in those type of clinical setting.

Methods
A new designed confocal microsocpy optic for the access to the in part fo the oral caviy has been desingned and realized by the ingeniers from Memorial Sloan Kettern Cancer Center of New York and initially tested on a series of 80 patients affected by oral cancer testing histopathology/confocal microscopy blinded agreement. Moreover, 110 different oral lesions of different type have been classified accordingly to the lesion colour (white, red and brouwn/black), convering a large spectrum of entities moving from inflammatory, pre-cancer and oral melanocitic and non melanocytic cancer, has been studied with the new confocal optic.
A video mapping has been beveloped staring from confocal microscopy videos in order to provide wide mosaics of confocal microscopy images for large confocal field of view of the lesions

Results
The new designed confocal optic lets the evaluation of lesions involving also the inner part of the oral cavity.
Comparison between confocal microscopy and histoloy demonstrated high agreement between blinded readers (95% for normal tissue and 81.7% for tumors), high specificity (98.3%) and negative predictive values (96.6%) for normal tissue identification, and high sensitivity (90%) and positive predictive values (88.2%) for tumor detection. Impact of video mapping in the interpretation of cinfical analysis of the tissue has been also demonstrated.
A simplified approach to the different oral lesions subtypes has been considered and tested on the large series of cases demonstrating the usefulness of a systematic approach to oral lesions.

Conclusions
The new designed confocal microscopy optic for oral mucosa represents a promising tool for the evaluation of the different mucosal lesions, moving from inflammatory conditons to oral cancer, affecting the inner part of the oral cavity. Diagnosis, clinical and therapeutic follow-up and lesions mapping can be done with confocal microscopy also in this difficult anatomical areas

A-437

New differential diagnosis of melanoma. ¿Induced?

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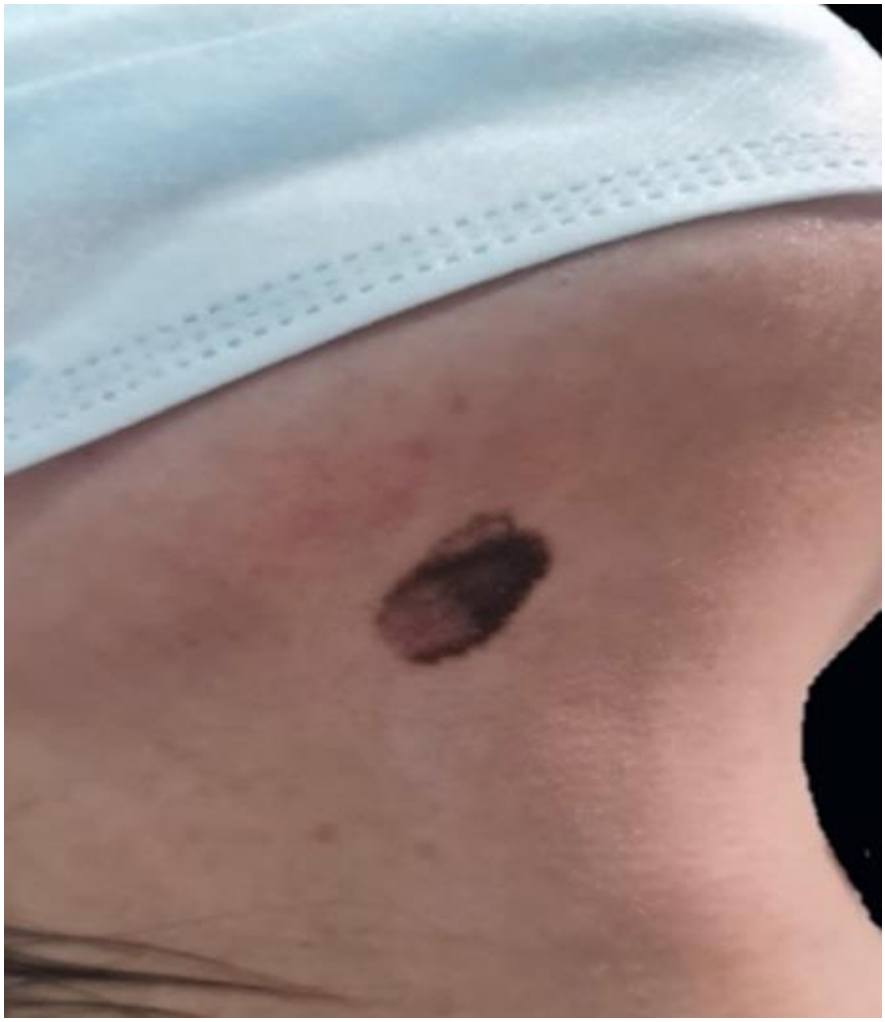
Background

Melanoma is a type of skin cancer that develops from malignant transformations of melanocytes. Its development has been described on congenital melanocytic nevi mainly in relation to its size [1]. However, with the advent of new technologies, especially for aesthetic treatments, changes can occur that simulate malignancy on previous melanocytic lesions, which might lead to uncertainties on the diagnosis and dermatological management.

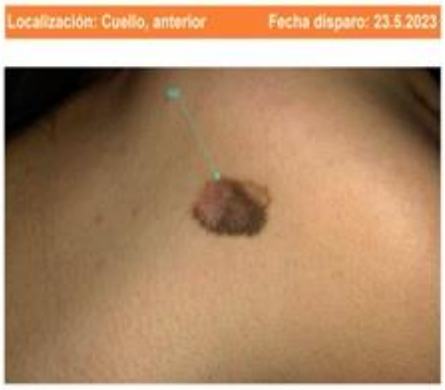
Methods

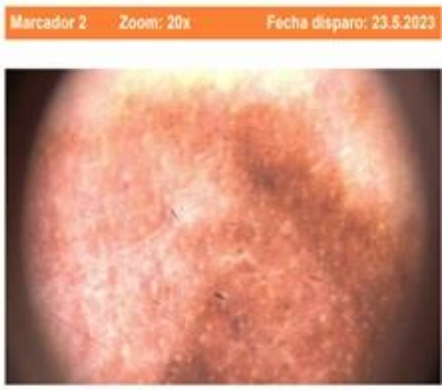
Descriptive observational study in the form of a case report.
We present the case of a 27-year-old patient who had a congenital melanocytic nevus in the cervical region. She noticed changes after undergoing a laser hair removal session on her facial area, which she has been doing for 2 years. Denies any additional treatments. She has no personal medical history,
Maintains consistent tanning routine, with more than 3 episodes of sunburn during childhood and adolescence, and the only family medical history is a maternal uncle with unspecified skin cancer. On physical examination, the patient with skin phototype III has an asymmetric plaque in the anterior right cervical region with irregular borders, heterochromia with a predominance of light and dark brown, measuring 20x11 mm. (Fig.1)

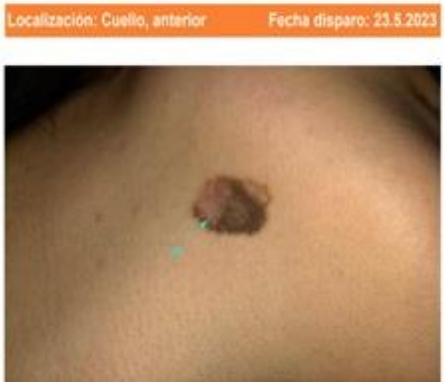


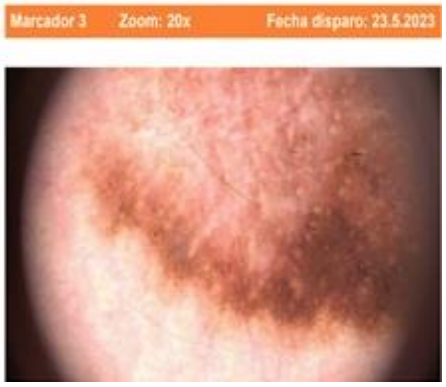
Results

Given the findings on the physical examination of an atypical lesion, a digital dermoscopy study was requested (Fig.2)









: Patient with Skin Phototype: III. Melanocytic lesion located in the right cervical region measuring 20 x 11 mm; with an atypical pseudoreticular pattern with globules and pseudopods in the light brown periphery, hypochromic area with irregular vessels and bright white structures; asymmetry along one axis is observed. Although the findings may be related to regression changes post-laser contact, resection is recommended for histological confirmation.
Based on the clinical and dermoscopic findings, it was indicated to proceed with the resection of the lesion and to carry out a pathology study in order to rule out malignancy.
The findings of the pathological study were a melanocytic nevus composed of congenital characteristics without signs of malignancy.

Conclusions

After laser hair removal on congenital and acquired melanocytic nevi, the clinical appearance, dermoscopy, and histology can be modified, generating doubts for both the doctor and the patient about the possible malignant transformation of these lesions [2]. Therefore, it is important to consider these possible modifications for decision-making regarding follow-up and management.
References:

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[2] Acle R, Zambrano-Mericq MJ, Navarrete-Dechent C, Uribe P, Abarzúa-Araya Á., (2022), Clinical and dermoscopic evaluation of melanocytic nevi changes during diode laser hair removal: A prospective study, Lasers Surg Med, Lasers Surg Med, 970-7., 54(7)

A-197

Novel, non-invasive method for classification of melanocytic lesions using a direct illumination multispectral imaging camera

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Background
In the context of rising incidence and mortality of melanoma, early detection and surgical removal of primary lesions are essential for promising prognosis. Multispectral imaging is a new non-invasive imaging technique which can assist dermatologists in skin cancer detection by measuring reflectance spectra of biological tissues. Currently used incident illumination allows only little light to be reflected from deeper skin layers due to high surface reflectance. We aimed to evaluate whether direct light coupling could extract more information from deeper skin layers for more accurate lesion classification.

Methods
This pilot study at the Dermatology Department of the University Hospital Basel included 27 melanoma-suspicious pigmented lesions from 23 patients (6 melanomas, 6 dysplastic nevi, 12 melanocytic nevi, 3 other). Lesions were imaged before excision using a snapshot-mosaic multispectral camera prototype with incident and direct illumination and classified by a pre-trained multispectral image analysis model.

Results
Using incident light, a sensitivity of 83.3% and specificity of 58.8% were achieved compared to true dignity determined by histopathological examination. Direct light coupling resulted in superior sensitivity of 100% and specificity of 82.4%. When comparing the accuracy results of the direct light coupling multispectral image analysis with the classification of corresponding red, green and blue (RGB) lesion images using a commercially-available convolutional neural network (CNN), multispectral imaging outperformed RGB image classification. The CNN RGB image analysis showed a 16.7% lower sensitivity (83.3%), detecting 5 out of 6 malignant lesions, and 20.9% lower specificity (61.5%) compared to direct light coupling multispectral image classification.

Conclusions
By including hyperspectral imaging into melanoma detection processes, the specificity of physicians can increase. As a proof of concept, we have demonstrated that direct coupling of light allows more information to be extracted from deeper skin layers for more accurate lesion classification compared to incident illumination. This newly evaluated illumination method has great potential to improve multispectral and hyperspectral applications in skin cancer detection, especially in combination with convolutional neural network classification.

A-192

Prediction of melanoma metastasis using dermatoscopy deep features. An international multicenter cohort study

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Background

Machine learning algorithms demonstrated modest accuracy on the prediction of melanoma metastasis, based on histological images and clinicopathological information. Whether dermatoscopy deep features could serve as biomarker for the prediction of melanoma metastasis, remains an underexplored area in medical research.

Methods

An international, multicenter, cohort study of cutaneous melanoma patients from 3 different continents was conducted. Patients with available clinical and dermatoscopic images and an adequate follow – up time for the development of metastasis (both locoregional and distant) were included. We utilized a support vector machine (SVM) classifier, to distinguish between melanomas that metastasized and those that did not. A pre-trained ResNet 50 network was used and the dataset was separated into training and testing set, stratified by TNM-stage. In order to guard against biased data selection, the split was repeated five times, resulting in five different training-test sets. The primary outcome was the comparison of the prognostic performance of deep dermatoscopy features based on SVM (model 1) to the performance of established prognostic factors of melanoma, such as Breslow and ulceration (model 2) and to a combined model using deep features and histologic factors (model 3). A secondary aim was to examine the performance of model 1 in stage IIB and IIC patients. The prognostic performance was assessed using the Area Under Curve (AUC) and the True Positive Rate (TPR) at a True Negative Rate at 70%.

Results

712 patients were included, 465 (65.3%) non-metastatic and 247 (34.7%) metastatic, within a median follow – up of 60 months. The SVM model demonstrated mean AUC 0.84 (95% CI 0.80 – 0.87) and TPR 0.81 (95%CI 0.73 – 0.90). Similar results were shown for model 2 and model 3, and no statistically significant differences among models were detected in terms of AUC and TPR (De Long's test, $p>0.05$ and ANOVA Kruskal-Wallis $p>0.05$). Regarding IIB/IIC patients and combining data from five test sets, SVM correctly classified as metastatic 21 out of 23 (91.3%) patients in each category, who eventually developed metastasis during follow-up.

Conclusions

Our findings suggest that dermatoscopy deep features could offer an immediate, in vivo prediction of melanoma metastasis prior to excision. This advancement holds significant clinical importance prioritizing high – risk patients for neoadjuvant treatment or guiding selection of patients who might benefit from adjuvant therapy.

A-161

Pregnancy-associated melanoma- a pilot study

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Background

Melanoma in pregnancy is a controversial topic gaining significance as the incidence of melanoma increases, with women delaying pregnancy into their 30s and 40s. This pilot study analyzes the characteristics of primary tumors and outcomes in 12 women diagnosed with melanoma during or within a year after pregnancy.

Methods

The study includes 12 women diagnosed with melanoma during or within a year after pregnancy. Data analysis was conducted using information gathered from the Melanoma registry of patients who were examined in the Clinical Hospital Center Sestre milosrdnice. The histopathological characteristics of melanoma were investigated, including type of melanoma, tumor thickness, presence of ulceration,regression, tumor-infiltrating lymphocytes, and lymphovascular invasion. Additionally, the study examined the presence of a diagnosis of dysplastic nevus syndrome in patients, diagnosis of multiple melanomas in the subsequent years of follow-up, and family medical history.

Results

In our study group, there were 15 primary melanomas diagnosed in 12 women; 11 melanomas were superficial spreading type, 1 was nodular melanoma, 2 were melanomas in situ, and 1 was malignant blue nevus. During follow-up, two women were diagnosed with a second or third primary melanoma. The average tumor thickness was 1.2 mm. Ulceration was observed in 2 women, tumor-infiltrating lymphocytes (TIL) were notably pronounced in 2 women, and lymphovascular invasion was absent in all tumors. During follow up three women were diagnosed with visceral metastases (brain, lungs, liver and abdominal lymph node), leading to the unfortunate demise of two of them.

Conclusions

Despite numerous studies, there is still insufficient data and guidelines regarding the treatment and approach for patients diagnosed with melanoma associated with pregnancy. Considering the percentage of metastases observed in our pilot study, it can be inferred that there may be a potentially unfavorable outcome in this group of patients. Further research including a greater number of patients is required to confirm this conclusion and enlighten this peculiar topic.

A-318

Prospective multicenter comparative study of dermoscopic images of a standard dermatoscope and an Autonomous TBP/Dermoscopic Imaging device (Deviskan^{R}) ("Deviskan QS"-Quality Study)

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Background

An autonomous medical device (Deviskan) has been recently developed. The device consists of a dedicated cabin with a robot for standard image acquisition that incorporates a photographic equipment for total body cross-polarised photography, a dedicated software to identify and segment pigmented lesions and a high-resolution camera for dermoscopic photography of individual lesions. In this study we compared the quality of the images using the innovative device and the traditional manual digital dermoscopic documentation.

Methods

A cohort of 316 patients that consulted for atypical mole syndrome from two clinics in Spain (Hospital of Figueres, Girona and Diagnosis Dermatologica, Barcelona) was prospectively recruited during the second half of 2023. Diagnostic classification and quality of dermoscopic images was compared between the scanner and digital dermatoscope (Dermlite Handiscope,US) independently by two dermatologists with a score from 1 to 10. Furthermore, the time efficiency of each imaging technique was recorded.

Results

Demographic results: Age (mean 47.13 years; range 13.23 years), sex (women 66.6%); clinical data (phototype I 2.4%,phototype II 56.4%, phototype III 29.7%, phototype IV 11.2%,; personal (n=67) and familial history of MM (n=69); carriers of Familar MM susceptibility genes (n=3).19.323 images from total body photography and 10,646 dermoscopic images of individual pigmented lesions from 3-10mm (mean number of lesions per patient=32, range=13 to 94) were collected in different localisations (trunk=74%; Upper arms=15%; lower extremities=10%; face =1%). The device showed a high quality of dermoscopic images (mean score of 9.84 vs the manual method of 9.44), with no significant differences in the quality depending on the body site, size or classes. Image classification by two independent dermatologists exhibited a 91.6% of agreement, with most discrepancies corresponding to equivocal benign small lesions of melanocytic nevus vs benign keratosis (86% of discrepancies)

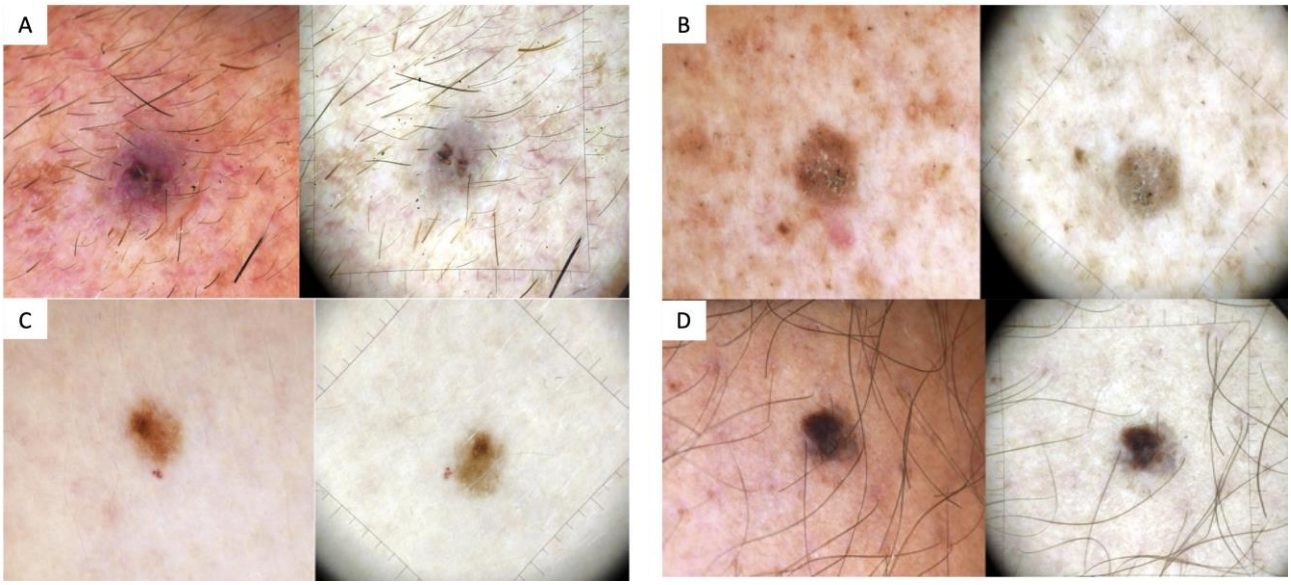

Figure 1. Comparison between Deviskan (left images) and standard contact polarised dermoscopy (right images). A) Basal Cell Carcinoma, B) Seborrheic Keratosis, C) Melanocytic nevus, D) Melanoma.

. Remarkably, the mean time of imaging of the autonomous device's was 570 seconds (SD of 169 and a range 351-992), compared to the 606 seconds of the manual method (SD of 286 and a range of 304-1135),which only included dermoscopic photography of the same lesions.

Conclusions

The autonomous device exhibited a high quality of the images like standard contact polarised digital dermoscopy and a lower time of acquisition.

A-374

Psychological distress and need for psycho-oncological support in high-risk patients for melanoma and melanoma survivors: Patient-reported outcomes of a prospective study

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Background
Although survival rates are increasing, emotional distress remains a serious issue for melanoma patients, leading to reduced quality of life and fear of cancer recurrence. While many advanced melanoma patients suffer from psychological distress, data on emotional distress and psycho-oncological needs among melanoma survivors in the adjuvant setting and at-risk patients are still under-researched. The aim of this study was to investigate the psychological distress and melanoma-related concerns of patients at increased risk of melanoma and melanoma survivors and to identify their need for psycho-oncological support.

Methods
We conducted a prospective monocentric study to assess distress and need for psycho-oncological support in patients at-risk for melanoma (≥100 nevi, ≥5 dysplastic nevi, known CDKN2A mutation and/or positive family history) and in melanoma survivors using questionnaires. Melanoma worry was assessed by the Melanoma Worry Scale (MWS, score range 4-17) and psychological distress by the distress thermometer (score range 0-10, ≥5 leads to support recommendation).

Results
Between 01/2021 and 04/2023, a total of 382 patients (mean age 53±15 years, 55% male, 58.9% at-risk, 41.1% melanoma patients) were included. The median MWS and distress scores were 7 and 3. Psychological distress was significantly higher in patients <65 years ($p<0.0001$), with multiple melanomas ($p<0.0001$), in patients without a partner ($p=0.0232$) and, surprisingly, in patients at-risk for melanoma compared to melanoma survivors ($p<0.0001$; mean score 3.9, respectively 2.9). MWS was significantly higher in melanoma patients who had received their diagnosis within the last two years ($p=0.0104$) and in women ($p=0.0486$). Neither melanoma stage or location nor family history of melanoma had an influence on distress or melanoma worry. At baseline, 31.4% of the patients (46 melanoma, 74 at-risk) expressed the need for a psycho-oncological consult (mean distress score 3.8).

Conclusions
Our findings reveal a high psycho-oncological burden among melanoma survivors and at-risk patients for melanoma. Even among non-metastatic patients, there is an unmet need for psycho-oncological support. Melanoma survivors and patients at-risk for melanoma should be given special attention in the future, and the cut-off of 5 for psycho-oncological support should be adapted.

A-354

Risk factors on developing brain metastasis from melanoma: A sistematic review

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Background
Melanoma is the biggest cause of death among skin cancers. This occurs since such an event can have additional catastrophic consequences, such as brain metastases, which have a poor prognosis. Therefore, this study aims to analyze the demographic characteristics and overall survival of patients with brain metastatic melanoma to identify their risk factors.

Methods
This is a systematic review of the literature carried out in accordance with the PRISMA guidelines, which used MEDLINE, Public Medline (PubMed), Cochrane Library and Scielo as databases. 17 articles were included to evaluate risk factors for the development of brain metastases in patients with melanoma. The variables analyzed were sex, age at diagnosis of brain metastasis, primary site of melanoma, ulceration, Breslow index, number of metastases, histological type and overall survival.

Results
Some variables were associated with a significant increase in the chance of brain metastasis in patients with melanoma, including male sex (p=0.003); Breslow index > 2mm (p=0.02); presence of mutation (p=0.01). Furthermore, the ANOVA analysis performed on the melanoma location variable revealed that the primary location in the head/neck and trunk are associated with a greater chance of metastasizing to brain tissues (p=0.03). The variables number of metastases, ulceration, lactate elevation and lesion histology were not associated with a higher prevalence in the development of brain metastases. The median time to brain metastases was 34,2 months from the time of the diagnosis, and the overall survival was 5 months.

Conclusions
It is concluded that risk factors may be related to a greater chance of developing brain metastasis due to melanoma, such as gender, Breslow index, mutation and primary location of the lesion. These results can promote improvements in screening strategies for patients at risk of developing brain metastases due to melanoma and advance their prognosis.

A-201

Role of the COVID-19 pandemic on the incidence and stage at initial diagnosis of cutaneous melanoma: a retrospective national study from the French Clinical Database of Melanoma Patients (RIC-Mel).

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Background
COVID-19 pandemic had a variable impact on the severity of melanomas.

Methods
Based on the French RIC-Mel database, new melanomas diagnosed in pre-COVID (01/01/2018 to 16/03/2020), lockdown (17/03/2020 to 10/05/2020), and COVID pandemic (referred as COVID) (11/05/2020 to 30/09/2022) were included in a retrospective study. Patient and melanoma characteristics at diagnosis, time intervals required for lymph node procedure and initiation of a systemic treatment, were retrieved. Statistical analyses were performed between pre-COVID and COVID periods.

Results
3650 patients in pre-COVID were included, 121 in lockdown and 2878 in COVID. Melanomas were thicker in COVID (median 1.5mm, IQR 0.7-3.6) than in preCOVID (median 1.2mm, IQR 0.5-3.0, p<0.0001) and more ulcerated (25.4% vs 20.6%, p<.0001). Number of melanomas diagnosed per day decreased from 4.53 in pre-COVID to 3.30 in COVID. The reductions of T stages in COVID, compared to expected numbers based on pre-COVID values, were mainly observed for Tis (-60.3%) and T1 (-67.5%) stages, and less for T2 (-22.6%) and T3 (-36.4%). In COVID compared to preCOVID, stages 0 (8.8% vs 10.3%) and I (39.5% vs 42.7%) were reduced whereas stage III increased (11.9% vs 6.3%), sentinel lymph node biopsy rates doubled (40.3% vs 23.4%, p<0.001). Interval time for lymph node procedure and initiation of a systemic treatment were similar.

Conclusions
In France, COVID pandemic was associated with more aggressive melanomas, partially explained by decreased number of thin melanomas diagnosed.

A-177

Sarcopenia as a prognostic indicator in advanced melanoma; a retrospective cohort study.

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Background
Recent research has shed light on the role of sarcopenia, a multifaceted condition characterized by skeletal muscle loss and dysfunction, we know that sarcopenia can lead to poor progression and overall survival in advanced solid tumours, however the role of sarcopenia in advanced melanoma is unclear. This study reviews our own population of advanced stage melanoma patients and their sarcopenia profile, how does it affect their overall survival?

Methods
A retrospective cohort study of stage 2b melanoma patients and above were assessed for sarcopenia on their follow up disease monitoring CT scans and their subsequent 1,5 and 10 year survival was analysed between those with and without sarcopenia.

Results
Between years 2006 and 2018, Galway University Hospital managed 150 patients with melanoma classified at stage 2B or above. The average age was 62.5years (range 19-96years), with n=73 females and n=77 males included. 114 patients (76%) had evidence of sarcopenia in the population cohort (80% (n=61) of males and 77% (n=56) females). At time of data retrieval 65% (n=97) of the patient group had died. Less than '1 year survival' was found in 13% (n=20)(n=9 females v n=11 males), '2-5 year survival' only was found in 43% of this patient group (n=29 females v n=36 males) and 39% (n=58)(n=34 females v n=24males) had over ten year survival with 4% lost to follow up (n=7, n=1 female, n=6 males). In the 1,5 and 10 year survival groups we found that 95% (n=19), 76% (n=50) and 67% (n=39) had evidence of sarcopenia respectively.

Conclusions
Sarcopenia has been linked to poorer response rates to immunotherapy and targeted therapies, suggesting its potential role as a predictive biomarker in treatment selection.
Our results demonstrate that sarcopenia is a poor prognostic indicator for survival in advanced melanoma, with the rate of sarcopenia decreasing in those who survived for 10 years or longer. We therefore propose and highlight the importance of comprehensive assessment tools for sarcopenia in the context of melanoma. To conclude, we emphasize the emerging significance of sarcopenia in melanoma, highlighting its potential as a novel prognostic factor and therapeutic target. Understanding the complex relationship between sarcopenia and melanoma may lead to the development of personalized treatment strategies aimed at mitigating muscle loss, improving treatment outcomes, and enhancing the quality of life for patients with melanoma

A-382

Single-cell and spatial transcriptomic analysis of primary (nevus-associated)-melanoma

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Background
The development and application of single-cell omics has made it possible to study cancer progression and metastasis in great detail. For melanoma, single-cell studies have primarily focused on advanced stage (metastatic) disease. However, nevus-associated-melanoma in which arises from benign nevi, creates the unique opportunity to study the molecular mechanisms that drive early cancer initiation and progression.

Methods
We used the recently published technique snPATHO-seq [1] which allows the RNA sequencing of single nuclei from FFPE archived tissue. Analysing nevus-associated-melanomas using targeted single-cell RNA-sequencing (n=12) enabled us to reconstruct the cellular trajectories from the premalignant to the malignant melanocyte state.
Additionally, we performed untargeted spatial transcriptomics on two primary human melanoma, at a resolution of 0.5 µm (Open-ST [2]), to study the behavior of tumor cells and their interactions with neighboring immune and stromal cells at a subcellular resolution.

Results
We detected a population of nevus melanocytes characterized by *PYGL* and *PCDH7* expression whereas the melanoma populations lossed the nevus-associated potential tumor suppressor genes *ARRDC3* and *CRTAC1*. By performing spatially-constrained receptor-ligand interaction analysis we identified signaling hubs that potentially drive cancer progression.

Conclusions
In summary, we performed high-throughput, single-cell and spatial transcriptomic analyses of primary human melanoma to gain deeper understanding of the tumor initiation and malignant transformation.
References:

[1] Taopeng Wang, (2023), snPATHO-seq: unlocking the pathology archives, CSH, bioRxiv, https://doi.org/10.1101/2023.12.07.570700
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A-350

Staging of Mucosal Melanoma of the Head and Neck

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Background

The staging of mucosal melanoma of the head and neck (MMHN) has been unsatisfactory. Whilst the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma is long established, staging for MMHN was only introduced in the 7th edition of the AJCC Staging System (AJCC7). Emerging evidence indicates only limited prognostic utility of AJCC staging for patients with MMHN. The current 8th edition (AJCC8) reflects this uncertainty for MMHN, and (unlike AJCC7) omits prognostic stage groups for MMHN, maintaining only TNM categories.

For MMHN, AJCC staging commences at T3, unlike any other disease. However, it remains unclear if staging MMHN from T3 onwards brings closer the survival outcomes of MMHN and those of cutaneous melanoma of the head and neck (CMHN) for matched stages. Despite differences in incidence, presentation, and biological behavior, there is clearly merit in standardizing prognostic staging for CHNM and MMHN to guide clinical practice and facilitate research.

The objectives of this study were to compare survival outcomes for MMHN and CMHN of matched stages, and to assess the prognostic value of the current AJCC staging system for patients with MMHN.

Methods

A multicenter, retrospective study of patients with MMHN (*n*=94) was conducted. Patients were classified into AJCC8 TNM categories, and AJCC7 prognostic groups. Kaplan-Meier curves and Cox regression models were used to investigate recurrence-free survival (RFS) and overall survival (OS). Survival endpoints were compared using Kaplan-Meier estimates for MMHN and a cohort of CMHN patients (*n*=2848) matched for stage.

Results

Comparison of the MMHN and CMHN cohorts showed no significant survival difference between matched stage III (OS, *p*=0.48; RFS, *p*=0.99) and stage IV (OS, *p*=0.94; RFS, *p*=0.36) patients (Figures 1 and 2). For MMHN, AJCC8 provided statistically-significant segregation of prognostic values between stages III and IV for both RFS (*p*<0.0001) and OS (*p*<0.0001), but demonstrated inadequate stratification of T3 and T4a for both survival endpoints.

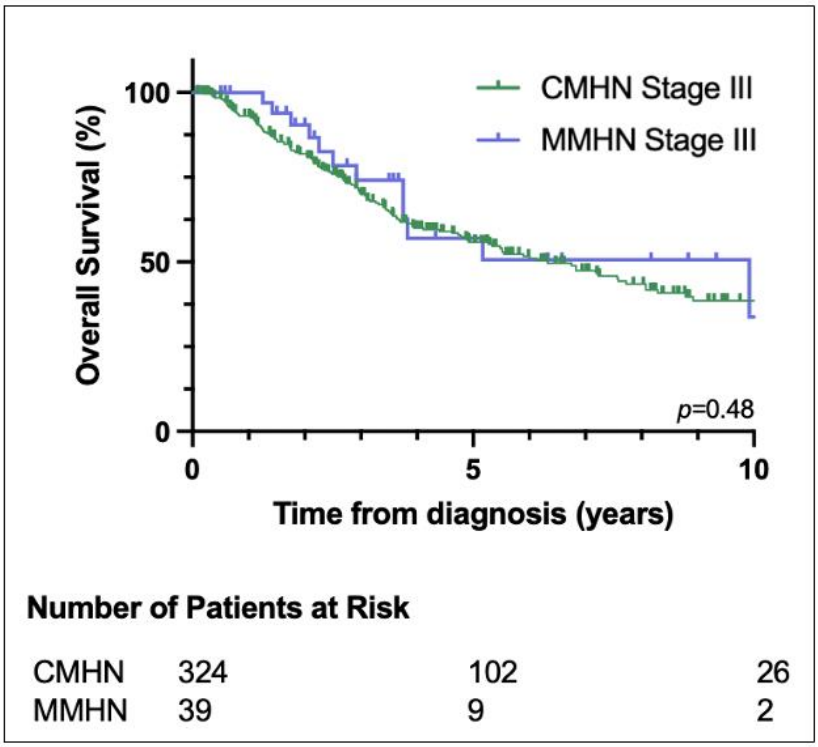

Figure 1

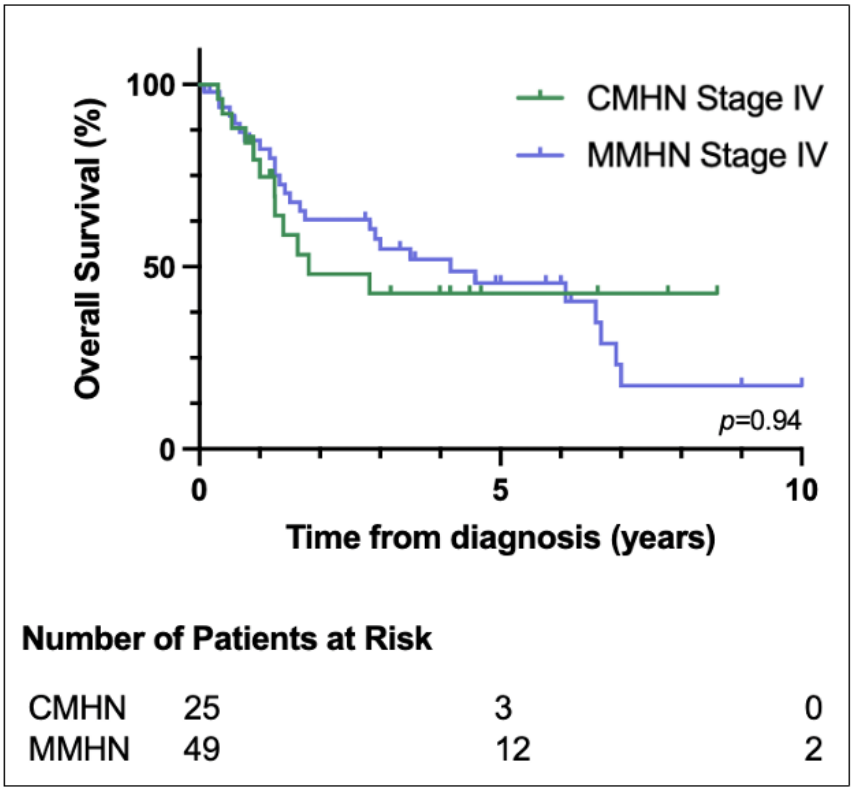

Figure 2

Conclusions

Matched AJCC stages for patients with MMHN and CMHN demonstrated comparable survival outcomes, supporting the unique case of staging MMHN from T3 (and stage III) upwards. However, better delineation between T3 and T4a is required.

A-223

The health economic impact of the 31-gene expression profile test for treatment and surveillance management plans in patients with cutaneous melanoma

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Background
Cutaneous melanoma (CM) is the fifth-most common malignancy in the United States, with a higher mortality rate than most skin cancers; however, most are diagnosed in early stages and have good outcomes. Under National Comprehensive Cancer Center (NCCN) guidelines, patients with <5% risk of sentinel lymph node biopsy (SLNB) positivity are not recommended for SLNB, those with a 5–10% risk may consider SLNB, and those with >10% risk are recommended for SLNB. NCCN guidelines recommend follow-up surveillance and imaging based on the risk associated with American Joint Committee on Cancer (AJCC) stage, and FDA-approved adjuvant therapy options are available for stages ≥IIB. However, certain qualifying patients may not benefit from increased procedures and therapy, which can cause complications and contribute considerable costs to patients and the healthcare system. The 31-gene expression profile test (31-GEP) stratifies risk as low (Class 1A), intermediate (Class 1B/2A), or high (Class 2B) and is validated to predict individual risk of SLNB positivity, melanoma recurrence, and metastasis. This study assessed the cost-effectiveness of 31-GEP guidance for melanoma management decisions versus using only clinicopathologic stage (AJCC-guided care).

Methods
We implemented a 2-step model to determine the cost-savings impact of 31-GEP-guided 1) SLNB and 2) clinical follow-up, imaging surveillance, and adjuvant therapy decisions in stage I–IIIA CM compared to AJCC-guided care using NCCN guidelines for 1,000,000 plan members from a commercial payor standpoint. Cost inputs were sourced from Merative MarketScan Commercial and Medicare Supplemental databases (2021-2022). Clinical inputs were sourced from SEER Incidence data (2018) and de-identified 31-GEP clinical order results (Castle Biosciences, Inc.).

Results
Compared to AJCC-guided management, 31-GEP-guided SLNB decisions saved $505,224.98, and 31-GEP-guided clinical visit follow-up, imaging, and adjuvant therapy decisions saved $2,681,951.58 over 5 years. The healthcare savings model calculated a total savings of $3,187,176.56 per 1,000,000 healthcare plan members over 5 years for 31-GEP-guided care compared to AJCC-guided care, a 29.6% decrease. Importantly, >90% of savings occurred during the first year post-diagnosis.

Conclusions
For patients with stage I-IIIA CM, 31-GEP-guided clinical management decisions result in substantial cost savings, especially in the first year, for commercial payors compared to AJCC-guided care.

A-436

The interest of dermascopy X400 technique interpreted by non dermatologists and an artificial intelligence software in the identification of pigmented genital lesions.

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Background
While genital mucosa-pigmented lesions are common, their clinical and dermoscopic appearance can be confusing. Confocal in vivo microscopy, however, has been shown in multiple studies to simplify the complexity of dermatoscopy pattern X20 (DX20). Our objective was to determine whether dermatoscopy X 400 (DX400), an alternative imaging technique, could further simplify the analysis of DX20 genital-pigmented lesions.

Methods
An observational, retrospective, monocentric study was conducted from October 2017 through April 2020, the time during which one hundred fifty-seven pigmented genital lesions seen in medical consultations were visualized under DX20 and DX400 dermatoscopes. DX20 images were read by three dermatologists with expertise in genital lesions dermatoscopy, while DX400 images were read by three general practitioners and three gynecologists with only one hour of dermatoscopy training in which four different dermatoscopy patterns were demonstrated to be sufficient to recognize characteristic melanosis.
The DX400 images were then analyzed by an artificial intelligence (AI)software: BelleAI Torus®.
Each physician and the AI were then evaluated on performance. The results were plotted on a ROC curve.

Results

Confidence Interval for AUC (Confidence level at 95%)			
Practitioner	ROC_AUC	Confidence Lower	Confidence Upper
AISystem	0,993	0,984	1
Gyneco3	0,914	0,887	0,938
Dermato3	0,888	0,859	0,916
G2	0,844	0,679	0,955
Dermato1	0,841	0,666	0,957
Dermato2	0,829	0,798	0,86
Gyneco1	0,806	0,773	0,838
G3	0,798	0,626	0,913
Gyneco2	0,793	0,758	0,825
G1	0,788	0,614	0,903

Distribution of pigmented genital lesions interpretation between non-dermatologists and general practioners G: General practioner
The results are shown in Table 1.

AI applied to Dx400 was the most performant . The dermatologist with the highest score was outperformed by the artificial intelligence and by a gynecologist without any prior experience in dermatoscopy. Through the new technique, the six non-dermatologist physicians excelled in using the DX400, demonstrating the ease with which the dermatoscopic patterns of the most common lesion, melanosis, can be simplified.

Conclusions
Our study suggests that by utilizing Dx400 for the exploration of pigmented lesions of the genital mucosa, non-specialists could be taught to recognize a limited but sufficient number of dermoscopic patterns. As a result, 1) identify melanosis, the most common benign tumor, 2) refer only pigmented tumors to specialist centers, and 3) improve the accessibility of these centers to complex and/or malignant tumors. Considering its high performance, ease of use, and affordability, 400x dermatoscopy could soon become a widely used screening tool for non-specialists, conducted in multidisciplinary health centers.

A-297

Unlocking Potential in Clinical Practice: A Comprehensive Assessment of an Artificial Intelligence Based Clinical Decision Support System for Cutaneous Melanoma Detection

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Background
Artificial intelligence (AI) based clinical decision support systems (CDSS) for cutaneous melanoma detection have demonstrated high diagnostic accuracy in retrospective studies. However, the transition to prospective clinical trials in authentic primary care settings remains limited.

Objective
To assess the diagnostic performance of an AI-based CDSS, operated through a dedicated smartphone application (app) for dermoscopic imaging, for cutaneous melanoma detection in real-life primary care settings.

Methods
Two prospective, multicentre trials were conducted in Sweden. The first trial involved fifteen primary care physicians (PCPs) in near-live simulations with the app [1]. The second trial, spanning 36 primary care centres, employed the app in a real-life clinical setting and provided a dichotomous decision support text to participating physicians [2]. Lesions underwent standard diagnostic procedures, which were compared to the app outcome.

Results
From the first trial, near-live simulations highlighted trust, usability and the clinical context when PCPs assessed the app's potential in practice. The second trial assessed a total of 253 lesions, identifying 21 melanomas. The AI-based CDSS app exhibited an area under the receiver operating characteristic (AUROC) curve of 0.960 (95% CI: 0.928-0.980) for all melanomas, indicating high diagnostic accuracy. For invasive melanomas (n=11), the AUROC was 0.988 (95% CI: 0.965–0.997), with a sensitivity and specificity of 100% and 92.6%, respectively.

Conclusions
The AI-based CDSS app shows promise in enhancing cutaneous melanoma detection in primary care. A following prospective, open, multi-centre clinical trial, with a cluster randomised crossover design, will evaluate the potential of the AI-based tool in real clinical decision making, underscoring its transformative potential in primary care for skin cancer detection.

References:

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[2] Panagiotis Papachristou, My Söderholm, Jon Pallon, Marina Taloyan, Sam Polesie, John Paoli, Chris D Anderson, Magnus Falk,, (2024), Evaluation of an artificial intelligence-based decision support for detection of cutaneous melanoma in primary care – a prospective, real-life, clinical trial, Oxford Academic, British Journal of Dermatology, https://doi.org/10.1093/bjd/ljae021

A-430

Usability of a smartphone app for skin cancer detection.

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Background
The incidence of skin cancer is increasing in Europe [1]. With new technologies available, there is growing interest in smartphone apps to assist the general population in early detection of skin cancer. Some of these apps have been officially classified as medical devices. However, few studies report on their performance in the hands of users in real-life conditions [2]. In this prospective study (ARTIS trial, ClinicalTRials.gov Identifier: NCT05246163), we investigated the influence of different conditions on the performance of one of the most documented skin cancer detection apps.

Methods
Between January 2021 and August 2023, we assessed the app in 1463 adult patients presenting with a suspicious lesion at the early access consultation of the Dermatology Department at Ghent University Hospital. Three different smartphones were used (Huawei P30 Lite, iPhone SE and Samsung Galaxy A52s5G).

Results
Between January 2021 and August 2023, 1904 lesions, of which 9.7% skin cancers, were assessed by a skin cancer app. Test performance is currently in analysis. In a subset of 625 lesions in 501 patients, including 53 skin cancers, 17 up to 19% of the lesions were undetectable by the app, depending on the smartphone type used. The primary reasons were the presence of distracting background details such as hairs, or the light color of the lesion.

In a second subset of 160 lesions in 147 patients, including 11 skin cancers, 71% of patients were unable to make an adequate picture for smartphone app analysis. In 9 out of 10 cases, this was because the lesion was in a hard-to-reach location. From a 45-degree angle, 43% of lesions could not be photographed. Notably, lighting conditions did not affect lesion detectability. The performance of the app did not differ between varying conditions of lighting and angle in which the smartphone was used.

Conclusions
Smartphone apps could have the potential to assist the general population in the early detection of skin cancer. Apart from the fact that clinical validation of the app performance is crucial, the presented results demonstrate that other conditions may also hamper real-life performance of skin cancer apps.
References:

[1] Adamson AS., (2023), The USPSTF I Statement on Skin Cancer Screening-Not a Disappointment but an Opportunity. , JAMA Dermatol., 579-581, 159(6)
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A-295

Use of 3-dimensional total body photography and digital dermoscopy with artificial intelligence algorithms for early melanoma detection in high-risk patients

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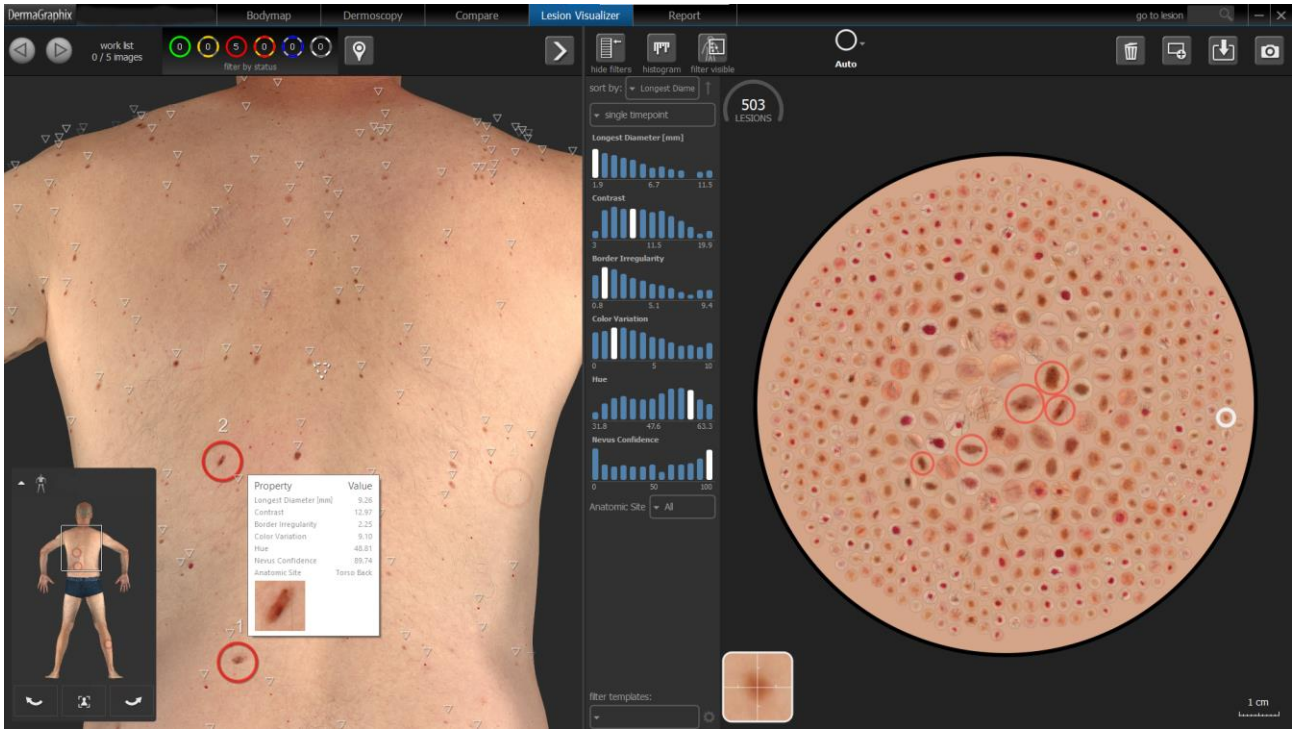
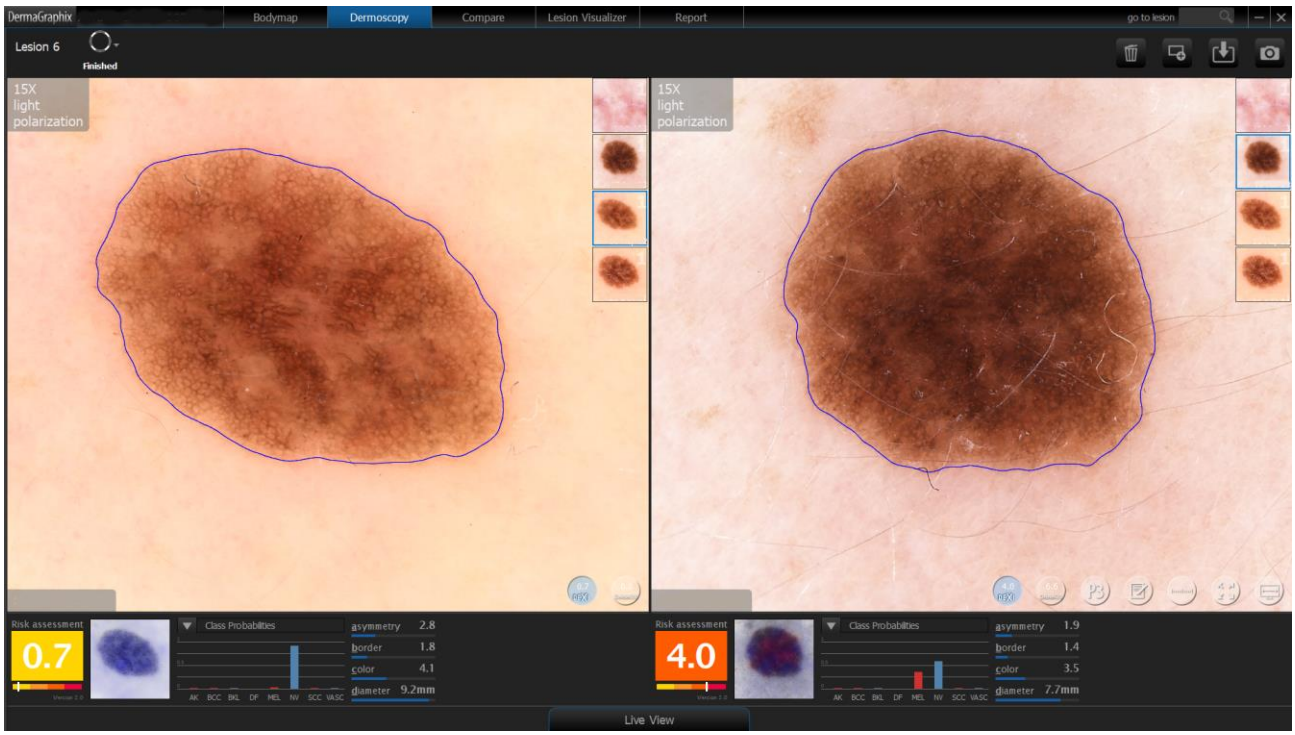
Background
Use of 3-dimensional total body photography (3D-TBP) improves visualization of anatomically complex areas and decreases image acquisition times. These devices include research-oriented '*machine learning*' (ML) algorithms which provide lesion counts, automatic change detection in maps and individual malignancy risk scores in digital dermoscopy (DD). The aim is to describe our experience with 3D-TBP and DD for early melanoma detection in patients at risk, and to describe ML algorithm outcomes.

Methods
Retrospective inclusion of high-risk melanoma patients on whom 3D-TBP and DD was performed between July 2021 and September 2023 in a tertiary center. Descriptive analysis of clinical, phenotypical, imaging and histological characteristics of excised lesions and ML results.

Results
A total of 2,929 3D-TBP maps were generated from 1053 patients (2.8 maps/patient); their mean age of 52.4 (SD 14.8) years and 558 (53.0%) were women. The total number of lesions under DD follow-up was 12,988 (12.3/patient). Three hundred and thirty-seven lesions were excised from 248 (23.6%) patients, 131 (38.9%) after the first 3D map and 206 (61.1%) after further maps. Of the lesions excised during follow-up maps, 47 (22.8%) were melanomas, 64 (31.1%) dysplastic nevi, 16 (7.8%) common nevi, 41 (19.9%) basal cell carcinomas, 8 (3.9%) squamous cell carcinomas, 8 (3.9%) solar lentigos and another 22 (10.7%) lesions were diagnosed. Of the melanomas diagnosed during follow-up, 28 (59.6%) were in situ, and the invasive melanomas (19, 40.4%) had a median Breslow index of 0.4 mm. Mean number of automatically segmented lesions per map was 816.8 (1195.6 in patients with excision *vs* 683.5 in patients with no excisions, $p < 0.005$). Mean malignancy DD score (in a scale from 0 to 10) was 5.3 for melanomas and 2.11 for dysplastic nevi. Of the melanomas diagnosed during follow-up 37 (78.7%) showed automatically detected changes, 1 (0.02%) did not present changes and in 9 no information was available.



3D total body photography and automatically segmented lesions from a patient at high-risk for melanoma



Digital dermoscopy images showing 'machine learning' malignancy score risk for a lesion with dermoscopic changes during follow-up

Conclusions

3D-TBP is useful for follow-up and early detection of melanoma in high-risk patients. It can be linked to ML algorithms with different applications which must be validated in clinical trials and may provide clinically useful information.

A-413

Using a clinicopathologic and gene expression model to predict prognosis in stage I-II primary cutaneous melanoma: a multicenter Danish cohort study

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Background
Melanoma patients without sentinel node metastasis (stage I-II) constitute a remarkably heterogeneous group regarding recurrence and survival. While adjuvant immunotherapy for stage IIB-C melanoma has gained approval from FDA and EMA, its use can lead to severe adverse effects and financial strain on healthcare systems. There is a need for new diagnostic approaches to more precisely identify early-stage melanoma patients at high risk of recurrence who could benefit from adjuvant treatment and intensified surveillance. The clinicopathological and gene expression profile model (CP-GEP), initially developed to predict sentinel node metastasis, has demonstrated promise in stratifying stage I-II melanoma patients into high and low risk of recurrence. This study aimed to validate the prognostic utility of the CP-GEP in an independent multicentre Danish cohort of stage I-II melanoma patients.

Methods
The study included 438 patients with T1-T3 cutaneous melanoma and negative sentinel node biopsies (stage I-II) performed between 2010 and 2015 at two university clinics in Denmark. Archived formalin-fixed paraffin-embedded primary melanoma tissue was collected, and CP-GEP was applied to each case. CP-GEP combines Breslow thickness and patient age with the expression of eight genes in the primary tumor, stratifying patients into high or low risk of recurrence. Data regarding recurrence was obtained from the Danish Melanoma Database. The primary outcome was 5-year recurrence-free survival (RFS), with 5-year overall survival (OS) as secondary outcome.

Results
CP-GEP stratified 199 patients as low-risk and 239 as high-risk. Preliminary results reveals that the CP-GEP low-risk group demonstrated a 5-year RFS of 92.0% (95% CI: 87.2-95.0) compared to 82.8% (95% CI: 77.4-87.1) in the high-risk group, with a hazard ratio (HR) of 1.75 (95% CI: 1.13-2.72), p=0.011). The 5-year OS was 92.5% (95% CI: 87.8-95.4) for the CP-GEP low-risk group vs. 86.6% (95% CI: 81.6-90.3) for the CP-GEP high-risk group (HR 1.65 (95% CI: 1.05-2.59), p=0.030).

Conclusions
CP-GEP can stratify stage I-II melanoma patients into high and low-risk for recurrence, suggesting its potential value in treatment decision-making and surveillance strategies for stage I-II melanoma.

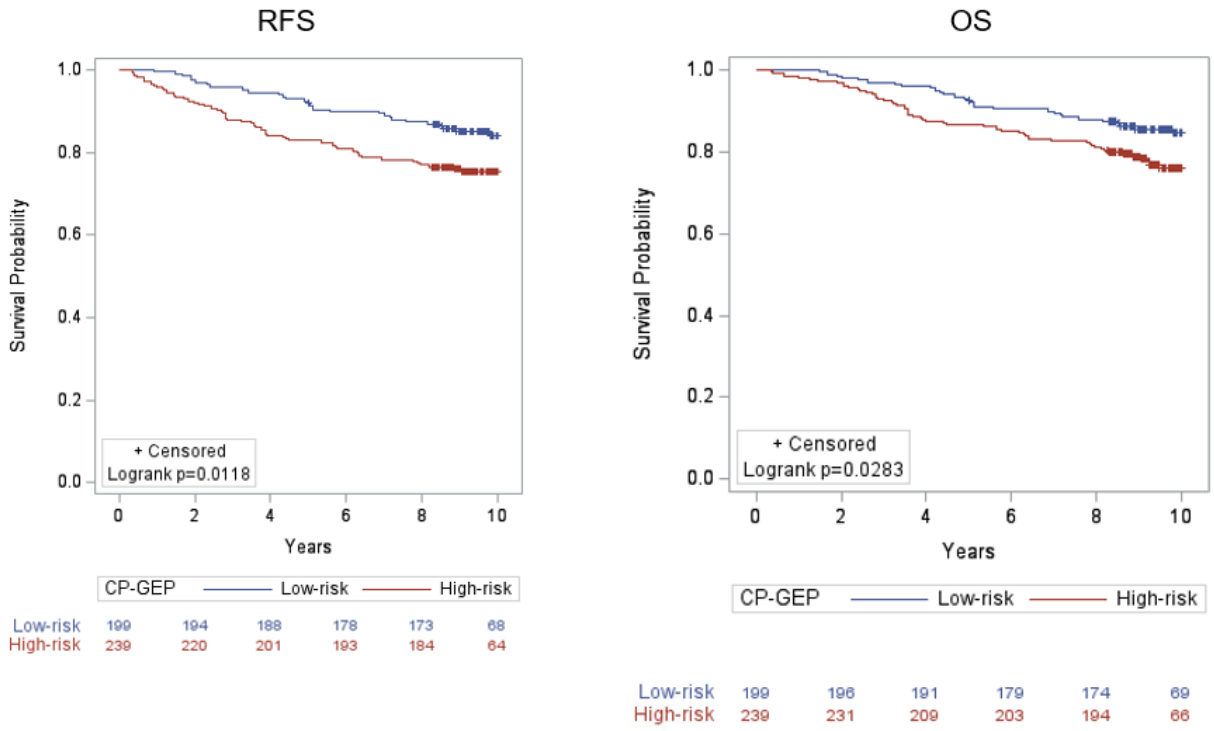

Figure 1. Kaplan–Meier survival curves (RFS, OS) for 438 stage I-II melanoma patients, stratified by CP-GEP classification. CP-GEP, clinicopathologic and gene expression profile model; OS, overall survival; RFS, recurrence-free survival.

A-356

Validation of the Melanoma Institute Australia Prediction Tool for Sentinel Node Metastasis Risk Amongst Patients with Cutaneous Head and Neck Melanoma

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Background

Accurate preoperative estimation of the risk of a positive sentinel node biopsy (SNB) is important for guiding individualised clinical decision-making regarding whether a patient should undergo this procedure. The Melanoma Institute Australia (MIA) Prediction Tool for Sentinel Node Metastasis Risk was developed to estimate the risk of a positive SNB based on 6 readily available clinicopathologic parameters. Cutaneous head and neck melanoma (CHNM) presents unique challenges for performing SNBs compared with cutaneous melanomas of other sites and may represent a biologically distinct entity. We aimed to validate the performance of the MIA Prediction Tool for patients with CHNM.

Methods

De-identified data for CHNM patients with an initial diagnosis between 2000-2018 who underwent a SNB were identified and extracted from the prospectively maintained MIA research database. ROC-curve and calibration plot analyses were performed using R 4.2.3.

Results

The analysis cohort consisted of 696 patients with all 6 input parameters available. The C-statistic for sentinel node positivity was 71.4% (95% CI 66.7-76.1). The calibration plot showed good calibration. Performance was similar in the CHNM population compared to the nomogram development population (p=0.33).

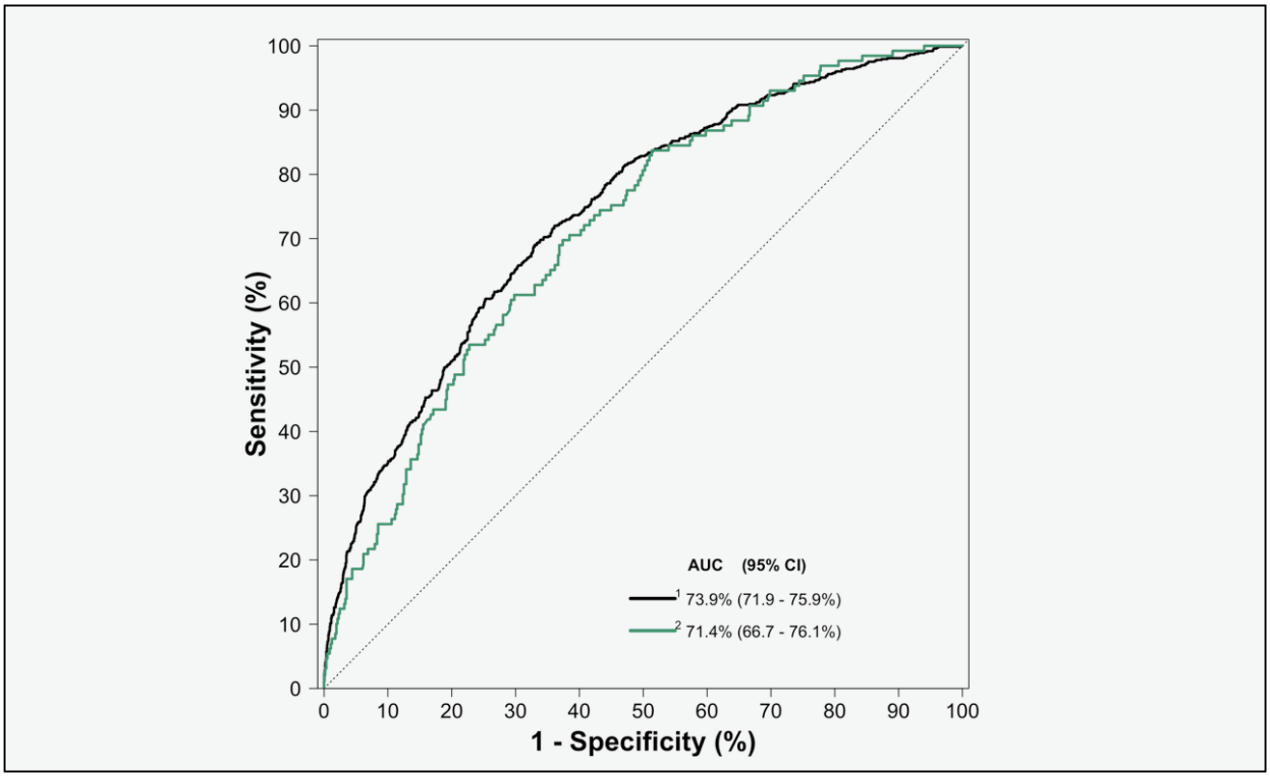

Figure 1 - ROC-curve for sentinel node positivity in the CHNM and nomogram development populations

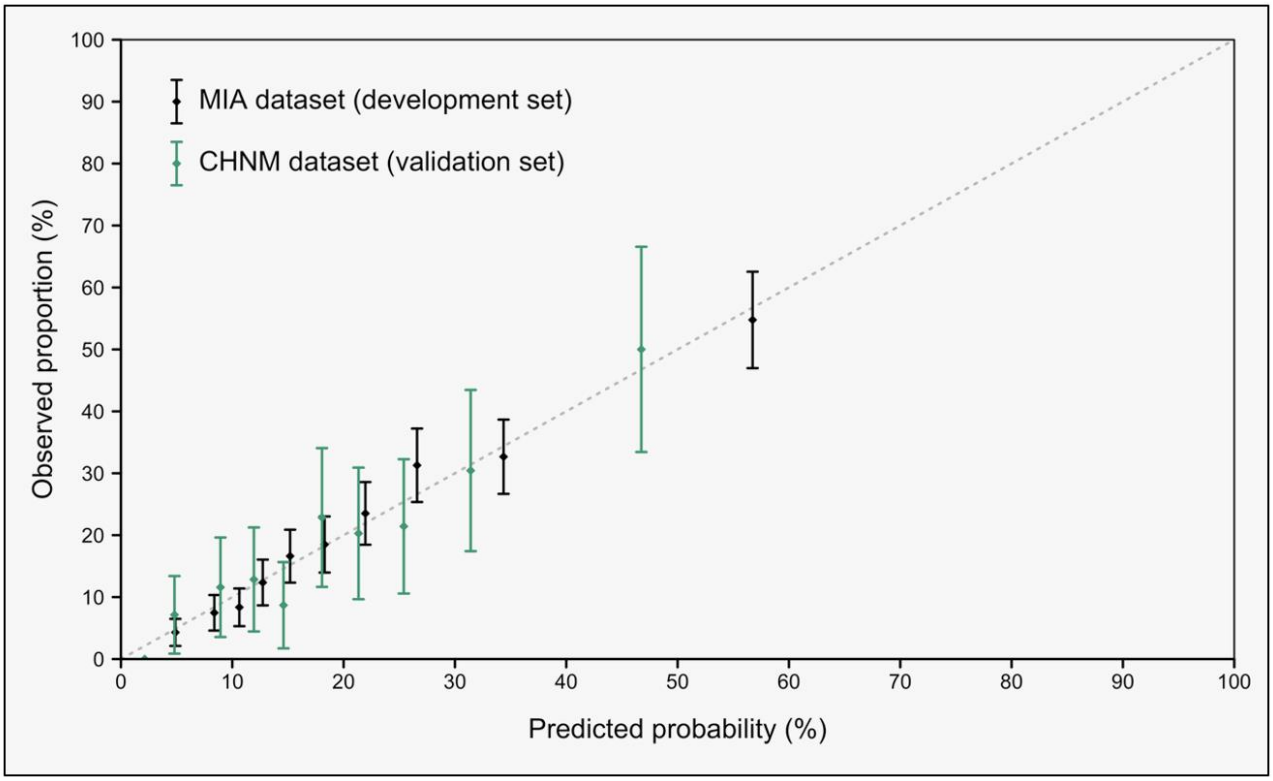

Figure 2 - Calibration plot for sentinel node positivity in the CHNM and nomogram development populations

Conclusions

The MIA Prediction Tool performed robustly in the CHNM population and is reliable for clinical use in this challenging patient subset.

A-429

“One spot check”; a new strategy to increase dermatology access for worrisome skin lesions.

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Background
According to the World Health Organization (WHO), one in three cancers diagnosed is skin cancer and its incidence will increase substantially in Europe by 2040. WHO recognizes that early diagnosis programs, aimed at reducing the number of late-stage diagnoses, are relevant for skin cancer. These programs should provide better access to healthcare. Nowadays dermatologists have long waiting lists and GPs often do not feel comfortable in evaluating skin lesions. Given the increasing incidence, we need strategies to ensure early diagnosis.
Conventional skin cancer screening is not cost-effective for the general population. To increase accessibility for the general population in case of worrisome skin lesions, our department of dermatology at the Ghent University Hospital offers the ‘one-spot check’, allowing individuals with a suspicious lesion to consult within 2 - 4 weeks [1]. Previous evaluation demonstrated a skin cancer detection rate of at least 10%. Additionally, it effectively reduces worry in patients diagnosed with a benign lesion [2].
We aim to provide an update on the skin cancer detection rate of the “one spot check” consultation.

Methods
This consultation is available to individuals aged 18 or more with a skin lesion meeting one of the following criteria: changing mole, 'ugly duckling’, new mole, non-healing or rapidly-growing lesion, or referred by GP or other healthcare provider.

Results
Between April 2021 and April 2023, 1517 individuals attended the early access consultation, of which 1246 adults gave informed consent. The median age was 54 years, with a male-female ratio of 2:3. The consultation provided access within 2 weeks in 80% of individuals, and within 4 weeks in 99%. [JK1] The skin cancer detection rate was at least 9.4% (142/1517), comprising 2.0 % melanomas (30/1517), 5.3% basal cell carcinomas (80/1517), and 2.4% squamous cell carcinomas (36/1517).

Conclusions
The high detection rate of skin cancer at the early access “one spot check” consultation was maintained in this larger updated series. The ‘one spot check’ could be a new strategy to increase dermatology access for worrisome skin lesions in view of the skin cancer epidemic.
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Melanoma – Experimental and translational studies

A-371

ALDH1A3-acetaldehyde potentiates melanoma heterogeneity

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Background
The perennial challenge in the clinical development of cancer therapies is that cancer cells frequently co-opt non-genetic mechanisms to switch between dynamic cellular states. This cellular plasticity enables cancer cells to adapt and thrive under environmental pressures such as immune surveillance, nutrient deprivation, or therapy. When patients with melanoma become resistant to MAPK inhibitor therapy, their tumour cells upregulate expression of the stem cell marker and aldehyde dehydrogenase enzyme ALDH1. Here, we uncover that ALDH1A3 functions as a master coordinator of metabolic and transcriptional cell states, fostering therapeutic resistance in melanoma by using acetaldehyde as an acetyl donor for histones to sustain glycolytic, stem-like gene expression programs.

Methods
We use a cross-disciplinary strategy of melanoma cell lines, low passage patient-derived melanoma cells, zebrafish models, and human patient datasets to discover how ALDH1A3 coordinates transriptional gene expression with metabolic states.

Results
We show ALDH1A3 forms an enzymatic partnership with acetyl-CoA synthetase 2 (ACSS2) in the nucleus to couple high glucose metabolic flux with acetyl-histone H3 modification of neural crest stem cells (NCSCs) and glucose metabolism genes. Importantly, NCSC cell states have been shown to be enriched in melanoma residual disease, and to be predictive of patient outcomes. Critically, we show acetaldehyde is a metabolite source for acetyl-histone H3 modification dependent on ALDH1A3, providing a physiologic function for this highly volatile and toxic metabolite. In a zebrafish model of melanoma residual disease and persister cells, a subpopulation of ALDH1A3-high cells emerges following BRAF inhibitor treatment and targeting these with an ALDH1 suicide inhibitor, nifurtimox, delays or prevents BRAF inhibitor drug-resistant relapse

Conclusions
Our work reveals that ALDH1A3-ACSS2 directly coordinates local acetaldehyde-acetyl-CoA metabolism with specific chromatin-based gene regulation and represents a potential therapeutic vulnerability in melanoma in residual and recurrent disease.

The conceptual framework we present here for melanoma may be broadly applicable to $ALDH^{High}$ cancer stem cell subpopulations in other cancer types, as ALDH isoforms potentially cooperate with lineage specific master transcription factors (often from developmental lineages) that are co-opted to regulate tumour cell states.

A-180

AMBRA1 is a predictive biomarker of melanoma response to targeted therapy

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Background
The application of mitogen-activated protein kinase inhibitors (MAPKi) in the treatment of melanoma continues to pose a therapeutic obstacle due to the pre-existence or emergence of therapy resistance. Genetic alterations or tumor evolution processes have been described as mechanisms that coordinate this event. Prior data suggests that the absence of the Autophagy and Beclin 1 Regulator 1 (AMBRA1) enhances the growth and metastasis of melanoma [1]. In this study, we demonstrate the clinical significance of AMBRA1 expression levels as a predictive biomarker for both intrinsic and acquired resistance to MAPKi in melanoma.

Methods
This study was performed using an Ambra1-depleted $Braf^{V600E}/Pten^{-/-}$ genetically engineered mouse model of melanoma, as well as a panel of human/murine melanoma cell lines with different levels of AMBRA1. Molecular and biochemical approaches were used to analyse the effects of AMBRA1 loss in MAPKi response. Resistant melanoma cell lines were generated upon chronic exposure to MAPKi. Transcriptome analyses of human melanoma patients (The Cancer Genome Atlas, GSE50509, GSE65185) and proteomic analyses of human melanoma cells (The Cancer Cell Line Encyclopedia) were applied to associate MAPKi response to AMBRA1 expression levels. Tumor growth kinetics in Ambra1-depleted $Braf^{V600E}/Pten^{-/-}$ mice and colony formation assay in $AMBRA1^{HIGH/LOW}$ human melanoma cells were evaluated after administration of MAPKi alone or in combination with focal adhesion kinase 1 (FAK1) inhibitor.

Results
Functional studies reveal that the loss of AMBRA1 activates FAK1 and promotes phenotype switching. Melanomas with low AMBRA1 expression show innate resistance to MAPKi treatment but increased sensitivity to FAK1 inhibition both *in vitro* and *in vivo*. Lastly, we demonstrate that pre-existing subclones with low AMBRA1 expression are responsible for the fast development of resistance in initially MAPKi-sensitive melanomas, and that co-treatment of MAPKi and FAK1 inhibitors effectively halts the development of resistance in these tumors.

Conclusions
Our research highlights the significance of AMBRA1 in predicting the melanoma response to MAPKi and provides proof of the therapeutic effectiveness of FAK1 inhibitors in overcoming MAPKi resistance.

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A-392

Cell cannibalism: a possible source of therapy resistant melanoma-fibroblast hybrids

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Background

Cell cannibalism is classified as a form of cell-in-cell interaction that can be formed between a non-professional phagocytic dermal fibroblast and melanoma cells inside the primary tumor. However, its relations to fibroblast-melanoma hybrid cell formation and functional (possible therapeutic) aspects are partially elucidated. Therefore, we aimed to visualize and enrich the spontaneously formed fibroblast-melanoma hybrids by in vitro coculture experiments using high-content fluorescent microscopy.

Methods

By in vitro coculturing of the stable transfected human UACC 257-GFP-NeoR (zeocin sensitive) melanoma cells and human HDF-RFP-ZeoR (zeocin resistant) fibroblasts, the morphology of the spontaneously formed double positive melanoma-fibroblast hybrids were visualized and underwent detailed cellular phenotyping. To enrich the scattered and rare spontaneous melanoma-fibroblast hybrids, single zeocin selection was preferred for eliminating the parental single melanoma cells but for preserving the zeocin-resistant fibroblast stroma to elongate the lifespan of the rare hybrid cells for the long-term coculturing.

Results

After a spontaneous melanoma cell was engulfed by stromal fibroblast, the visualized cellular morphology of this cell-in-cell formation called intermediate hybrid was dominated by stromal phenotype. However, the double (GFP-RFP) positive fibroblast-melanoma hybrid cells often ended up in various cancer associated- or myofibroblast-like forms. These heterotypic tumor-stromal hybrids were indistinguishable from the surrounding stromal parental fibroblasts but showed double (GFP-RFP) positive fluorescent signals. Interestingly, all of these hybrid morphologic variants were significantly enriched by the single zeocin-treated coculture experiment, in which the survived GFP-RFP positive fibroblast-melanoma hybrids originating from zeocin-sensitive melanoma parentals became resistant to zeocin.

Conclusions

The heterotypic melanoma-fibroblast cellular cannibalism can be considered as a defensive mechanism by the stromal cells for the elimination of the melanoma cells. However, as an escape, it may result in melanoma-fibroblast hybrids gained stromal cell mimicry and new functional abilities on therapy resistance.

A-167

Circulating tumor DNA: a promising biomarker in stage III BRAF+ melanoma

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Background

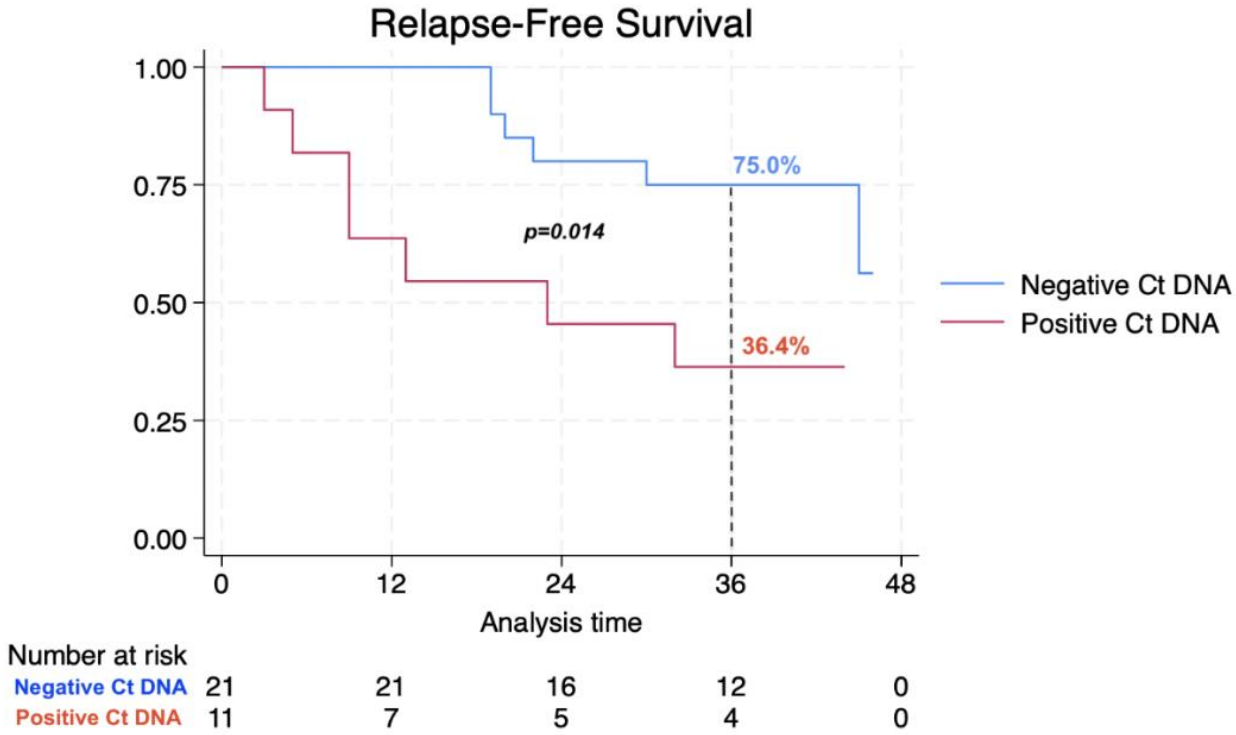
In recent years, various melanoma biomarkers have undergone investigation in both preclinical and clinical settings. Among these, circulating tumor DNA (ctDNA) has emerged as a promising candidate. However, in the adjuvant setting, only a limited number of exploratory analyses have been conducted, and uncertainties persist regarding the link between ctDNA detection and patients' relapse.

Methods

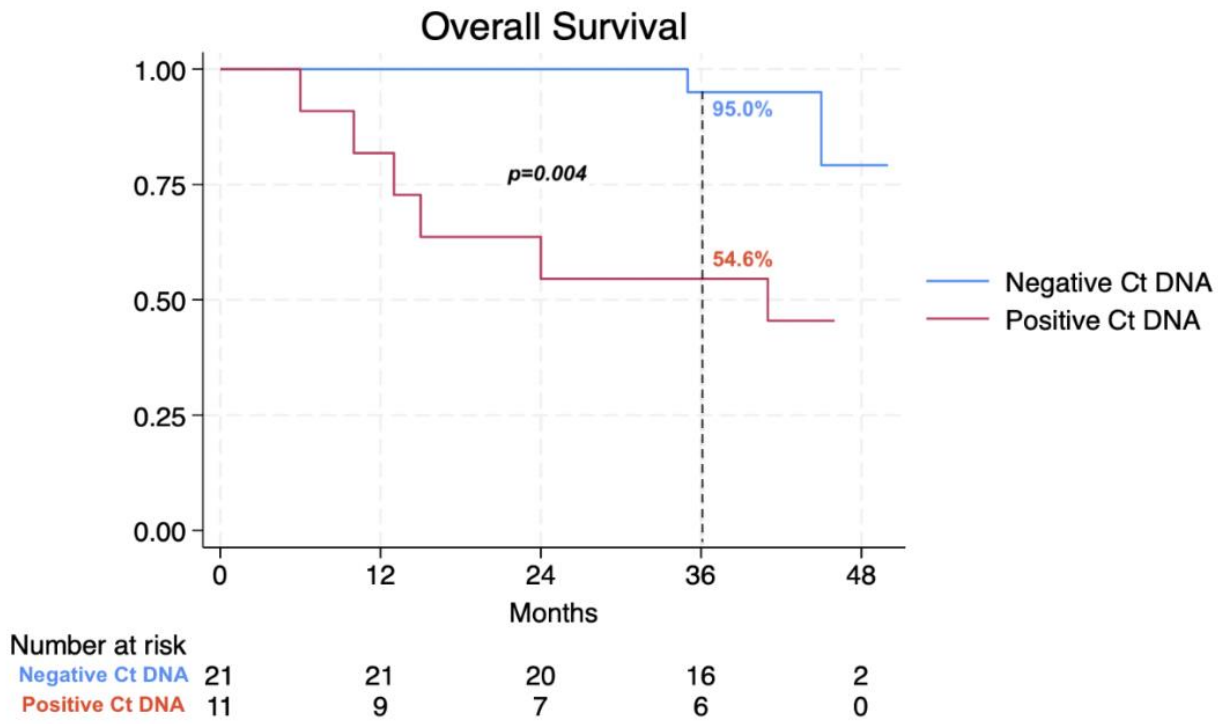
A cohort of 32 patients with resected stage III BRAF+ melanoma, who were diagnosed and underwent adjuvant therapy with either anti-PD1 or dabrafenib/trametinib, was collected from 2019 to 2021 and followed up until December 2023. A sensitive multiplexed digital droplet (dd)-PCR was used to detect and quantify the three most common hotspot mutations in codon 600 (V600E, V600R, V600K) of the BRAF oncogene in circulating free DNA isolated from plasma. Blood samples were retrieved monthly post-surgery, starting from the initial administration of adjuvant therapy. Samples were classified as mutated when the number of copies/reaction exceeded the limit of blank (LOB = meanblank + 1.645*SDblank).

Results

At 36 months, the overall recurrence-free survival (RFS) for the cohort was 61.6%. Stratifying by basal circulating tumor DNA (ctDNA) status, those with negative ctDNA exhibited significantly higher 36-month RFS (75.0%) compared to the positive group (36.4%) (p=0.014). Cox univariate analysis identified in-transit metastasis (HR 4.20, 95% CI 1.11-15.87, p=0.034) and positive basal ctDNA (HR 3.79, 95% CI 1.20-12.00, p=0.023) as significant risk factors for relapse.



The 36-month overall survival (OS) rate was 80.8%, with a significant difference between negative basal ctDNA (95.0%) and positive groups (54.6%) (p=0.004). Cox univariate analysis for OS revealed in-transit metastasis (HR 9.44, 95% CI 1.89-47.16, p=0.006), relapse during adjuvant therapy (HR 24.58, 95% CI 2.65-228.08, p=0.005), and positive basal ctDNA (HR 7.92, 95% CI 1.56-40.36, p=0.013) as significant predictors of death.



Notably, basal ctDNA showed no correlation with clinical stage or basal LDH levels (p=0.324, Spearman test, logit p=0.1621).

Conclusions

Basal ctDNA status may outperform clinical stage and LDH values in predicting relapse and survival in stage-III melanoma. It shows significant potential for forecasting treatment response and outcomes, advocating for broader evaluation in patients undergoing adjuvant therapy.

A-387

Discoidin domain receptor 1, a melanoma immunomodulator

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Background

While immune checkpoint inhibitors (ICIs) have revolutionized the management of melanoma, increasing the overall 5-year survival to 50%, treatment failure is a frequent phenomenon that greatly limits their clinical benefit. One of the main mechanisms of resistance is immune exclusion [1]. The discoidin domain receptor 1 (DDR1), a tyrosine kinase receptor involved in cancer progression, has been shown to play a role in immune exclusion of triple-negative breast cancer by preventing immune cell infiltration via collagen fibers reorganization [2]. Our aim in this preliminary study is to study the potential role of DDR1 in tumor-induced immunomodulation in melanoma.

Methods

The impact of DDR1 inhibition on immune cells activation was studied through co-culture experiments of peripheral blood mononuclear cells (PBMC) from healthy donors with the human melanoma cell line A375 wild type (WT) or presenting DDR1 down-expression upon introduction of DDR1-shRNA. Analyses of the modulation of immune cell activation (NK and T cells) were explored by flow cytometry. Cytokines synthesis has been assessed using Simoa Quanterix multiplexing assay and confirmed by flow cytometry.

Results

In vitro inhibition of DDR1 expression in A375 human melanoma cell line leads to the detection of increased percentage of activated T lymphocytes and NK cells. Indeed, higher percentage of CD69+ and interferon gamma (INF-γ) expressed by T and NK lymphocytes are observed in A375-DDR1 shRNA cells when compared to shRNA control cells. Moreover, analysis of cytokines release in the co-culture supernatants shows decreased level of IL-6 when PBMC are co-cultured with A375-shRNA DDR1 cell compared to control cells.

Conclusions

Our preliminary results suggest a role in immunomodulation of DDR1 expressed in A375 melanoma cells, prompting to further confirmation and explorations to better decipher its mechanism of action in melanoma immunotherapy resistance.

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A-217

Effects of temozolomide on tumor mutation burden and microsatellite instability in melanoma cells

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Background
The efficacy of combination therapy with an immune checkpoint inhibitor (ICI) and cytotoxic chemotherapeutic agents has been investigated in cancer including melanoma. Before ICIs were introduced, dacarbazine or temozolomide (TMZ) were used to treat melanoma. Several studies using glioma or colorectal cancer cells showed that TMZ can increase the tumor mutation burden (TMB) and induce mismatch repair (MMR) deficiency associated with microsatellite instability (MSI). These could increase immunoreactivity to ICI, but this has not been evaluated in melanoma cells. We investigated the effects of TMZ on MSI status and TMB in melanoma cells.

Methods
To evaluate the TMB, we performed whole-exome sequencing using genomic DNA from the human melanoma cell lines Mel18, A375, WM266-4, G361, and TXM18 before and after TMZ treatment. PCR amplification of five mononucleotide repeat markers BAT25, BAT26, NR21, NR24, and MONO27 was performed, and we analyzed changes in the MSI status.

Results
In all cell lines, the TMB was increased after TMZ treatment (the change amount of TMB with 5% ≤VAF [variant allele frequency] was 18.0–38.3 mutations per megabase) even in the condition without obvious cytological damages. MSI after TMZ treatment was not observed in any cells.

Conclusions
TMZ increased TMB but did not change MSI status in melanoma cells.

A-368

Elevating MAPK Pathway Suppression with Combinatorial ERK Inhibitors

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Background

The advent of small molecule inhibitors specifically designed for BRAF mutations at V600, along with their downstream target MEK, marked a significant advancement in treating BRAF mutant melanoma. Despite their notable anti-tumor activity and enhanced patient survival, the rapid emergence of resistance poses a significant challenge, limiting their clinical efficacy. Various resistance mechanisms have been documented, with a common feature being the reactivation of the MAPK signaling pathway, primarily mediated by extracellular signal-regulated kinases 1 and 2 (ERK1/2).

Methods

The ERK1/2 inhibitor (ERKi) **ravoxertinib (GDC0994)** was tested in monolayer culture on different melanoma cell lines with/without an acquired resistance to either BRAF inhibitor (BRAFi) monotherapy or its combination with a MEK inhibitor (BRAFi + MEKi). To evaluate the efficacy of the drug, we tested its short-term impact on cell viability, the induction of apoptosis via cell cycle analyses, the pathway blockade/induction via Western Blot and the long-term effect in a colony formation assay.

Results

Melanoma cell lines with an acquired resistance to BRAF inhibitors or to the combination of BRAF and MEK inhibitors as well as the respective parental cells responded to long-term treatment with the ERK1/2 inhibitor by reduction of melanoma cell growth, which seemed to be independent of the sensitivity to BRAF or MEK inhibitors. Moreover, cell cycle analyses and cell viability assays revealed a distinct benefit of adding ERK1/2 inhibitor to BRAF and/or MEK inhibitors to effectively target the melanoma cells with BRAF mutation.

Conclusions

In conclusion, our results show that the ERK1/2 inhibitor ravoxertinib (GDC0994) exerts only limited anti-tumor activity as a monotherapy. However, the combination of ERKi and BRAFi/MEKi causes growth inhibition and apoptosis in BRAF mutated melanoma cells irrespective of the sensitivity to BRAF or MEK inhibitors. Additional ERKi is effective especially in a chronic, long-term setting. Combinatorial treatment regimens including ERK1/2 inhibitors might be an attractive, novel therapeutic strategy in BRAF mutated melanoma cells.

A-426

Gene Signatures predict immune-related skin adverse events in melanoma patients

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Background
Immune checkpoint inhibitors (ICIs) has radically changed the prognosis of patients (pts) with melanoma. Starting from metastatic disease, indeed anti-PD1 have also become the standard of care as adjuvant therapy in high-risk resected melanoma. Nevertheless, 65–80% of pts treated with ICI experience immune-related adverse events (irAEs) causing morbidity and a potential decrease in benefit/risk ratio. Currently, there are no biomarkers that can predict which pts are at risk of developing irAEs after PD-1 inhibition. The aim of this study is to identify predictive biomarkers of irAEs secondary to anti-PD1 treatment.

Methods
Gene profiling analysis was performed using NanoString IO360 panel from PBMCs of pts with cutaneous melanoma treated with anti-PD1 (pembrolizumab or nivolumab) in both clinical setting (adjuvant and first line therapy). Sparse Partial Least Squares Discriminant Analysis (sPLS-DA) was applied to identify the most predictive gene signature, ROC curves to determine the optimal predictive cut off.

Results
Among 161 melanoma pts included, 75 received anti-PD1 as adjuvant therapy (AT) and 86 as first line therapy (FLT). Skin toxicity were observed in 45% of total population (51% and 41% respectively in AT and FLT). Specific gene signatures for predicting the onset of skin toxicity in AT has been identified and characterized by the most representative genes such as: ITGA1, EGFR, DUSP5, DLL1 and ADAM12 involved in the leukocyte adhesion and cell proliferation. Differently, the gene signature for predicting the onset FLT is mainly characterized by genes related to responses and cells grown such as: VHL, TNFRSF8, HIF1A, ESR1 and CXCR3. In both cases, the high signature score is associated with a greater probability of toxicity onset. These results were also confirmed using the toxicity free survival curve in AT (HR: 6.4, 95% CI 2.22–18.04; p=0.0001) and FLT group (HR: 4.60, 95% CI 1.19–11.20; p=0.0002). In contrast no skin toxicity were observed in pts with low signature scores. Furthermore, body mass index (BMI) was associated with a greater risk of skin irAEs (p=0.02) in FLT group.

Conclusions
In this retrospective study, we identify gene signatures model associated with the onset of skin toxicities related to anti-PD1 treatment in stage III/IV unresectable and resected stage III melanoma pts. Further investigations are needed in order to validate the signature in an independent dataset.

A-292

High dose Vitamin D supplementation does not improve outcome in a cutaneous melanoma population: results of randomized a double-blind, placebo-controlled study (ViDMe trial)

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Background
Observational studies in cutaneous melanoma have indicated an inverse relationship between levels of 25-hydroxy vitamin D and Breslow thickness, as well as a protective effect of high 25- hydroxy vitamin D levels on clinical outcome.
This study aimed to evaluate whether high vitamin D supplementation in curatively resected malignant melanoma reduces melanoma relapse.

Methods
In a prospective, double-blind, placebo-controlled trial, 436 patients with resected cutaneous melanoma stage IA to III (8th American Joint Committee on Cancer staging) were randomized. Among them, 218 received a placebo while 218 received monthly 100,000 IU cholecalciferol for a minimum of 6 months and a maximum of 42 months. Following randomization, patients were followed for a median of 52 months, with a maximum follow-up of 116 months. The primary endpoint was relapse-free survival. Secondary endpoints were melanoma-related mortality, overall survival, and the evolution of 25-hydroxy vitamin D serum levels over time.

Results
In our population (mean age 55 years, 54% female) Vitamin D supplementations increased 25- hydroxy vitamin D serum levels after 6 months supplementation in the treatment arm by median 17 ng/ml (9;26) compared to 0 ng/ml (-6;8) in the placebo arm (P< 0.001; Wilcoxon test) and remained at a steady state during the whole treatment period. The estimated event rate for relapse-free survival at 72 months after inclusion was 26.51% in the vitamin D supplemented arm (95% CI: 19.37;35.64) versus 20.70% (95%CI: 14.26;29.52) in the placebo arm, [hazard ratio 1.27 (95%CI 0.79;2.03), P=0.32]. After adjusting for confounding factors (including baseline stage, body mass index, age, gender, and baseline season), hazard ratio was 1.20 (95% CI 0.74;1.94, P=0.46). Deaths from progression of cutaneous melanoma and non-melanoma related deaths were similar in both vitamin D supplemented and placebo group (n=10 and 11 and n=3 and 2, respectively). Vitamin D supplementation was safe, and no major adverse events were observed during the study.

Conclusions
In cutaneous melanoma patients, monthly high dose vitamin D supplementation was safe, resulted in sustained increase in 25-hydroxy vitamin D levels during the treatment, but did not improve relapse-free survival, melanoma-related death or overall survival.

A-369

Identification of patients at high risk for relapse by Merlin Assay (CP-GEP) in an independent cohort of patients with melanoma who did not undergo sentinel lymph node biopsy: head and neck subgroup analysis

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Background

Sentinel lymph node biopsy (SLNB) is still the gold standard for nodal assessment used in the clinical staging of cutaneous melanoma (CM) pts by AJCC v8. Recently, we showed in a small cohort that CP-GEP also has the potential to risk stratify pts who did not undergo SLNB in low and high-risk for recurrence (Amaral et al., EJC 2023). SLNB may be challenging in pts with head and neck (H&N) melanoma due to the regional course of cranial nerves and lymphatic drainage. Here, we focus on the ability of CP-GEP to stratify pts with H&N melanoma who did not undergo SLNB for their risk of recurrence.

Methods

We analyzed formalin-fixed paraffin-embedded primary tumor samples of 451 pts with stage I/II CM diagnosed between 2000-2017, included in the Central Malignant Melanoma Registry, who did not receive SLNB. The CP-GEP model used combines the expression of 8 genes (SERPINE2, GDF15, ITGB3, CXCL8, LOXL4, TGFBR1, PLAT, and MLANA) by quantitative reverse transcription polymerase chain reaction with age and Breslow thickness to obtain a binary output: CP-GEP Low- or High-Risk. Relapse-free survival (RFS), distant metastasis-free survival (DMFS), and melanoma-specific survival (MSS) were evaluated using Kaplan-Meier curves.

Results

We included 451 pts (stage IA-IIC); 40% were females, the median age was 63 years old, the median Breslow thickness was 0.5 mm, and 20% (n=90) were diagnosed with H&N melanoma. An interim analysis was performed on samples from 159 pts, showing the following survival: 5-year RFS 85.8%, DMFS 94.1, and MSS 95.7%. Survival analysis for pts with H&N melanoma is currently being conducted and will be presented at the time of the congress.

Conclusions

CP-GEP has the potential to risk stratify pts with early-stage melanoma who did not undergo SLNB according to their risk for recurrence. Pts with CP-GEP Low-Risk have a good long-term survival compared to pts with High-Risk, even though SLN status was not assessed. This also seems true for patients with H&N melanoma, which may allow clinicians to skip SLNB in this difficult anatomic localization.

A-140

Immunohistochemical analysis of AMBRA1 and loricrin expression reveals maintained expression in the epidermis overlying a range of benign melanocytic naevi but which may be altered in some melanoma in situ cases.

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Background
The epidermal expression of AMBRA1 and Loricrin overlying primary melanomas has recently been validated as a prognostic biomarker able to identify genuinely low risk non ulcerated AJCC Stage I/II tumours (Ewen et al 2024, BJD, in press). It has previously been shown that the loss of these biomarkers is due to secretion of TGFbeta by the underlying melanocytes. The objective of the present study was to evaluate the potential for the combined expression of AMBRA1 and loricrin to characterise a range of benign melanocytic naevi and melanoma in situ.

Methods
Formalin fixed paraffin embedded tissue sections derived from 5 intradermal naevus , 16 dysplastic naevus (severe/moderate), 5 junctional naevus, 5 compound naevus and 26 melanoma in situ cases from the Cellular Pathology archive of Newcastle upon Tyne Hospitals NHS Foundation Trust were subjected to automated immunohistochemical analysis for AMBRA1 and loricrin expression. Staining patterns and expression were evaluated using consensus scoring by the study cellular pathologists (AH, PS).

Results
All of the benign and dysplastic melanocytic naevi examined showed maintenance of both AMBRA1 and loricrin in the epidermis overlying the lesion, in line with their expression in normal skin. A maintained pattern was also seen in 24/26 melanoma in situ cases but two cases displayed focal losses of both AMBRA1 and Loricrin. On review both cases showed no evidence of melanoma in further levels and there was no clinical progression.

Conclusions
The maintained pattern of AMBRA1 and loricrin was expected in the melanocytic naevi and is consistent with their benign nature. However, loss of expression of AMBRA1/Loricrin in two cases of melanoma in situ was unexpected, suggesting that some melanoma in situ cases may contain melanocytes with malignant potential. Collectively these data warrant the further investigation of AMBRA1 and Loricrin expression in a larger cohort to investigate their potential as biomarkers to distinguish between benign melanocytic lesions and melanomas at risk of malignant progression.

A-259

Is There a Distinctive Molecular Identity for Sinonasal Malignant Mucosal Melanoma Compared to Cutaneous Melanoma?

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Background

Sinonasal malignant mucosal melanoma (SNMM) is an aggressive, rare melanoma subtype with a 5-year survival rate of approximately 25%, significantly lower than the 53-97% observed in localized cutaneous melanoma (CM). Characterized by a diminished response to immunotherapy and targeted therapies, SNMM highlights limited treatment options and the urgent need for effective systemic therapies. This necessitates a deeper understanding of its pathophysiology and molecular characteristics to identify novel therapeutic targets. The objective of this study was to identify genetic signatures in SNMM that could enhance the understanding of its molecular mechanisms.

Methods

This retrospective study analysed 37 primary tumour samples of melanoma (SNMM: 13; CM: 24) diagnosed at the Melanoma Unit, Dermatology, Hospital Clinic of Barcelona. Gene expression of all primary tumours was analysed using 1402 Immuno-Oncology probes via HTG EdgeSeq technology, a next-generation sequencing-based method. Unsupervised hierarchical cluster analysis (UHCA), differentially expressed genes (DEGs) analysis and gene set enrichment analysis (GSEA) were performed to identify potential molecular pathways differences. Statistical analysis included the use of Fisher's exact test for categorical data and Student's t-test for continuous variables.

Results

UHCA revealed two primary clusters. Cluster A exclusively contained CM tumours (20/24) and Cluster B included all SNMM (13/13) and some CM (4/24), further divided into Subcluster B1, containing the majority of SNMM cases (9/13), and Subcluster B2, mixed SNMM (4/13) and CM (4/24). Clinically, Cluster B showed a higher average age (70.21 years, SD = 14.91) compared to Cluster A (58.61, SD = 13.06; $p = 0.018$). BRAF mutations were significantly more prevalent in Cluster A (45%, 9/20) compared to Cluster B (0%, 0/17; $p = 0.002$). No significant mitotic index differences were observed. Differential gene expression analysis between Cluster B and A identified 602 DEGs. The GSEA indicated a positive enrichment of cell cycle-related pathways and a negative enrichment of immune-related pathways in Cluster B.

Conclusions

This study highlights the molecular differences between SNMM and CM, providing insights into the molecular behaviour of SNMM. The distinct pathways identified in SNMM contribute to understanding its biology and identifying new therapeutic targets.

A-375

Kindlin-3 inactivation mediates melanoma agressiveness through crosstalk with the collagen-activated tyrosine kinase receptor DDR1

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Background

The role of the focal adhesion protein Kindlin-3 as a tumor suppressor and its interaction mechanisms with extracellular matrix constitute a major field of investigation to better decipher tumor progression. Besides the well-described role of kindlin-3 in integrin activation, evidence regarding modulatory functions between melanoma cells and tumor microenvironment are lacking and data are needed to understand mechanisms driven by kindlin-3 inactivation. In this study, we explored the inactivation of the tumor suppressor kindlin-3 in promoting melanoma progression through microenvironment regulation.

Methods

The impact of kindlin-3 inactivation on proliferation, migration, invasion and adhesion was studied through knockdown or somatic mutations in 4 melanoma models (A375, A2058, SKMEL5, WM266.4) *in vitro* and *in vivo.* Mechanisms involved in the aggressive phenotype of kindlin-3 inactivated melanoma cells were explored using transcriptomic analyses, functional assays, western blot and proximity ligation assays. The prognostic role of kindlin-3 expression and its partners in clinical setting was studied by immunohistochemistry performed on 45 *in situ* patient melanoma lesions.

Results

In vitro, kindlin-3 inactivation through knockdown or somatic mutations decreases cell adhesion and enhances proliferation, migration and invasion thus increasing *BRAF*^{V600mut} melanoma cells oncogenic properties via collagen-related pathways. In mice, kindlin-3 somatic mutations (p.Glu25Gly, p.Gly44Arg, p.Pro95Leu and p.Gly396Arg) increase tumor growth.

Mechanistic analysis reveals that kindlin-3 interacts with the collagen-activated tyrosine kinase receptor DDR1 (Discoidin domain receptor 1) modulating its expression and its interaction with β1-integrin. Kindlin-3 knockdown or mutational inactivation disrupt DDR1/β1-integrin complex *in vitro* and *in vivo* and its loss improves the anti-proliferative effect of DDR1 inhibition. These data were strengthened in a primary melanoma cohort demonstrating that kindlin-3 downregulation is associated with worse prognosis (overall survival) and with DDR1 over-expression.

Conclusions

Our study reveals a unique mechanism of action of kindlin-3 in the regulation of tumorigenesis mediated by the collagen-activated tyrosine kinase receptor DDR1 thus paving the way for innovative therapeutic targeting approaches in melanoma.

A-123

Macrophages: A Key Population for the Resistance Acquisition in BRAF Mutant Melanoma

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Background

Melanoma is one of the most aggressive human tumours that arises from the uncontrolled proliferation of melanocytes. Despite many important advances, development of resistance remains a significant obstacle to melanoma curability. One of the key components of the resistance is the cancer–associated inflammation that promotes tumorigenesis at many levels.

We aimed to characterize macrophages that infiltrate tumors of BRAF inhibitor sensitive and resistant melanoma and to describe how melanoma resistant cells support alternatively activated macrophages that promote tissue repair and tumor progression.

Methods

Syngeneic mouse modelsemploying 5555 basal and 5555 Vemurafenib (Vem) resistant melanoma cells were performed using C57BL/6mice. Once the tumour was established, mice were sacrificed. Subsequently, we performed a protocol to achieve rapidly a single–cell suspension from tumor to further describe the phenotype of the immune cells by flow cytometry analysis.

Peripheral blood mononuclear cells (PBMCs) from healthy donors were obtained from anonymized human blood supplied by the Hospital Universitari Arnau de Vilanova de Lleida. The PBMCs isolation was performed by a Ficoll–Paque density gradient separation. Finally, we study the macrophage phenotype after treatment with the conditioned media (CM) of Vemurafenib–sensitive and resistant melanoma cells.

Results

The macrophage population that infiltrates tumors from Vemurafenib resistant melanoma cells shows an increase of M2–type TAMs positive for CD206+ and Arg+ compared with Vemurafenib sensitive melanoma tumors. Furthermore, phenotyping of human monocytes showed that CM of resistant melanoma cells promote a pro–tumor phenotype (M2: positive CD163+CD206+) in comparison with monocytes differentiated under Vemurafenib sensitive CM. In addition, a decrease in the percentage of dead melanoma cells (CFSE+DAPI+) was observed after performing coculture assays of activated macrophages of resistant CM plus human melanoma cells.

Conclusions

The increase in M2–type TAMs in resistant melanoma tumor models indicates the existence of a more immunosuppressive and pro–tumor activity in such condition vs sensitive ones. All of this data indicates that the study and description of the immune system that surround or infiltrate melanomas during tumor progression and resistance acquisition is particularly interesting.

A-131

miR-146a-5p and miR-21-5p as Potential Biomarkers of Malignant Melanoma

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Background

Background: Cutaneous melanoma (CM) is the most lethal tumor among skin cancers and its incidence is rising worldwide. Recent evidences support the role of microRNAs (miRNAs) in melanoma carcinogenesis and as potential biomarkers.

Methods

Methods: We quantified the expression of miR-146a-5p and miR-21-5p in 170 formalin-fixed paraffin embedded (FFPE) samples of CM. We further correlated the results with specific histopathologic features such as Breslow thickness (BT), histological subtype, ulceration and regression status and mitotic index.

Results

Results: miR-146a-5p and miR-21-5p are statistically significantly higher in nodular melanoma (NM) compared to superficial spreading melanoma (SSM) and lentigo maligna melanoma (LMM). The strong positive correlation between miR-146a-5p and miR-21-5p expression and BT was confirmed for both miRNAs. Considering the ulceration status, we assessed that individual miR-21-5p expression was significantly higher in ulcerated compared to non-ulcerated CMs. The combined expression was also higher in ulcerated samples compared to them without ulceration (p=0.0093). Moreover, a significant higher miRNA expression was described in CM with higher mitotic rate (≥1/mm2) (p=0.005). Overall survival (OS) and time to relapse (TTR) were statistically significant lower in NM subtype (p<0.0001). Interestingly, CMs with BT≥0.8mm and miRNA expression ≥1.5 have lower OS and TTR compared to those with BT≥0.8mm and miRNA expression <1.5, confirming the prognostic role of miRNAs.

Conclusions

Conclusions: The combined miRNA expression could be used in addition to BT and ulceration status for patient prognostication, especially among those with BT≥0.8mm and without ulceration. Our findings provide further insights for the characterization of CM with specific adverse prognostic features.

A-249

Next generation sequencing (NGS) in melanoma patients: a descriptive study of a Canarian cohort with suspected cutaneous melanoma-dominant syndrome.

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Background

Unravelling the genetic signature of melanoma has brought an unprecedented paradigm shift of diagnostic, prognostic and therapeutic relevance, especially in the context of suspected hereditary melanoma-dominant syndromes (MDS) such as familial atypical multiple mole melanoma syndrome, predominantly associate with CDKN2A/CDK4 mutations, BAP1 tumor predisposition syndrome and MITF-related melanoma and renal cell carcinoma predisposition syndrome.

Methods

Forty-five consecutive patients with suspected MDS were included over the period of January to June 2023. Cases were eligible if they met the following criteria: patients who, having had a melanoma, also had either a) a personal history of other melanoma(s) or at least one first- or second-degree relative with melanoma(s) or b) a personal or first- and/or second-degree relative history of at least one tumour associated with MDS. Demographic, epidemiological, phenotypic, clinical and histological variables were recorded for these patients. Blood samples were obtained and processed for analysis by next generation sequencing using a customized 50-gene panel. The study was approved by the institutional ethics committee.

Results

We identified nine patients with a pathogenic or probably pathogenic mutation, with two cases of CDKN2A mutations. Only six cases exhibited no mutations. The remaining patients had mutations of uncertain significance, including 21 patients who, interestingly, displayed the same TYR (tyrosinase) gene mutation (c.1205G>A; p.Arg402Gln).

Conclusions

Our cohort exhibits a lower proportion of CDKN2A mutation carriers compared with other series. Moreover, given the unexpected frequency of the TYR mutation c.1205G>A; p.Arg402Gln (variant of uncertain significance), we hypothesize that this mutation might have pathogenic significance in our population and a possible foundational effect. Further research is needed in order to elucidate the nature of this mutation.

A-171

PBX1 deregulation promotes melanoma progression and metastasis through alternative splicing

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Background

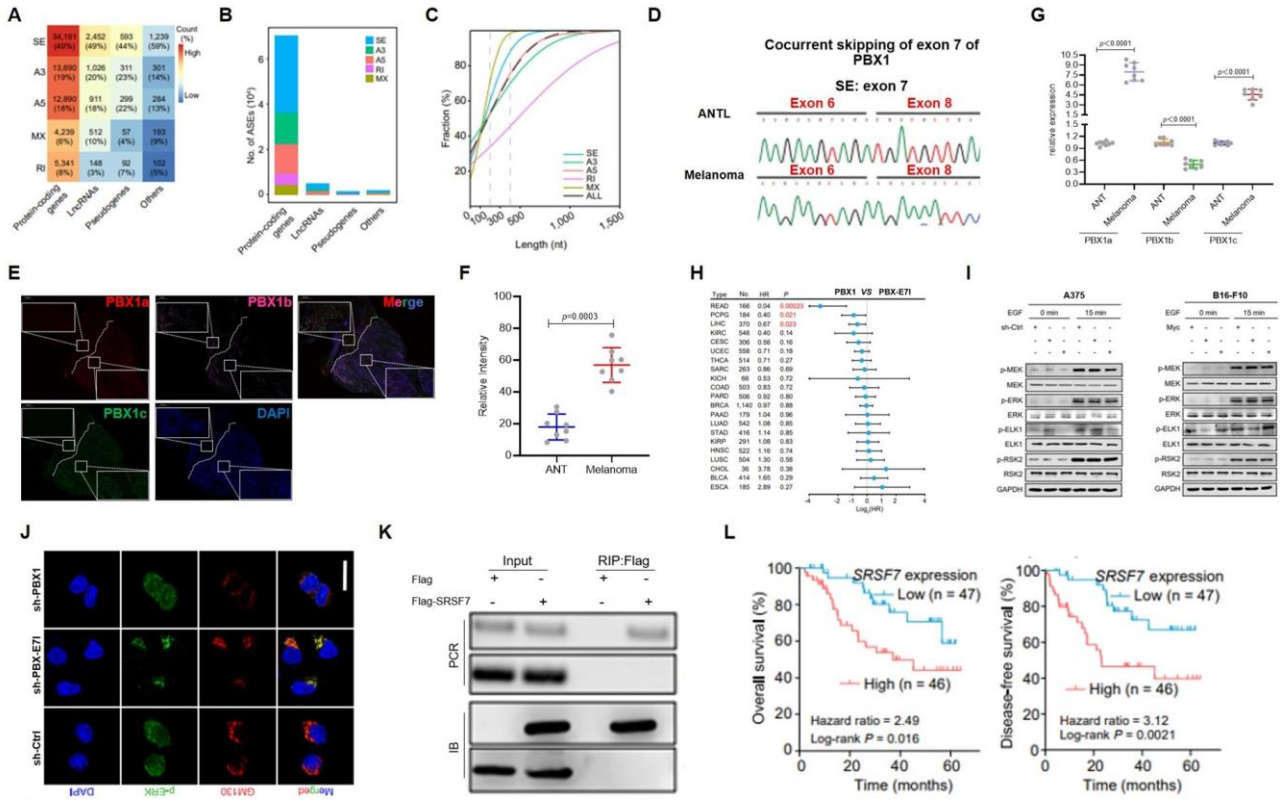
Pre-B-cell leukemia homeobox transcription factor 1 (PBX1) is identified at t(1;19)chromosomal translocations in acute pre-B-cell leukemia and involves in regulating multiple biological processes. Importantly, accumulating evidences have suggested that dysregulation of PBX1 have been shown to involve in tumorigenesis, poor prognosis and drug resistance. Our previous work revealed the clinical impact of PBX1 on melanoma and a novel regulatory mechanism for governing PBX1 expression and provided an out-of-the-box G4-targeting therapeutic strategy for melanoma. It has been shown that approximately 95% of multi-exon human genes produce multiple transcripts through alternative splicing (AS), which shapes the diverse delivery of genetic information and contributes to temporal and spatial diversification of biological function. Dysregulation of AS plays important roles in the development of various diseases, including cancers. However, the impact of PBX1 AS on melanoma and the molecular are largely unknown.

Methods

We investigated the expression of PBX1a and PBX1b by performing RNA Scope and assays. Proliferation, colony formation, cell migration and invasion were measured. Formation of A375 or B16-F10 cells-derived xenograft tumors and melanoma patient-derived xenograft (PDX) tumor from cell lines was monitored in nude or C57BL/6 mice. EGFP reporter, immunocytochemistry, RNA immunoprecipitation, RNA pull-down and chromatin immunoprecipitation assays were performed.

Results

We performed a transcriptome-wide analysis of ASs in melanoma and established a comprehensive AS landscape. Among them, we identified PBX1 as a prognostic indictor for melanoma patients. Further functional assays indicated that the exon skipping-induced loss of tumor suppressive isoform of PBX1, which is driven by SRSF7, promotes melanoma progression and enhances the resistance of melanoma cells to MEK inhibitors via nuclear activation of the MAPK pathway (Figure 1).



Conclusions

Defining mechanisms regulating PBX1 splicing function in cancer will be critical to further our understanding of the context dependency of the PBX1 splicing program driving metastasis in melanoma.

A-325

Redefine Individual Melanoma Patient Stratification with Artificial Intelligence and Computational Analysis

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Background
Personalized medicine in melanoma requires a deep understanding of multidimensional patient data. Therefore, we introduce a triad of interconnected initiatives: Athena (https://athenatechai.com/), a platform designed for sophisticated oncological data management and consumption; the formation of a collaborative consortium of 38 centers contributing to a shared data repository; and the development of interpretable AI algorithms, aiming to surpass the current melanoma patient stratification standards provided by the AJCC.

Methods
We dispose of a relational database that integrates melanoma patient records from 38 centers in a dedicated tenant. Multi-tenant databases refer to the ability to maintain separate entities, such as organizations or clients, within a single instance of the application or system, ensuring that the data for each entity is isolated and managed independently. We recruited 21,400 cases from the last three decades. Compiled by healthcare professionals, the database spans 104 tables, detailing clinical details, demographics, genetics, family history, treatments and disease events, alongside other key data. Subsequent to its autonomous pseudonymization, the data is subjected to a rigorous processing regimen, rendering it suitable for subsequent analytical endeavors, the training of AI models, and secure exportation. Additionally, we released an auxiliary apprentice portal designed to enhance user competency with the platform and uphold data quality through specialized training modules.

Results
Multiple collaborative projects utilizing this platform have been successfully published. This unified multidimensional data management approach facilitated the development of AI models. When assessed over a 5-year period, specific and relapse-free survival algorithms demonstrated a concordance of 88-90% at the time of initial staging in the analyzed cohort. Reflecting on these findings, we highlight the algorithms' capability to handle time-series data and extended dimensions.

Conclusions
By effectively managing multidimensional data with machine learning, this collaborative research platform has the potential to improve personalized patient risk stratification. The outcomes of these initiatives represent a significant stride in implementing big data management, computational analysis, and artificial intelligence ecosystems for melanoma care.

A-268

RNA helicase DHX9 enables PBX1 mRNA translation by unfolding RNA G-quadruplex in melanoma

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Background

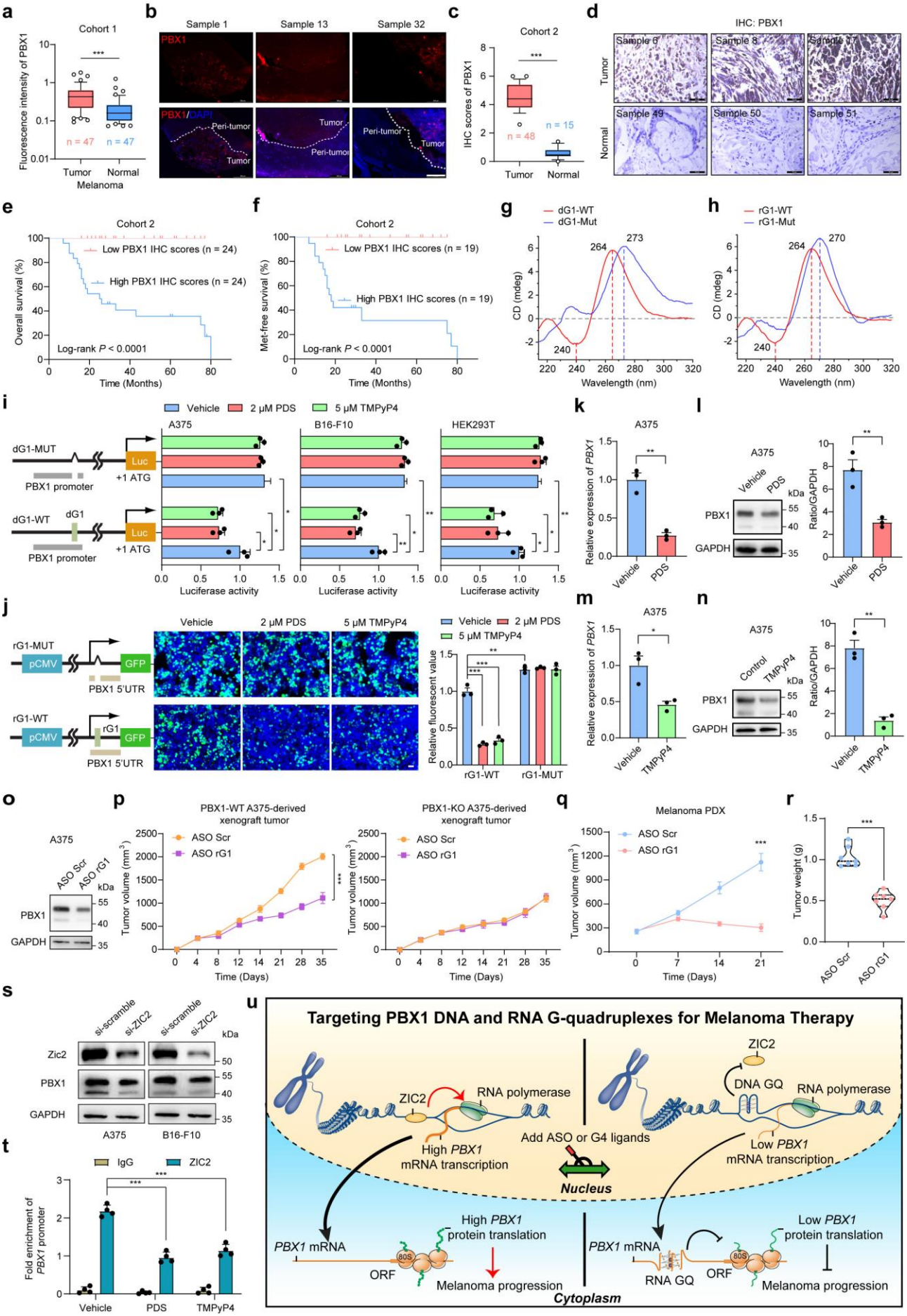
Pre-B-cell leukemia homeobox transcription factor 1 (PBX1) is identified at t(1;19)chromosomal translocations in acute pre-B-cell leukemia and involves in regulating multiple biological processes. Importantly, accumulating evidences have suggested that dysregulation of PBX1 have been shown to involve in tumorigenesis, poor prognosis and drug resistance. It has been shown that the expression of PBX1 is increased in melanoma cells and overexpression of PBX1 significantly promotes the melanoma cell growth. However, the clinical impact of PBX1 on melanoma and the molecular mechanisms regulating PBX1 expression in melanoma are largely unknown.

Methods

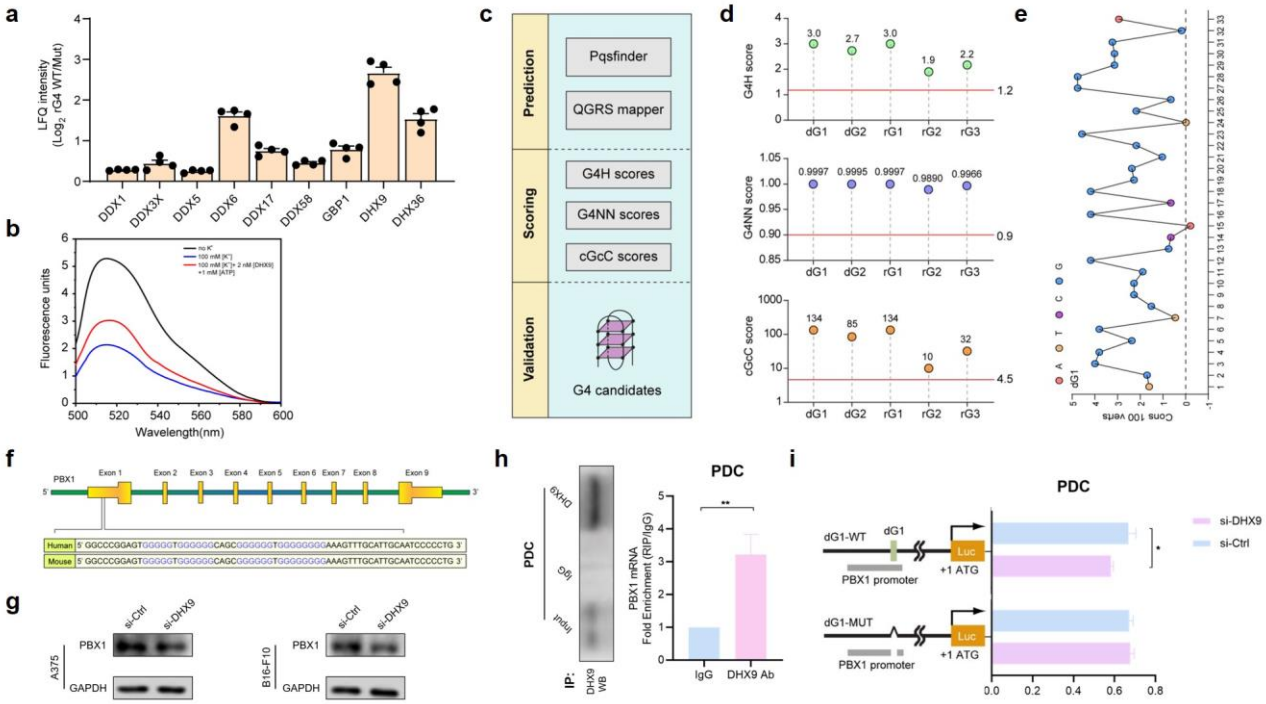
We investigated the expression of PBX1 in two melanoma cohorts by performing immunofluorescence (IF) and immunohistochemistry (IHC) assays. The PBX1 was expressed transgenically or knocked out in primary melanocytes, A375 or B16-F10 cell lines; proliferation, colony formation, cell migration and invasion were measured. Formation of A375 or B16-F10 cells-derived xenograft tumors and melanoma patient-derived xenograft (PDX) tumor from cell lines was monitored in nude or C57BL/6 mice. EGFP reporter, RNA immunoprecipitation, RNA pull-down, DMS footprinting, electrophoretic mobility shift assay (EMSA), fluorescence anisotropy experiments, G4 Unfolding test and chromatin immunoprecipitation assays were performed.

Results

We had shown that PBX1 is up-regulated in melanoma and its high expression predicts poor prognosis of patients with melanoma. In addition, we proved the presence of G-quadruplex (G4s) motifs in the promoter and 5’ untranslated region (5’ UTR) of PBX1. Importantly, we designed specific ASO targeting G4 in 5’ UTR of PBX1 and conformed that PBX1 G4 formation induced by ASO is a promising anti-melanoma therapeutic strategy. Mechanistically, PBX1 DNA G4 formation blocks ZIC2 occupancy in PBX1 promoter regions to inhibit the transcription of PBX1 (Figure 1).


a
Cohort 1
Fluorescence intensity of PBX1
n = 47
n = 47
Tumor
Normal
Melanoma
b
Sample 1
Sample 13
Sample 32
PBX1
PBX1/DAPI
Peri-tumor
Tumor
c
Cohort 2
IHC scores of PBX1
n = 48
n = 15
Tumor
Normal
d
IHC: PBX1
Sample 6
Sample 8
Sample 37
Sample 49
Sample 50
Sample 51
e
Cohort 2
Low PBX1 IHC scores (n = 24)
High PBX1 IHC scores (n = 24)
Overall survival (%)
Log-rank P < 0.0001
Time (Months)
f
Cohort 2
Low PBX1 IHC scores (n = 19)
High PBX1 IHC scores (n = 19)
Met-free survival (%)
Log-rank P < 0.0001
Time (Months)
g
dG1-WT
dG1-Mut
CD (mdeg)
Wavelength (nm)
h
rG1-WT
rG1-Mut
CD (mdeg)
Wavelength (nm)
i
Vehicle
2 μM PDS
5 μM TMPyP4
A375
B16-F10
HEK293T
dG1-MUT
PBX1 promoter
Luc
+1 ATG
dG1-WT
dG1
Luciferase activity
j
Vehicle
2 μM PDS
5 μM TMPyP4
rG1-MUT
pCMV
GFP
PBX1 5'UTR
rG1-WT
rG1
Relative fluorescent value
rG1-WT
rG1-MUT
k
A375
Relative expression of PBX1
Vehicle
PDS
l
A375
Vehicle
PDS
PBX1
GAPDH
kDa
Ratio/GAPDH
m
A375
Relative expression of PBX1
Vehicle
TMPyP4
n
A375
Control
TMPyP4
PBX1
GAPDH
kDa
Ratio/GAPDH
o
A375
ASO Scr
ASO rG1
PBX1
GAPDH
kDa
p
PBX1-WT A375-derived xenograft tumor
PBX1-KO A375-derived xenograft tumor
ASO Scr
ASO rG1
Tumor volume (mm3)
Time (Days)
q
Melanoma PDX
ASO Scr
ASO rG1
Tumor volume (mm3)
Time (Days)
r
Tumor weight (g)
ASO Scr
ASO rG1
s
si-scramble
si-ZIC2
Zic2
PBX1
GAPDH
kDa
A375
B16-F10
t
IgG
ZIC2
Fold enrichment of PBX1 promoter
Vehicle
PDS
TMPyP4
u
Targeting PBX1 DNA and RNA G-quadruplexes for Melanoma Therapy
ZIC2
RNA polymerase
High PBX1 mRNA transcription
Add ASO or G4 ligands
DNA GQ
Low PBX1 mRNA transcription
Nucleus
PBX1 mRNA
ORF
High PBX1 protein translation
Melanoma progression
RNA GQ
Low PBX1 protein translation
Cytoplasm

Additionally, we demonstrate that DHX9 regulates PBX1 mRNA translation by resolving RNA G-quadruplex (rG4) structure. PBX1-rG4 edited cell lines were resistant to rG4-stabilising compounds. Immunohistochemistry of normal and tumors demonstrated that absence of DHX9 corresponded to absence of PBX1. Significantly, knockdown of DHX9 in melanoma reduced the tumor progression (Figure 2).



Conclusions

Our results uncover a function of DHX9 in resolving RNA G4 and suggest a molecular target to suppress PBX1 for melanoma intervention.

A-442

Role of eIF6 in Modulating Response to BRAF Inhibitors and Acquired Resistance in Cutaneous Melanoma

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Background

Translation rewiring plays a pivotal role in oncogenesis and experiences dysregulation in various cancer types, including melanoma. Melanoma, particularly cutaneous melanoma (CM), the most lethal form of skin cancer, frequently exhibits mutations in the BRAF gene. While targeted drugs aimed at BRAF initially show effectiveness, they quickly lead to acquired resistance through mechanisms related to the translation process. The translation initiation factor eIF6 is responsible for regulating the maturation of the 60S ribosomal subunit and the formation of the 80S ribosome. Recent reports have highlighted its involvement in CM progression, suggesting a potential role in selectively translating mRNAs that could promote tumorigenesis. Nevertheless, its specific contribution to CM progression and its impact on the response to targeted therapy remain unclear.

Methods

To establish cell lines with stable overexpression of eIF6, a lentiviral approach was employed. Five distinct human and mouse melanoma cell lines, each representing a different subtype of CM, were utilized. The determination of the IC_{50} for vemurafenib in each instance was carried out through a resazurin assay. To investigate the impact of eIF6 on protein synthesis, puromycin staining and analyses of ribosome and polysome profiles using sucrose density gradients were conducted. The assessment of key signaling pathways affected in each case was performed through Western immunoblotting.

Results

In all cases, the overexpression of eIF6 resulted in increased levels of 60S ribosomal subunits. However, the response to vemurafenib varied across different subtypes. Interestingly, two of the cell lines displayed heightened resistance to vemurafenib in the presence of eIF6, while the remaining three showed enhanced susceptibility to BRAF inhibition. This observed response correlated with the distinct expression patterns of the central mTOR kinase and the phosphorylation state of ERK. Furthermore, contrasting effects on the translation machinery were noted, indicating a multifaceted regulatory role of eIF6.

Conclusions

Overcoming acquired resistance to targeted therapies is a crucial challenge in managing CM patients. Our discoveries highlight the participation of eIF6 in the response of melanoma cells to BRAF inhibitors, providing valuable insights that could pave the way for innovative therapeutic approaches aimed at overcoming resistance to vemurafenib.

A-204

Targeting autophagy as a therapeutic intervention in BRAFV600E melanoma cells through ULK-1 inhibition

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Background
Melanoma is characterized by poor prognosis in advanced stages. Autophagy, a cellular mechanism activated in stressful conditions, plays a crucial role in tumor survival. Melanoma cells with $BRAF^{V600E}$ mutation exhibit constitutive activation of autophagy, and increased autophagic flux is associated with resistance to BRAF inhibitors (BRAFi) such as Vemurafenib. The lack of specific autophagy inhibitors hampers validation of autophagy as a therapeutic target. Hydroxychloroquine (H-CQ) has entered in clinical trials as an autophagy inhibitor, but it is far from being specific, given that it alters lysosomal function. This study explores the potential of ULK-101, an inhibitor of ULK1 protein during early autophagy stage, in overcoming resistance in $BRAF^{V600E}$ melanoma cells.

Methods
We perform *in vitro* assays with murine melanoma cells with $BRAF^{V600E}$ mutation (5555 cells). Wound healing and MTT assays assessed cell migration and viability after treatment with H-CQ or ULK-101 in combination with Vemurafenib. Long-term treatment (over 30 days) and proliferation assay with these drugs evaluated resistance acquisition to Vemurafenib. Western Blot identified autophagy-related proteins.

Results
ULK-101 treatment inhibited ULK1 and early autophagy in 5555 cells, reducing p-ATG13 and LC3-II protein levels. H-CQ treatment increased LC3-II levels, indicating late autophagy blockade. ULK-101 reduced cell viability and migration in melanoma cells and ULK-101 and Vemurafenib combination therapy synergistically reduced these processes. In a 60-day in vitro treatment, H-CQ with Vemurafenib avoided Vemurafenib resistance, while early-stage autophagy inhibition by ULK-101 accelerated resistance acquisition. However, pre-treated cell with ULK-101 for 30 days delayed resistance acquisition, suggesting a temporal attribute to autophagy inhibition.

Conclusions
The autophagy blocking stage determines the ability to acquire resistance mechanisms to BRAFi in melanoma cells.
These findings suggest potential therapeutic strategies and underscore the need for precise autophagy inhibitors in melanoma treatment.

A-335

Tebentafusp effect on the tumoural landscape in metastatic uveal melanoma – a post-mortem study

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Background

Metastatic uveal melanoma (mUM) is a lethal disease characterised by an immunosuppressive tumour microenvironment (TME). Liver metastases occur in 90% of mUM and are associated with a poor prognosis. Tebentafusp, a bispecific antibody engaging gp100 (melanocytic lineage marker) and anti-CD3, is the first systemic treatment to improve survival in patients with mUM. Mechanisms of resistance to this drug are still unknown. In this post-mortem study, we aim to describe the immune landscape of metastases in patients treated with tebentafusp to explore resistance mechanisms.

Methods

The PEACE (Posthumous Evaluation of Advanced Cancer Environment) study is a research autopsy program. Here, we will present the uveal melanoma cohort. Immune infiltration in metastases has been evaluated on H&E slides, classifying this infiltrate into four categories (inflamed, altered immunosuppressive infiltrate, altered excluded infiltrate and non-infiltrated). Gp100 expression was assessed by immunohistochemistry (IHC) and categorised into quartiles.

Results

The cohort includes 12 patients: 8 have BAP-1 mutation, 2 SF3B1 and 2 unknown secondary mutations. Regarding treatment, 8 received immune checkpoint inhibitors, and 5 received tebentafusp. Among those 5, 1 had a partial response, and the others experienced progressive disease. The median duration of tebentafusp treatment was 5 months (2-14). The median overall survival for tebentafusp-treated patients was 1 year (0.3-3.1). There were 359 tumour samples analysed with a median of 26 metastatic regions per patient (11-58). Immune infiltration was higher in metastases treated with tebentafusp compared to tebentafusp naive (p=0.036). This was driven mainly by an increased immune infiltrate in the hepatic lesions. Tebentafusp-treated metastases had a lower expression of gp100 (p=0.046), mainly in the hepatic metastases (p=0.028).

Conclusions

At post-mortem, tumours treated with tebentafusp appear to have a higher immune infiltrate and a lower gp100 expression compared to those without. This effect is more pronounced in the liver. These findings suggest that after treatment with tebentafusp, its targets are variably expressed across tissues and that downregulation of gp100 might be a potential mechanism of resistance. More work is ongoing to refine the assessment of gp100 expression with a quantitative method and explore the immune TME. This will be presented at the conference.

A-409

The Dutch Early-Stage Melanoma Study (D-ESMEL): a Discovery Set and Validation Cohort to Predict the Absolute Risk of Distant Metastases in Stage I/II Cutaneous Melanoma

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Background

Early-stage cutaneous melanoma usually has a favorable prognosis. However, many patients diagnosed with metastatic melanoma were initially diagnosed at this early stage. This highlights the necessity for better risk assessment methods using novel prognostic markers. We collected samples from stage I and II melanoma patients to create an absolute risk prediction model. This model integrates clinical, imaging, and multi-omics data from formalin-fixed paraffin-embedded (FFPE) samples.

Methods

Based on the Netherlands Cancer Registry, linked with the nationwide network of histopathology, we collected FFPE primary tumor specimens of stage I and II melanomas with and without distant metastases. A discovery set was formed with metastatic cases matched with controls on key prognostic factors to identify novel prognostic markers. A nationwide validation cohort in a nested case-control setting was established for absolute risk calculations. (Figure 1) Hematoxylin & eosin (H&E) and multiplex immunofluorescence (MxIF) images, exome-enrichment RNAseq, and targeted DNAseq data were obtained, including clonality data of metastases. (Figure 2)

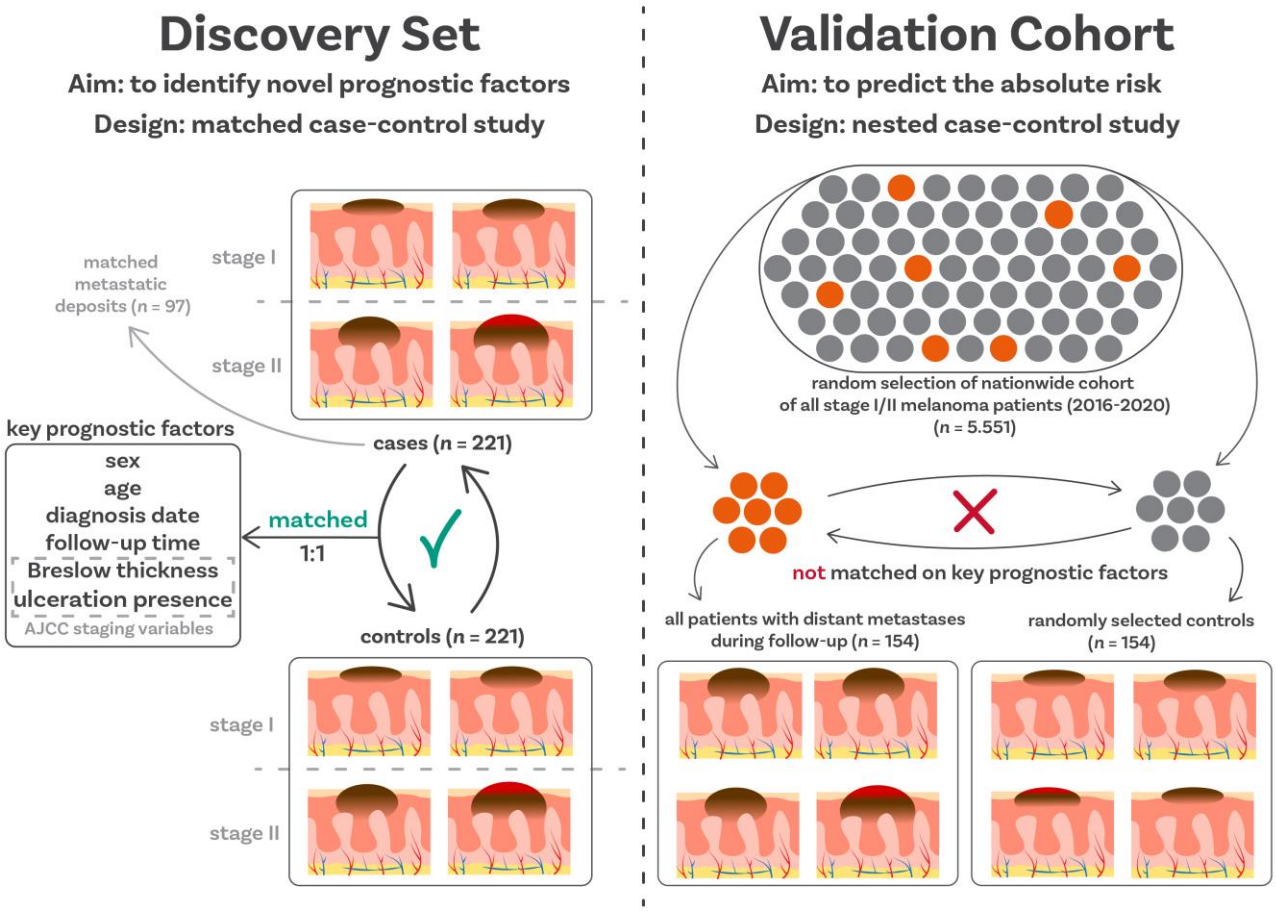

Figure 1. Overview of the discovery set and the validation cohort. The cases and controls are matched 1:1 based on key prognostic factors in the discovery set. The validation cohort is derived from a nationwide population of early-stage melanoma patients. AJCC = American Joint Committee of Cancer.

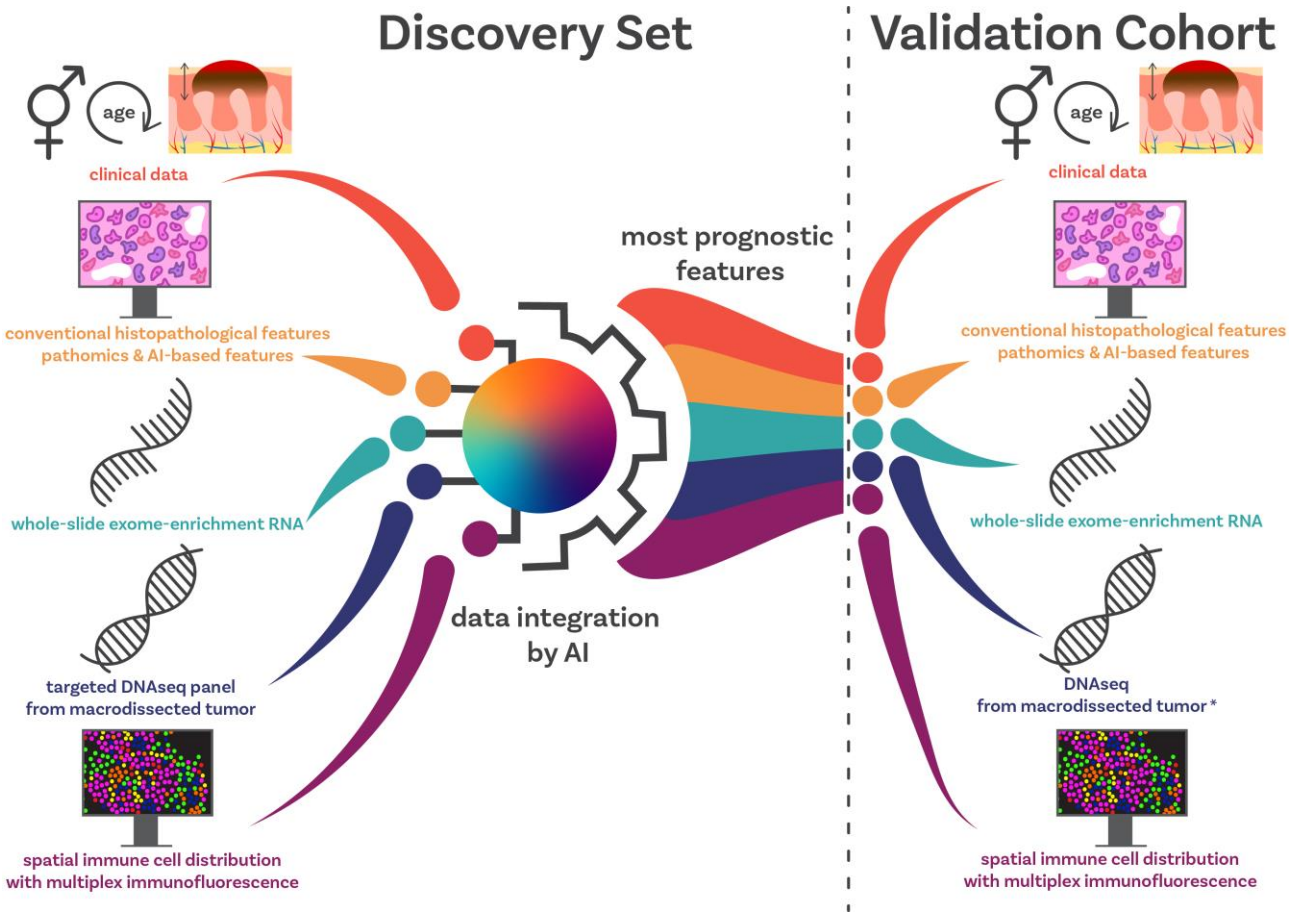

Figure 2. Schematic overview of the data of the discovery set, which will be integrated using artificial intelligence. The most prognostic features will be validated within the validation cohort. *sequencing technique based on outcomes discovery set.

Results

For the discovery set, 442 samples were included after reviewing the histopathological data and requesting them from pathology laboratories. This set consisted of 202 (46%) stage I melanomas and 240 (54%) stage II melanomas. The median Breslow thickness was 1.97 mm (IQR 1.04-3.30 mm). The median time to distant metastases was 3.4 years (IQR 1.7-5.5 years). The median follow-up time was 5.5 years (IQR 3.6-8.0 years), with 51% followed for ≥5 years. The H&E slides are available for all these samples, RNAseq data for 356 samples, DNAseq data for 282 samples, and the MxIF data are underway. Matched metastatic deposits could be retrieved for 97 cases. For the validation cohort, drawn from 14,198 stage I/II melanoma patients, we requested 275 case-control sets, and included 154 in our final selection. H&E slides are available for all samples and RNAseq for 147. MxIF and DNAseq will follow based on discovery set insights.

Conclusions

Our approach enabled the collection of a significant number of early-stage melanoma samples with clinical, imaging and multi-omics data from a nationwide cohort with extensive follow-up. Our methodology in prognostic cancer research holds the potential to impact clinical decision-making through absolute risk prediction.

A-275

Tumor microenvironment (TME) features and serum cytokines in patients with metastatic uveal and cutaneous melanoma treated with tebentafusp

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Background
Tebentafusp, an ImmTAC bispecific (gp100xCD3) targeting gp100 in the context of HLA-A*02:01 and activates T cells to kill tumor cells, was approved for the treatment of HLA-A*02:01+ patients (pts) with unresectable or metastatic uveal melanoma (mUM). Many pts demonstrate OS benefit despite radiographic progression. We compared the TME and blood biomarkers in HLA-A*02:01+ pts with 2L+ metastatic cutaneous melanoma (mCM) (NCT02535078) and mUM (NCT02570308) treated with tebentafusp.

Methods
Immunohistochemistry analysis was completed on baseline tumor biopsies, with gp100 quantified by H-score (mCM n=64; mUM n=112) and number of immune cells digitally quantified (up to: mCM n=17; mUM n=117). Data are reported as medians. Changes in 11 peripheral cytokine/chemokines were determined after the 1st tebentafusp dose in 79 mCM and 142 mUM pts. Cytokine release syndrome (CRS) was grouped as max. CRS grade versus no CRS.

Results
Median OS in both studies were comparable: 17.2 months mCM; 17.4 months mUM. 91% of mCM and 62% of mUM pts received prior checkpoint inhibitors (CPI). In mCM, baseline tumor gp100 expression was lower than in mUM (H-score 107 (range 0-280) versus 169 (range 0-300), respectively). Levels of gp100 tumor expression did not associate with CRS in either melanoma type.

Baseline CD3+ T cells within the TME were comparable between tumor types (mCM 733 cells/mm^2 and mUM 754 cells/mm^2); however, there were fewer CD163+ macrophages in mCM (1632 cells/mm^2) compared to mUM (2565 cells/mm^2).

Baseline cytokine levels were higher in mCM compared to mUM. Transient induction of cytokines/chemokines were seen at 8 hours post dose, with higher levels induced in pts who experienced any grade CRS. Cytokine/chemokine induction relative to baseline was lower in mCM (1-23 fold) compared to mUM (2-452 fold).

Conclusions
The TME in mCM is characterized by fewer immunosuppressive tumor-associated macrophages but higher levels of baseline serum inflammatory markers than in mUM. CPI are known to alter macrophage polarity from M2-M1 and may explain differences in CD163+ cells. CD163+ cells are also highly localized within the liver, the most common biopsy type for mUM. High levels of cytokine induction was more common in mUM and was associated with CRS but did not impact OS.

A-320

Unraveling the Impact of Microbiome on Immunotherapy Efficacy in Melanoma

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Background

The gut microbiota has sparked interest as a predictive factor for immunotherapy response in melanoma patients. Previous studies have identified specific fecal taxa and metabolites linked to positive treatment outcomes in patients with unresectable cutaneous melanoma undergoing targeted or immunotherapy. Our study aims to investigate the gut microbiome's potential as a predictor of immunotherapy response in melanoma[REF1].

Methods

Seventy-two melanoma patients from Hospital Clinic de Barcelona were enrolled in this study. Faecal samples were collected post-treatment decision and prior to treatment initiation, then e 16S rRNA gene was sequenced using MySeq Illumina for gut microbiome composition and microbiome analysis were performed by Qiime2 version 2023.2 (cohort details provided in TABLE1 and TABLE2). Alpha and beta diversity were assessed for sex, clinical benefit, and treatment decision groups, analyzing differences between groups. Linear discriminant analysis (LDA) identified differences in microbial composition between groups.

TABLE 1: Clinical variables description			
Variable		Level	N (%)
Sex		Female	33 (45,83)
		Male	39 (54,17)
Treatment		Adjuvant	20 (27,78)
		Metastatic	32 (44,44)
		None	20 (27,78)
Disease at sampling		Yes	42 (58,33)
		No	30 (41,67)
Treatment + benefit	Progression during first 12 months - adjuvant treatment	Yes	8 (11,11)
		No	12 (16,67)
	Progression during first 6 months - metastatic treatment	Yes	17 (23,61)
		No	15 (20,83)

Clinical variables description

TABLE 2: Description combination of Sex, Treatment and Benefit variables				
Sex	Treatment	Benefit	N (%)	N grouped (%)
Female	Adjuvant*	Yes	4 (12,12)	8 (24,24)
		No	4 (12,12)	
	Metastatic**	Yes	8 (24,24)	14 (42,42)
		No	6 (18,18)	
	No	-	11 (33,34)	11 (33,34)
Male	Adjuvant*	Yes	8 (20,51)	12 (30,77)
		No	4 (10,26)	
	Metastatic**	Yes	7 (17,95)	18 (46,15)
		No	11 (28,20)	
	No		9 (23,08)	9 (23,08)

*Follow up during 12 months
**Follow up during 6 months

Description combination of Sex, Treatment and Benefit variables

Results

Alpha and beta diversity analysis revealed significant differences among sex, clinical benefit, and the combined variable of treatment decision and clinical benefit (CHAO1/ Unweighted UniFrac and Adonis; $p<0.05$). LDA of sex identified five microbial taxa overrepresented in females and five in males, with *Prevotellaceae* taxon, highlighted in females with an LDA score of log10 > 4.5. In the combined variables of treatment decision and clinical benefit, ten microbial taxa were found to be overrepresented, with *Prevotella* in metastatic patients with progression (LDA score-log10 > 4.25), and *RF32* overrepresented in metastatic patients with no progression (LDA score -log10 > 4.5). *Prevotella copri*, contrary to our results, was previously associated with response to anti-PD-1 immunotherapy. Also it was found overrepresented in the melanoma patients' microbiome. *RF32*, previously linked to immunotherapy in non-small cell lung cancer patients, was overrepresented in non-respondents, differing from our findings[REF2].

Conclusions

The results obtained are significant, particularly with respect to the association of Prevotella and RF32, which contrasts with previous literature findings. Further exploration of these results may prove beneficial in enhancing our understanding of the intricate relationship between the microbiome and immunotherapy response.

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[REF2] Björk, Johannes, Laura Bolte, Andrew Thomas, Karla Lee, Niccolo Rossi, Thijs Wind, Lotte Smit, Federica Armanini, Francesco Asnicar, Aitor Blanco-Míguez, Ruth Board, Neus Llopart, Lisa Derosa, Nathalie Dhomen, Kelly Brooks, Mark Harland, Mark Harries, Paul Lorigan, Paolo Manghi, Richard Marais, Julia Newton-Bishop, Luigi Nezi, Federica Pinto, Miriam Potrony, Susana Puig, Patricio Serra-Bellver, Heather Shaw, Sabrina Tamburini, Sara Valpione, Levi Waldron, Laurence Zitvogel, Moreno Zolfo, Elisabe, (2023), Longitudinal Gut Microbiome Changes in Immune Checkpoint Blockade in Advanced Melanoma, 10.21203/rs.3.rs-3086925/v1

Melanoma – Immune checkpoint inhibitor (ICI) therapy

A-144

A case of delayed onset immune-related optic neuritis after combined immunotherapy treatment for metastatic melanoma

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Background
Immune checkpoint inhibitors are increasingly utilised to manage a variety of cancers, however there remains significant side-effects associated with their use and not all of these present while patients are on active treatment. Ipilimumab, an anti–cytotoxic T lymphocyte antigen-4 agent, and Nivolumab, an anti–programmed death-1 agent are approved as doublet therapy in the treatment of advanced melanoma. The combination has been proven to have greater efficacy but has also shown to have a higher incidence of immune-related adverse events (irAEs). irAEs can affect nearly all organ system and neuro-ophthalmic immune-related adverse events, which includes optic neuritis, are estimated to amount to less than 1% of all irAEs.

Methods
The case was identified in a tertiary hospital setting and data was collected retrospectively from the medical notes.

Results
We report a case of a 53-year-old woman with a background of recurrent BRAF-mutated metastatic melanoma who was initially treated with Ipilimumab/Nivolumab combination. She developed a Grade 3 skin toxicity after the first dose which required treatment with intravenous steroids. Following a treatment break, she went on to receive further doses of single agent Nivolumab. Unfortunately, her disease progressed and she was challenged with second-line BRAF and MEK inhibitors. Shortly thereafter, she was admitted with acute vision loss; optic disc swelling and a left relative afferent pupillary defect (RAPD) suggested optic neuritis. Concomitant irAEs included hepatitis. Neuro-imaging and cerebrospinal fluid analyses were unremarkable and negative for leptomeningeal disease or an ischaemic event. Despite methylprednisolone 1 mg/kg and intravenous immunoglobulin (IVIG), which resolved her other irAEs and preserved vision in the right eye (0.3 LogMAR), she has residual visual loss in the left eye (no perception of light).

Conclusions
This patient developed multi-system delayed irAEs more than 3 months after cessation of ICI treatment. Her case exemplifies the fact that delayed irAEs, including rare events such as optic neuritis, can present months post-treatment and raises the need for further research to identify at-risk patients.

A-308

A phase 3 study of the efficacy, safety, and pharmacokinetics profile of subcutaneous vs intravenous nivolumab + relatlimab fixed-dose combination in previously untreated metastatic or unresectable melanoma (RELATIVITY-127)

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Background

The fixed-dose combination (FDC) of nivolumab (NIVO) + relatlimab (RELA) has shown clinical efficacy, safety, and tolerability in advanced melanoma for intravenous (IV) infusions. Subcutaneous (SC) administration may provide benefits over IV administration for patients and clinicians due to improved comfort and convenience, ease of administration, and reduced risk of complications such as infections. SC injections of NIVO + RELA are co-formulated with the recombinant human hyaluronidase PH20 enzyme (rHuPH20), which enhances drug permeation in the SC space, decreasing dose administration time. In CheckMate 67T (NCT04810078), noninferiority of exposure (time-averaged serum concentration over the first 28 days [C_{avgd28}] and trough serum concentration at steady state [C_{minss}]) and efficacy (objective response rate [ORR] by blinded independent central review [BICR]) were previously reported for NIVO SC 1200 mg + rHuPH20 vs NIVO IV in patients with locally advanced/metastatic clear cell renal cell carcinoma. RELATIVITY-127 (NCT05625399) has been designed to evaluate the SC formulation of NIVO + RELA in patients with previously untreated metastatic or unresectable melanoma.

Methods

RELATIVITY-127 is a multicenter, randomized, open-label, double-arm phase 3 study comparing the PK, efficacy, and safety of SC vs IV administration of NIVO + RELA FDC in patients with previously untreated metastatic or unresectable melanoma. Key inclusion criteria are histologically confirmed stage III or IV (unresectable or metastatic) melanoma, measurable disease per RECIST v1.1, age ≥ 12 years, ECOG performance status ≤ 1 or Lansky performance score ≥ 80% (age ≥ 12 to < 18 years), and weight ≥ 40 kg (age ≥ 12 to < 18 years). The study is currently recruiting to randomize (1:1) ~570 patients to receive NIVO + RELA + rHuPH20 FDC SC or NIVO + RELA FDC IV until progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or study termination. The study drugs' exposure levels and the PK non-inferiority of SC vs IV administration of NIVO + RELA FDC are evaluated using two PK co-primary endpoints: C_{avgd28} and C_{minss}. ORR by BICR non-inferiority of SC vs IV is a secondary endpoint. Other secondary endpoints include additional PK parameters, safety, overall survival, progression-free survival, and patient-reported outcomes.

Results

Not applicable.

Conclusions

Not applicable.

A-405

A systematic review of changes in melanocytic naevi during immune checkpoint inhibition and targeted therapy

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Background

Immune checkpoint inhibitors (ICIs) and targeted therapies (TTs) are effective treatments for metastatic melanoma and other metastatic cancers. However, cutaneous adverse events (cAEs) due to autoimmune or autoinflammatory reactions are common and can alter the clinical and dermatoscopic features of melanocytic nevi. Furthermore, the development of new benign and malignant melanocytic lesions during these therapies has been reported. The rate and characteristics of these changes in preexisting and new melanocytic neoplasms remain poorly investigated. This systematic review aimed to assess the literature on reported morphological changes in melanocytic nevi following ICI and TT treatment to guide clinical practice.

Methods

A search (PROSPERO: CRD42023416858) of the Ovid (Medline), Embase, and Scopus databases (inception to December 1, 2023) was performed to identify eligible peer-reviewed patient-based studies reporting changes in preexisting nevi or new cutaneous melanocytic eruptions following ICIs and TTs in the oncological setting. Studies evaluating pigmentation disorders and reports discussing changes in other oncologic conditions were excluded. The evaluated outcomes were 1) clinical changes, 2) histopathological changes, and 3) the emergence of secondary primary melanomas.

Results

A total of 104 articles were identified, comprising 57 case reports, 6 case series, 12 (non-) randomized controlled trials, and 29 observational studies, 13 of which were prospective and 16 were retrospective. Among these studies, 980 patients from 24 countries had affected or de novo melanocytic neoplasms following either ICIs (22%) or TT (78%). The most commonly reported changes include increased clinical atypia, growth, hyperpigmentation, and involution, with or without a halo phenomenon. There were 49 reported cases of eruptive nevi and 132 newly diagnosed primary melanomas during treatment. Limitations of this study resulted from inconsistent reporting of outcomes, lack of correction for other risk factors, and predominantly small sample sizes across studies, many of which were limited to single cases.

Conclusions

Dynamic changes in nevi during anticancer treatment are not uncommon and may resemble clinically atypical nevi or present in an eruptive fashion. Melanocytic nevi should be examined by a dermatologist before ICI or TT treatment to determine the baseline clinical and dermatoscopic morphology, as secondary primary melanoma may occur.

A-118

Adjuvant lymph node radiotherapy and immunotherapy in stage III melanoma

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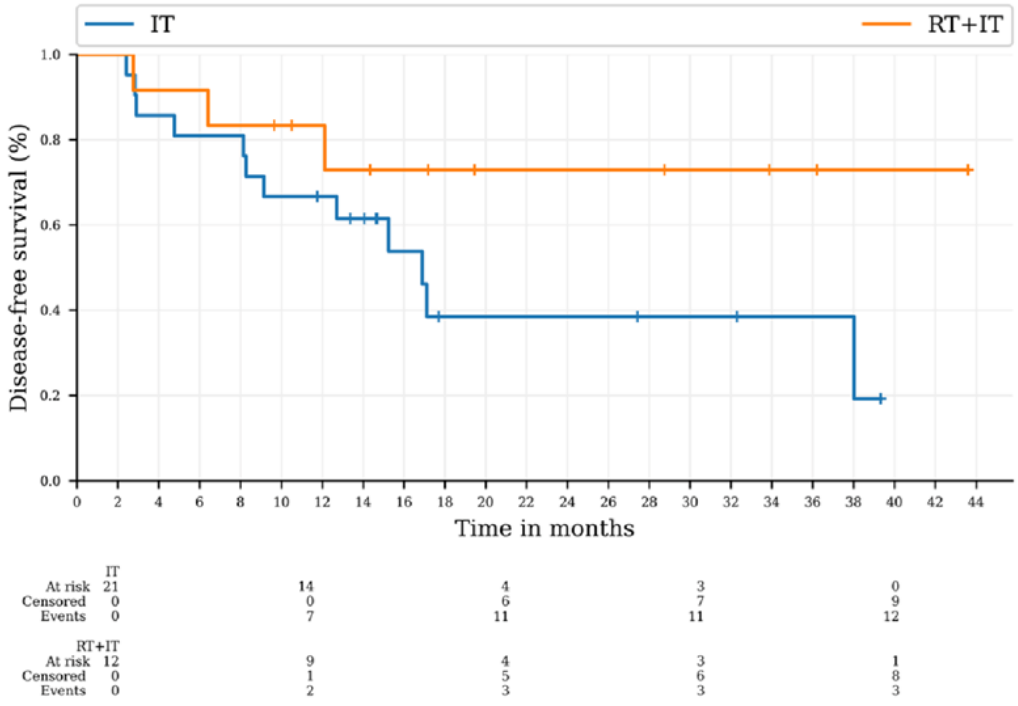
Background

With the promising results of immunotherapy (IT) in patients with stage III melanoma, the role of adjuvant radiotherapy (RT) after resection and complete lymph-node dissection (CLND) must be reassessed. We evaluate outcomes and safety of adjuvant RT and IT versus IT only in patients with resected stage III melanoma (AJCC 8th edition).

Methods

This retrospective and single institution study included all consecutive patients treated for a stage III melanoma with CLND and adjuvant IT (anti-PD1) from January 2019 to December 2022. The radiotherapy associated with immunotherapy (RT+IT) group was defined by completion of IT and adjuvant RT in the lymph-node dissection area. The primary endpoint was disease-free survival (DFS). The secondaries endpoints were locoregional (lymph-node field) progression (LRR), incidence of adverse events ≥ grade 3 according to Common Terminology Criteria for Adverse Events (CTCAE) and DFS in patients with high risk of locoregional recurrence.

Results



Disease-free survival comparing treatment groups

Thirty-three patients were included and all received adjuvant IT (pembrolizumab or nivolumab). Among them, twelve received adjuvant lymph-node field radiotherapy. The median duration of follow-up was 17 months (8-45). Patients in RT+IT group had a significantly higher disease stage and more frequent extracapsular extension. At 12 months, the disease-free survival was 66.7% (95% IC: 42.5-82.5) for the IT group and 83.3% (95% IC: 48.2-95.6) for the RT+IT group (p=0.131). After multivariate analysis, compared to patients with IT treatment, the hazard ratio (HR) was 0.216 ([0.0481, 0.965], p<0.05) for patients treated with RT+IT. The locoregional progression rates were respectively 24% and 8% in patients for which treatment was IT and RT+IT (p=0.379). After surgery, 21% of patients presented with ≥ grade 3 adverse events. After adjuvant treatment, 6% of patients developed ≥ grade 3 immunotherapy-related events and none developed ≥ grade 3 radiation-related adverse events.

Conclusions

In patients with resected stage III melanoma (AJCC 8th edition), adjuvant lymph-node field radiotherapy combined with immunotherapy seems to be associated with longer disease-free survival, with acceptable tolerance. However, these results need to be confirmed by long-term and prospective studies.

A-250

Benefit of immunotherapy for advanced melanoma in two patients with xeroderma pigmentosum.

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Background

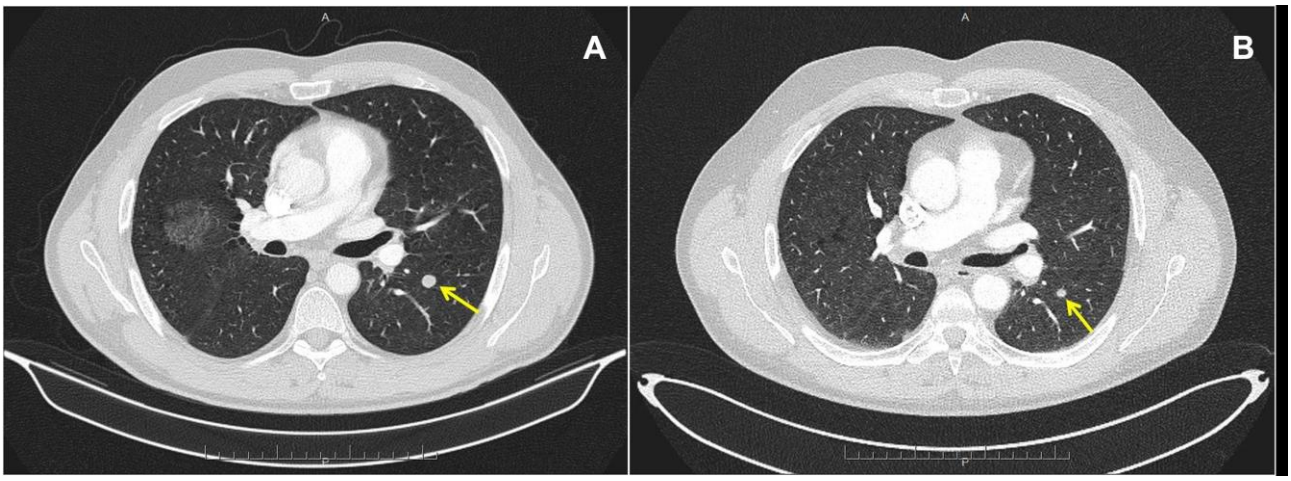
Xeroderma pigmentosum (XP) is a rare autosomal-recessive genodermatosis. In these patients, melanoma (MM) and squamous cell carcinoma (SCC), are the main causes of death at an early age[1]. The standard treatment for advanced MM is therapy with immune checkpoint inhibitors (ICIs), mainly anti programmed cell death-1 (anti-PD-1) antibodies.

Methods

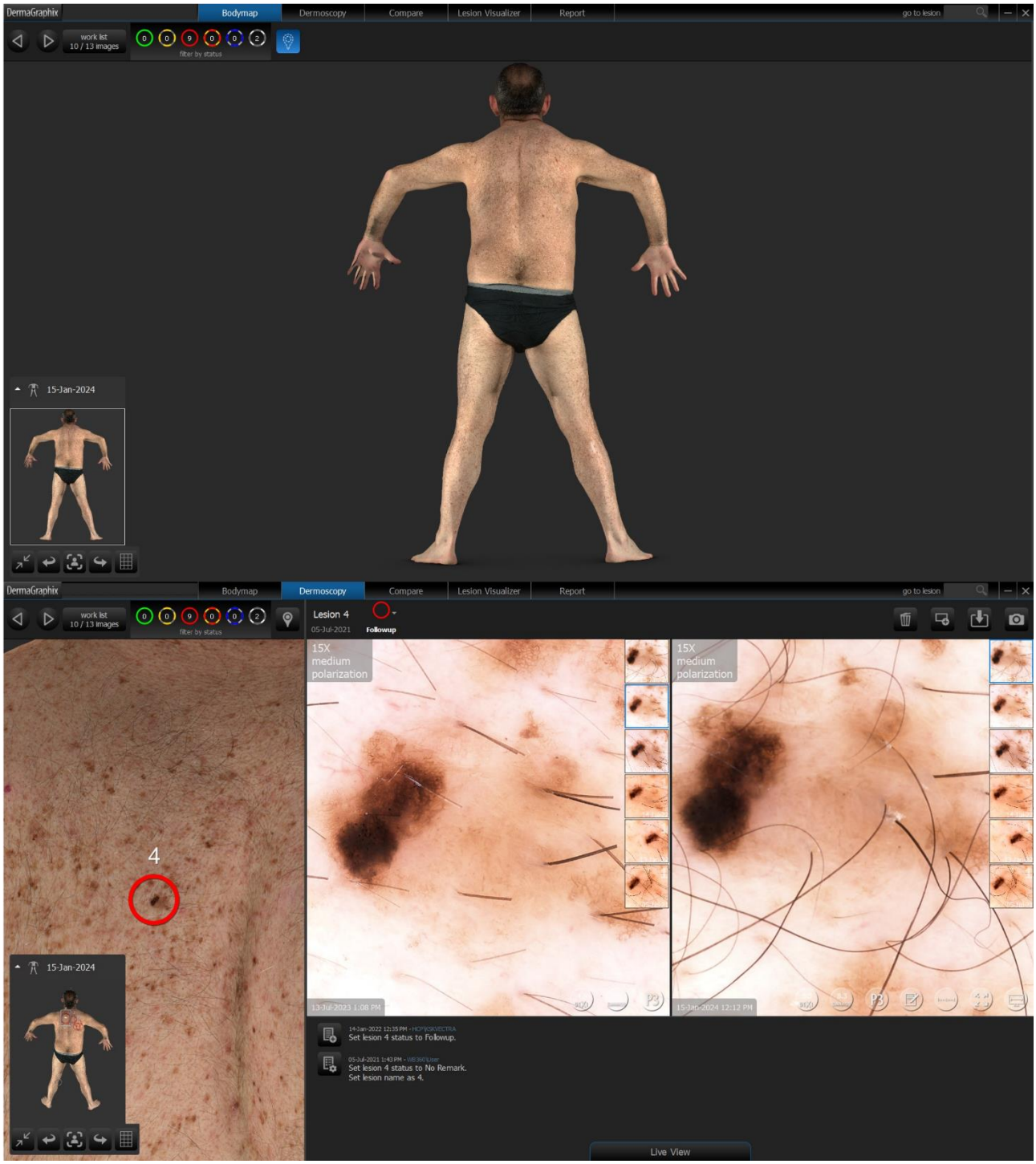
We present the outcomes of two XP patients with advanced MM, one of them treated with immunotherapy and the other one with immune plus target therapy: a programmed cell death-ligand 1 (PD-L1) inhibitor, atezolizumab, and a MEK inhibitor, cobimetinib.

Results

Case 1: A 44-year-old man with a family history of XP (his sister) was examined clinically and dermoscopically for the first time. Histopathology confirmed 2 basal cell carcinomas (BCCs), 5 *in situ* MM, 7 invasive MM and 1 dermic MM metastasis (*BRAF* wild type). Genetic testing confirmed XP-V. Body computed tomography (CT) revealed melanoma metastasis in the lungs, left suprarenal gland, and subcutaneous infra umbilical region (stage IVC). The patient was enrolled in a clinical trial including cobimetinib (anti-MEK) plus atezolizumab (anti-PD-L1) and the disease has remained stable for 64 months (trial and compassionate use). During the treatment, only one nodular BCC was excised. Case 2: A 52-year-old man was diagnosed with XP-C at the age of 42. During the first six-year follow-up period, ten MM, two desmoplastic relapses on the scalp and two BCCs were diagnosed. At the end of the sixth year, body CT revealed multiple pulmonary nodules corresponding to melanoma metastasis. He received immunotherapy with pembrolizumab and metastatic disease remained stable for 5 years; in that moment, anti-PD-1 had to be discontinued due to autoimmune pancreatitis. One BCC, one keratoacanthoma, and one *in situ* melanoma were diagnosed during this period. During the last 3 years, without any treatment, he developed two *in situ* melanomas and one additional BCC, with no new metastasis observed during follow-up.



Evolution of pulmonary metastases under treatment of patient 2, axial computed tomography (CT) with contrast. A. February 2016, prior to the start of immunotherapy treatment: solid-looking nodule in the left lung (yellow arrow). B. December 2023: slight decrease in size of the pulmonary nodule in the left lung.



Total body map and dermoscopy in VECTRA WB360 imaging system of patient 2. A. 3D body map (avatar). B. Dermoscopy screen mode (15x) showing the same lesion at 6 months follow-up.

Conclusions

Immunotherapy has demonstrated effectiveness in treating skin malignancies, emerging as a promising approach to improve the prognosis of XP patients with advanced tumours and potentially playing a role in preventing skin cancer. The efficacy of treatment may hinge on the mutational load of the tumour, which is heightened by the presence of a DNA repair defect in XP. Further investigation with a larger number of patients and an extensive long-term follow-up is needed to support our findings.

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A-143

Comparative Analysis of Pembrolizumab Dosing Schedules in the Adjuvant Treatment of Malignant Melanoma

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Background

Boa_Image_Frame treatment for resected stage III melanomas typically involves a fixed dose of 200 mg of pembrolizumab every three weeks (Q3W). The FDA approved an alternate dosing of 400 mg every six weeks (Q6W), based on pharmacokinetic modelling, without conducting formal comparative studies. These modelling suggest that flat dosing schedules achieve comparable target engagement. The safety of the Q6W dosing has not been thoroughly investigated. There is a lack of direct comparison between the Q3W and Q6W regimens for completely resected Stage III melanoma.

Objective: To compare the safety & efficacy of Q3W & Q6W schedules in a real-world clinical setting

Methods

Retrospective study, conducted from 2019-2023, included patients with high-risk node-positive melanomas. Eligible participants were those with Stage III melanoma & lymph node involvement who had undergone complete resection and received at least one cycle of pembrolizumab. The study examined two dosing regimens: 200 mg Q3W & 400 mg Q6W. Pre-specified baseline characteristics & reported toxicities were analyzed. Systemic therapy details were retrospectively collected through the SVUH pharmacy database. Toxicities were graded according to the Common Terminology Criteria for Adverse Events. The primary outcomes were recurrence-free survival (RFS), & the occurrence and severity of immune-mediated adverse events (irAEs) across the dosing schedules.

Results

A total of 60 consecutive patients with resected stage III malignant melanoma were treated with pembrolizumab between 2019-2023.
24 patients received a 200 mg dose Q3W, while 36 patients received a 400 mg dose Q6W.
The median time to onset of irAEs was 103 days for Q3W & 128 days for Q6W (p = 0.34).
Any-grade irAEs were observed in 70% of the Q3W group & 52.7% of the Q6W group.
Grade ≥ 3 irAEs occurred in 19% of the Q3W group & 18% of the Q6W group.
The estimated 12-month RFS was 72.1% for Q3W & 76.8% for Q6W (HR 0.93; 95%CI 0.50-1.73). Three-year RFS was 69.1% for Q3W & 68.9% for Q6W (HR 0.56, 99% CI 0.39-0.8).

Conclusions

This real-life experience shows that Q6W regimen is safe & effective.
Both Q3W & Q6W regimens offer comparable effectiveness, as evidenced by similar RFS rates at 12 months & 3 years. The incidence of irAEs was marginally lower in the Q6W group, but the difference was not statistically significant. The Q6W dosing schedule may reduce the burden on health service resources, providing significant time savings & potentially reducing financial toxicity

A-247

Complete response as prognostic marker of prolonged survival in metastatic melanoma

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Background
Immune checkpoint inhibitors (ICIs) and BRAF/MEK targeting agents (TAs) are treatments for metastatic melanoma (MM), inducing often disease's complete response (CR) and occasionally prolonged survival (S). The study investigated whether MM patients being alive > 5 years, had shown CR during the first year of treatment with these agents, and whether this CR could be marker of prolonged S.

Methods
From a pool of 170 MM patients treated with ICIs, TAs or both, during the last decade, 28 patients with S> 5 years (group A) were identified. Another 38 patients (group B; control) from the same pool with S <5 years were selected for comparison regarding CR during the first year of treatment. All patients were stratified and the control patients were selected to match those of group A, regarding disease stage, metastatic type, age, BRAF status and treatment type. Patients' characteristics, including metastatic disease stage (M1a to M1d, according to AJCC 8th Edition) and response to treatment were analyzed by univariate and multivariate regression analysis.

Results
CR was noted in 64% and 5% of group A and group B, respectively, and was found to be independently associated with significant higher probability of S>5 years, both by univariate and multivariate analysis ($p<0.0001$).No patient in group A had shown progressive disease (PD), while PD was the case for 42% of group B patients ($p<0.0001$). M1a stage was also independent factor of increased probability for S> 5 years ($p=0.046$). Group A patients were more probable to have normal serum LDH, non-visceral metastases and received fewer treatment lines, compared to group B.Median S ranged from 62 to 126 months (median 74) months in group A and from 3 to 54 (median 12) in group B. Melanoma's characteristics did note differ between the two groups. Among patients with S> years, 15 had received only ICIs, 5 only TAs and 8 both treatment types.

Conclusions
These findings suggest that CR during the first year of treatment is strong prognostic factor of S> 5 years among MM patients under ICIs and/or TA treatment.

A-316

Dermatological adverse events due to oncotherapy: the necessity for a new classification

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Background

Dermatological adverse events (dAEs) are very frequent in course of oncotherapy. They are currently evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), which is mostly based on the body surface involved. As dermatologists, we know that skin lesion type, anatomical localization and duration are sometimes more important in determining the severity of a skin reaction.

There is necessity for a more peculiar classification of dAEs, with a better correlation with the severity of the skin reaction and the need to reduce or discontinue the ongoing oncologic treatment.

Herein we want to propose an alternative classification for dAEs with the aim of better identify patients forced to interrupt anti-cancer therapy, and who require systemic dermatological therapy (steroids, biologics, immunosuppressants).

Methods

We conducted a one-year retrospective analysis of data from patients on systemic anticancer therapy at the Istituto Oncologico della Svizzera Italiana for whom a dermatological evaluation for a dAE was requested.

We classified dAEs according to the CTCAE and according to a new proposed classification based on the type of skin reaction divided in two groups: A mild toxicity (maculo-papular, urticarial and eczematous rash, pigment alteration and alopecia) and B severe toxicity (pustular, exfoliative and bullous rash, nail and mucosal changes). In case of combined lesions, we chose the more severe classification.

To investigate the correlation of one of the two groups with the need to interrupt anti-cancer therapy, and the need to use systemic therapy to treat dAE, we used a univariate logistic regression analysis.

Results

We collected the data of 36 eligible patients, 24 classified as mild (A) and 12 as severe (B). 10/24 (41.6%) patients with a mild reaction and 8/12 (66.6%) patients with a severe reaction had to interrupt (in some cases permanently) the anti-cancer therapy. Moreover, 8/24 patients with a mild reaction and 8/12 patients with a severe reaction needed a systemic therapy for their dAEs.

Due to the small sample size, univariate logistic regression analysis didn’t show statistically significant results.

Conclusions

Although our preliminary data-analysis does not show a statistically significant difference, the disparity in the two groups of our classification is evident.

Our objective is to continue collecting data and, once a sufficient number of eligible patients has been reached, to re-evaluate the two classifications.

A-194

Dupilumab for the treatment of bullous pemphigoid triggered by melanoma immunotherapy

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Background

Immune checkpoint inhibitors (ICIs) for the treatment of melanoma, among other malignancies, have been associated with a variety of cutaneous adverse events, including bullous pemphigoid[1]. According to a 13-year lasting UK observational study, the incidence of ICI-induced bullous cutaneaous reactions is 0.3%[1]. There are few reports of interleukin (IL) 4/IL13 inhibitors achieving satisfactory results, when administered for the treatment of ICI-induced bullous pemphigoid not adequately controlled with systemic cortisteroids or other systemic agents[2]. We present the case of a patient with stage III melanoma treated with pembrolizumab, who developed bullous pemphigoid and was successfully treated with dupilumab.

Methods

A 74-year-old Caucasian male with an 18-month history of stage III nodular melanoma (Breslow 4mm) of the left arm, treated with pembrolizumab, presented with a severely pruritic generalized erythematosquamous rash with subsequent interspersed small bullae and crusted erosions of 4 months duration. The patient had been treated with apremilast for psoriasis prior to his presentation in our department, without success. Biopsy, direct and indirect immunoflueresence were performed and were consistent with bullous pemphigoid. The patient was hospitalized and started on oral methylprednisolone 32mg once daily (0.44 mg/kg of body weight prednisone) and topical clobetasole propionate with gradual tapering after 23 days. One month after steroid commencement the patient was started on dupilumab SC injections 600mg on day 0 and 300mg every 14 days thereafter.

Results

One month after dupilumab initiation the patient had significant improvement (mostly post-inflammatory damage) and methylprednisolone was tapered to 4mg every other day within a month with no relapse.

Conclusions

Anti-IL4/13 medications seem to be successful steroid-sparing agents in individuals with melanoma and bullous pemphigoid, a group of patients with significant morbidity and already difficult prognosis. However, concerns have been expressed regarding their use, as Th2 immunity (the target of anti-IL4/13 drugs), especially eosinophilia, possibly facilitate the therapeutic effect of ICIs in melanoma[3].

A-283

Early recurrence in a pooled international cohort of melanoma patients treated with adjuvant nivolumab in a real-world setting

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Background

Adjuvant nivolumab was approved for the treatment of completely resected stage III/IV melanoma based on CheckMate 238 data. Limited adjuvant treatment studies evaluating post-recurrence treatment patterns and outcomes exist. A descriptive pooled analysis was performed using data from 4 noninterventional studies in 5 countries, focusing on early-recurrence patients.

Methods

The overall cohort included 982 patients with stage III/IV disease treated with adjuvant nivolumab in the French AdjuMel (n=350), German NICO (n=331), Belgian/Luxembourg PRESERV MEL (n=152), and Australian PRESERV MEL (n=149) studies. Effectiveness and safety outcomes were evaluated for the overall cohort and a cohort with early recurrences (during treatment or ≤6 months aftertreatment discontinuation); subsequent first-line (1L) systemic therapy data in patients with a distant recurrence are also described.

Results

Median time between index and data cutoff for the overall and early-recurrence cohorts were 28.1 and 20.6 months, respectively. Poor prognostic factor prevalence was slightly higher in the early-recurrence cohort. In the overall cohort, median recurrence-free survival was 45.7 months (95% CI, 34.5-not reached), with an 18-month rate of 66% (95% CI, 63-69); median distant metastasis-free survival was not reached with an 18-month rate of 78% (95% CI, 76-81). Early recurrence occurred in 24% (236/982) of patients; of these, patient recurrence types were: 23% only local, 25% ≥1 regional, and 52% ≥1 distant. Among patients with early distant recurrences, 80% (98/122) initiated subsequent systemic therapy and the median time from recurrence to subsequent therapy was 1.8 months (range, 0.03–30.8). The most common subsequent 1L therapy was anti-PD-1+anti-CTLA-4 (43%), followed by BRAF+MEK inhibitor (31%); 26 of 40 (65%) patients with a documented *BRAF* mutation received a BRAF+MEK inhibitor. Among the 98 patients with 1L subsequent systemic therapy, median progression-free survival on 1L systemic therapy after early distant recurrence was 5.2 months. Treatment-related adverse events were similar in the overall and early-recurrence cohorts.

Conclusions

In this large, multicountry RW cohort of melanoma patients treated with adjuvant nivolumab, outcomes were consistent with findings from CheckMate 238. These results highlight the continued unmet medical need for patients with an early distant recurrence following adjuvant anti-PD-1 therapy.

A-114

Exploring "Decision regret" in Adjuvant-Treated Melanoma Patients– results from a cross-sectional survey on 200 participants

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Background
Adjuvant therapy with nivolumab, pembrolizumab, or the combination of dabrafenib and trametinib has been approved for patients with melanoma for several years. The topic of "decision regret" in patients becomes particularly relevant when the risk-benefit assessment varies from individual to individual.
The primary objective of this study was to assess the percentage of patients with melanoma regretting their decision to undergo adjuvant treatment.
A secondary objective was to determine if any influencing factors could be identified. We also investigated whether it was decisive who made the final decision e.g. whether the decision was made together with the physician.

Methods
All patients who initiated adjuvant therapy at our centre between 1 July 2018 and 1 April 2022, were invited to participate in a questionnaire-based study. More than half of the patients (n=200, 57%) replied. In addition, patients' files were analysed with regard to tumour and treatment specific data.

Results
Only a small percentage of patients regretted the treatment (7.5%). Patients who made the treatment decision together with their physician regretted it significantly less often ($p = 0.007$). Interestingly, it was not the occurrence of a relapse, that was a significant factor influencing whether the decision was regretted, but rather the patients' subjective assessment that the adjuvant therapy had been successful for them. Binary logistic regression revealed the following independently significant influencing factors:

time effort required during adjuvant therapy was higher than assumed
experienced side effects were worse than expected
the patient rated the therapy as not successful
patient's age > 67 years.

Conclusions
Only a few patients regretted the decision. Shared decision-making was crucial for diminishing the rate of regret. The information provided at the time of informed consent should include the time effort required besides potential side effects to avoid any uncertainties among patients.

A-343

First-line Nivolumab plus Ipilimumab in patients with advanced melanoma previously treated with adjuvant systemic therapy

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Background

The combination of nivolumab and ipilimumab (NIVO+IPI) is associated with the highest rate of long-term survival in patients diagnosed with locally advanced/metastatic melanoma and is the standard first-line treatment. An increasingly common situation in the clinical practice is the use of combined immunotherapy in patients who have previously received systemic adjuvant therapy. The aim of this study is to evaluate the efficacy and safety of NIVO+IPI combination in patients previously treated with BRAF/MEK inhibitors or anti-PD-1 antibodies in the adjuvant setting.

Methods

The retrospective analysis included patients with locally advanced, unresectable or metastatic melanoma of the skin or mucosa treated with the NIVO+IPI between 01/2022 and 12/2023 in 5 oncology centers in Poland. All patients included in the study had previously received adjuvant treatment for stage III/IV melanoma.

Results

The study included 75 patients. The median age was 52 years. Women constituted 34.7% of the study group and *BRAF V600* mutation was present in 42.7% of the patients. 83% of patients received anti-PD-1 antibody in adjuvant setting. At baseline, 17.6% of patients had unresectable stage III disease, remaining patients were diagnosed with stage IV melanoma: 19.1% M1a, 17.6% M1b, 35.3% M1c and 8.8% M1d. Median follow-up time was 13 months. The objective response rate (ORR) was 21.3% and was numerically higher in the subgroup of patients who were immunotherapy-naive (23.7%) compared to those who received adjuvant anti-PD1 antibody (20%). The median progression-free survival (mPFS) was 5.7 (95%CI 3.1–9.7) and was insignificantly longer in patients who received BRAF/MEK inhibitors as adjuvant therapy compared to patients treated with adjuvant immunotherapy (11.1 vs 3.9 months, p= 0.4). The overall survival (OS) rate at 12 months was 62% (95%CI: 51-75). The safety profile of immunotherapy was typical, with treatment-related adverse events (TRAEs) grade 3/4 observed in 26.7% of patients.

Conclusions

NIVO+IPI immunotherapy has lower clinical effectiveness in patients previously receiving adjuvant immunotherapy compared to registration trial data. This highlights a particularly challenging prognosis for patients relapsing after adjuvant immunotherapy, as disease recurrence in this situation may indicate some resistance to further immunotherapeutic interventions.

A-379

Hypertrophic Lichen Planus associated with Pembrolizumab

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Background

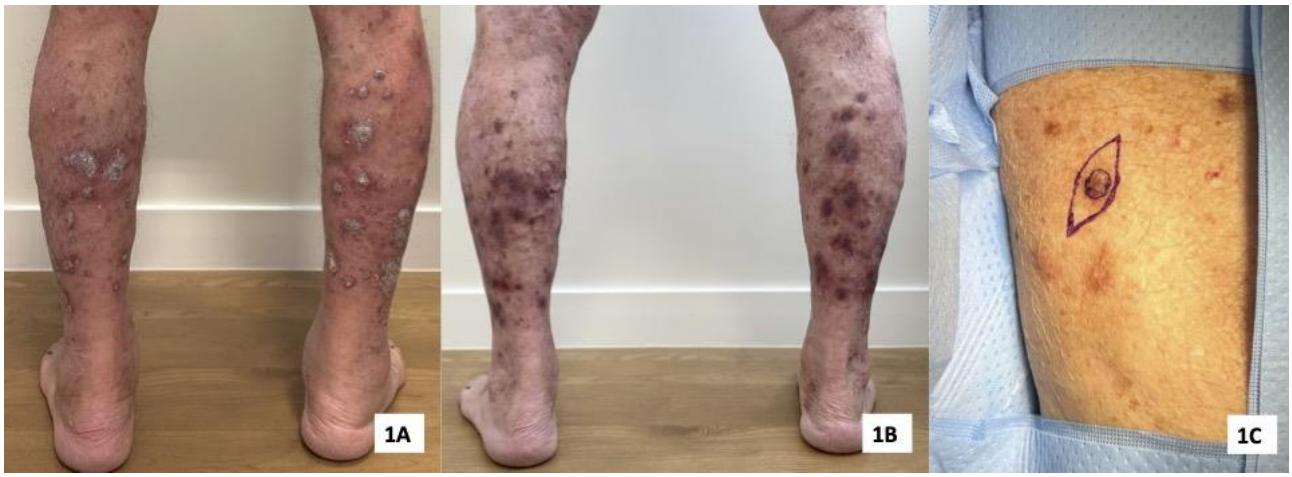
Hypertrophic lichen planus (HLP) is a variant of lichen planus associated with immunotherapy. When lacking classical characteristics, HLP mimics squamous cell carcinoma (SCC), delaying treatment. We present a patient with metastatic melanoma treated with Pembrolizumab who developed HLP initially diagnosed as SCC with an excellent response to topical treatment.

Methods

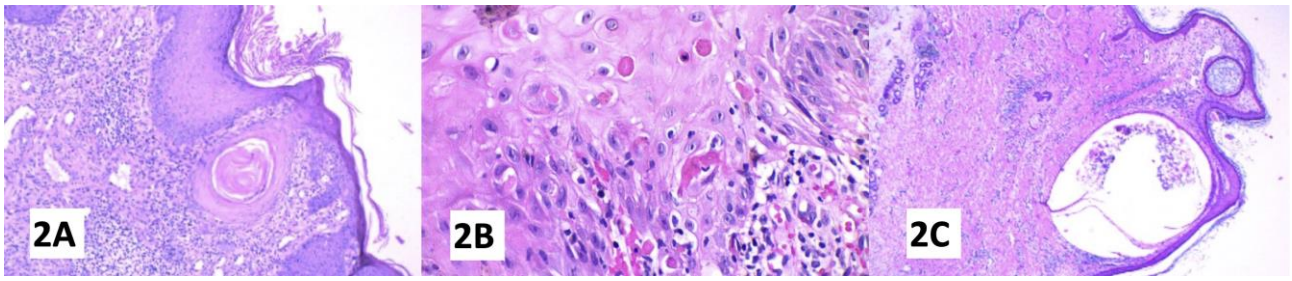
Review of medical records from the Hospital BP and from LB.

Results

An 89-year-old male patient with metastatic melanoma treated with Pembrolizumab presented with erythematous, keratotic papules and plaques on his lower limbs one month after ending immunotherapy. He was referred with the diagnosis of SCC, but as the clinical presentation and history suggested immune-induced adverse reaction (Figure1A), a new biopsy was performed. Histopathologic examination (HE) demonstrated epidermal hyperplasia, dyskeratosis and horn cysts associated with lichenoid infiltrate and apoptotic keratinocytes leading to the diagnosis of HLP associated with Immunotherapy (Figure2A/Figure2B). Treatment began with Clobetasol 0.05% ointment applied on the legs. After clinical improvement, the patient was started on adhesive tapes with Fludroxicortide on elevated areas (Figure1B). An isolated erythematous nodule with milia persisted on his left thigh and it was excised (Figure1C). HE demonstrated hyperkeratosis and corneal pseudocysts associated with lichenoid lymphocytic infiltrate also suggesting HLP (Figure2C).



1A: Erythematous and keratotic papules and plaques on the lower limbs. 1B: Brownish macules at sites of previous lesions. 1C: persistent isolated erythematous nodule with milia on the left thigh



2A(HE,10x): Epidermal hyperplasia, dyskeratosis, horn cysts, hyperparakeratosis, lichenoid infiltrate with ectatic vessels. 2B(HE,40x): Vacuolar degeneration of the epidermal basal layer, exocytosis of lymphocytes and apoptotic keratinocytes. 2C(HE,10x): Hyperkeratosis, corneal pseudocysts, lichenoid lymphocytic infiltrate, atrophic epidermis.

Conclusions

Dermatologic toxicity associated with Pembrolizumab is common and includes rash, Sweet syndrome and urticarial dermatitis[1]. Lichenoid reactions are present in 17% of cases, with HLP being an unusual variant characterized by keratotic papules and plaques on the lower limbs, which appear late or after ending treatment[1]. When it does not present with classic findings on HE, it mimics SCC and the clinical context and the response to treatment help in the diagnosis[1]Multiple treatments were described, such as topical and intralesional corticosteroids for localized lesions and phototherapy, acitretin, prednisolone, methotrexate, tofacitinib and thalidomide for extensive cases[2]. Herein, the patient had an excellent response to topical corticosteroids without systemic therapy. Surgery was performed in one resistant lesion. We conclude that differential diagnosis between HLP and SCC is important to avoid delays in treatment and topical corticosteroid can be effective for HLP.

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A-412

Immune-related adverse events with adjuvant anti-PD-1 therapy in high-risk resected melanoma: a single-center experience

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Background
Adjuvant anti-PD-1 therapy resulted in improved relapse-free survival of resected stage III and IV melanoma patients. Immune-related adverse events (irAEs) occur in more than three quarters of patients. Up to 15% is grade 3 or greater and some of them is chronic, requiring long-lasting treatment. Our objectives were to determine the incidence, characteristics and outcomes of irAEs during adjuvant anti-PD1 therapy.

Methods
We conducted a retrosepctive study in the dermatooncological center in Szeged, and analyzed data of melanoma patients treated with adjuvant anti-PD-1 monotherapy between 2017 and 2023.

Results
Fifty-two patients receiving adjuvant therapy for high-risk resected melanoma were included in the final analysis. The median age at treatment initiation was 59 (31-78) years, 29 patients (55.8%) were male. Patients received therapy for resected stage III and IV disease in 86.5% and 13.5%, respectively. IrAEs developed in 27 (51.9%) patients, of which 15 (55.6%) led to treatment discontinuation. Endocrinopathies (n=15, 55.6%) were the most common, whilst among non-endocrinopathies skin was the most affected organ (n=6, 22.2%). Grade 3 or greater and multi-organ AEs occurred in 5 (18.5%) and 8 (29.6%) patients, respectively. Sytemic steroid therapy was introduced in 13 (48.2%) cases. In 19 patients (70.4%) irAEs became chronic and persisted for more than 12 weeks after discontinuation of the adjuvant treatment. The median follow-up time was 15.9 months. The 3-year relapse-free survival rate proved to be 59.1%. The 3-year relapse-free survival rates in the group that completed 1-year adjuvant treatment versus discontinued due to irAEs were 66.9% and 76.0%, respectively.

Conclusions
In this cohort study irAEs occurred in half of the patients receiving adjuvant anti-PD-1 therapy and often persisted, requiring treatment and long-term follow-up. These findings are important to integrate in the analysis of the risk-benefit ratio when deciding on the adjuvant treatment for melanoma.

A-203

Immunotherapy after progression to immunotherapy: Pembrolizumab and Lenvatinib versus conventional chemotherapy for patients with metastatic melanoma after failure of PD-1/CTLA-4 inhibition

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Background

PD-1 inhibition as monotherapy following by CTLA-4 inhibition in case of progression or as upfront double co-inhibition have drastically improved the survival outcomes of metastatic melanoma (MM). Still many patients develop primary or acquired resistance to both agents, relapse soon and survive less. For these patients, the therapeutic options remain limited and for many years, conventional chemotherapy(CC) was the standard of care. Recently the phase II LEAP-004 trial supported that pembrolizumab/lenvatinib combination could potentially overcome anti-PD-1/anti-CTLA-4 immunotherapy refractoriness.

Methods

In the absence of any prospective comparative study and to evaluate in a real-world context the clinical benefit of re-administering a PD-1 inhibitor(pembrolizumab 200mg iv Q3W) with a multi-kinase inhibitor(lenvatinib 20mg po daily) in this population of unmet need, we conducted here a retrospective comparison of LEAP-004-proposed combination with CC(carboplatin 4AUC and dacarbazine 850mg/m^2 iv Q3W) in MM patients who relapsed to both checkpoint inhibitors, either in combinatorial or in sequential setting, between July 2022 and January 2024. Baseline demographics, disease characteristics as well as treatment outcomes(ORR, PFS and OS) were recorded. Survival analyses were performed using the Kaplan-Meier method. All patients were also considered for safety analysis.

Results

A total of 84 patients were included in the efficacy and safety analysis (pembro/lenva,n=39 and CC,n=45). The median age was 67(45-87) and 64(34-87)years and males were 33.3% and 46.7%, respectively. The distribution of their metastatic sites was comparable, including 12.8% and 20% with brain involvement. Most patients had a good PS<2(69.9% and 56.5%), increased LDH(71.8% and 84.4%), BRAF-wild status(82.1% and 84.8%) and received>=2 previous systemic therapies(61.5% and 53.3%).

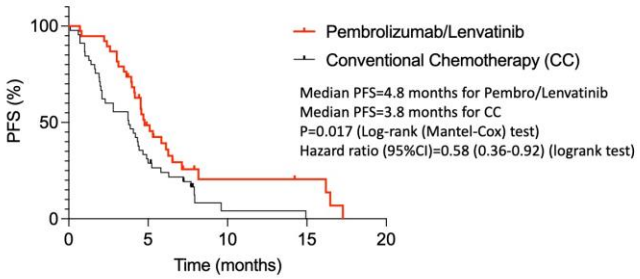
Table 1. Baseline Demographics and Disease Characteristics of Pembrolizumab/Lenvatinib and standard chemotherapy arms

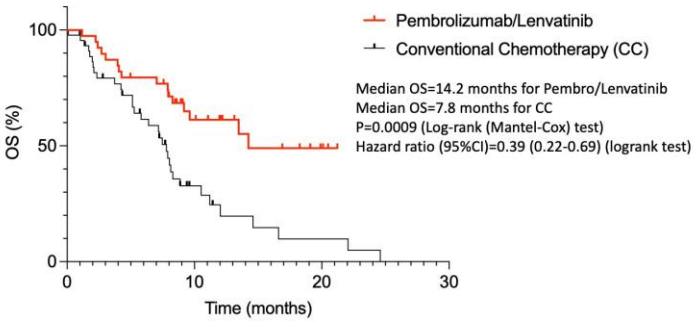
	Pembrolizumab+Lenvatinib Group (n=39)	Standard chemotherapy Group (n=45)	P-value (Mann-Whitney, two-tailed)
Males, number (%)	13 (33.3)	21 (46.7)	0.267
Age, median, years (range)	67 (40-87)	64 (34-87)	0.892
ECOG PS >=2, number (%)	12 (30.1)	20 (43.5)	0.261
Stage IV, M1a, number (%)	10 (25.6)	12 (26.7)	>0.999
Stage IV, M1b, number (%)	8 (20.5)	10 (22.2)	>0.999
Stage IV, M1c, number (%)	16 (41.0)	14 (31.1)	0.370
Stage IV, M1d, number (%)	5 (12.8)	9 (20.0)	0.559
BRAF mutated status, number (%)	7 (17.9)	7 (15.2)	>0.999
LDH >ULN, number (%)	28 (71.8)	38 (84.4)	0.189
Previous therapies >=2, number (%)	24 (61.5)	24 (53.3)	0.511
Nivolumab/Ipilimumab combination, number (%)	22 (56.4)	25 (55.6)	>0.999
Anti-PD-1+anti-CTLA-4 in sequent lines, number (%)	17 (43.6)	20 (44.4)	>0.999

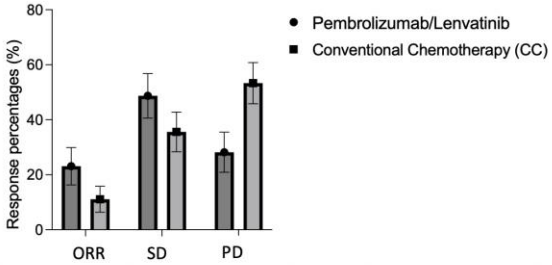
Baseline Demographics and Disease Characteristics of Pembrolizumab/Lenvatinib and standard chemotherapy arms

The median follow-up was 18 months. The median OS for pembro/lenva and CC arms was 13.5 and 7.8months(HR[95%CI]:0.47[0.27-0.82],P<0.001), and the median PFS was 5.3 and 4.2 months(HR[95%CI]:0.57[0.35-0.92];P=0.014), respectively.

Graph 2. Efficacy and toxicity outcomes of Pembrolizumab/Lenvatinib and standard chemotherapy arms







	Pembro/Lenvatinib group	CC group	P-value[HR(95%CI)]
Total number	39	45	
ORR, n (%)[95% CI]	9 (23.1) [12.4 to 38.5]	5 (11.1) [4.4 to 23.9]	P<0.0001
BOR, number (%)			
CR, number (%)	2 (5.1)	1 (2.2)	P=0.494
PR, number (%)	7 (17.9)	4 (8.9)	P<0.0001
SD, number (%)	19 (48.7)	16 (35.6)	P<0.0001
PD, number (%)	11 (28.2)	24 (53.3)	P=0.019
PFS, median (months)	4.8	3.8	P=0.017 [HR(95%CI)=0.57 (0.36-0.92)
OS, median (months)	14.2	7.8	P=0.0009 [HR(95%CI)=0.39 (0.22-0.69)]
Treatment-Related AE, Grade >=3, number (%)	19 (48.7)	34 (75.6)	P=0.034
Led to discontinuation, number (%)	4 (10.3)	8 (17.8)	P=0.200

Efficacy and toxicity outcomes of Pembrolizumab/Lenvatinib and standard chemotherapy arms

ORR was 23.1% and 11.1%, respectively(P<0.0001). Grade 3-5 TRAEs were documented in 48.7%(pembro/lenva) and 75.6%(CC) of patients(P=0.034), leading to treatment discontinuation in 10.3% and 17.8% of cases, respectively.

Conclusions

This is the first comparative study in patients with MM refractory to PD-1/CTLA-4 inhibition showing significantly improved outomes in cases treated with pembro/lenva versus CC.

A-227

Impact of Immune-Related Adverse Events on Melanoma Outcomes: A Comprehensive Analysis

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Background
Immune checkpoint inhibitors (ICIs), including anti-PD1 & anti-CTLA4, are pivotal in treating melanoma, utilized both in advanced and adjuvant therapies. These ICIs can induce a range of immune-related adverse events (irAEs) affecting various organs, primarily the skin, gastrointestinal tract, endocrine glands, liver, lung, & musculoskeletal system. While generally manageable, irAEs can sometimes lead to treatment discontinuation or, rarely, be fatal. Combined anti-CTLA4/anti-PD1 therapy shows higher irAE frequencies & severity compared to monotherapies. steroids are standard for managing most irAEs, with other immunomodulators effective in steroid-refractory cases. The study also examines the prognostic role of irAEs in melanoma & the impact of steroids & immunomodulators on clinical outcomes.

Methods
A retrospective single-centre cohort study, including 149 melanoma patients treated with ICIs. The study analyzed the onset, grade, and resolution of irAEs, along with their treatment approaches.
Time-to-event outcomes (duration of corticosteroids and immunosuppressive agents, time to resolution, Overall Survival (OS), progression-free survival (PFS) were visualized by Kaplan–Meier curve

Results
Demographics: 149 patients were analyzed, with 73.6% in palliative and 26.3% in an adjuvant setting. The median age was 64 years.
Adverse Events: A high incidence of irAEs was observed across different treatment regimens. The most common were thyroiditis, colitis, and rash. Severe toxicities were more common in combined immunotherapy.
Treatment-related Toxicities: In the non-adjuvant/unresectable setting, 64.6% of patients experienced toxicities, leading to discontinuation in 21% of cases. In the adjuvant setting, 66.7% experienced adverse events, with 22% discontinuing treatment.
Efficacy: In the non-adjuvant setting, patients with irAEs showed more favourable progression-free survival (PFS) across all treatment regimens ($p = 0.0036$ for anti-CTLA4, $p = 0.0022$ for anti-PD1, $p < 0.0001$ for combined therapy).OS also showed benefits except for anti-PD1 ($p = 0.22$).
Immunomodulatory Agents: Treatment with steroids and immunomodulatory agents did not significantly impact PFS or OS in both settings.

Conclusions
The presence of irAEs is correlated with increased treatment efficacy in the palliative setting for melanoma. The use of steroids and immunomodulatory agents does not affect ICI efficacy. This suggests that irAEs could be considered as potential prognostic markers for ICI treatment in melanoma.

A-458

InterPATH-001 trial in progress: Adjuvant V940 (mRNA-4157) with pembrolizumab versus placebo in patients with high-risk stage II-IV melanoma

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Background
Pembrolizumab, an anti−PD-1 antibody, is approved as adjuvant therapy for stage IIB-C and stage III melanoma by AJCC 8th ed, following complete resection. Adjuvant pembrolizumab has improved recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) in patients with high-risk melanoma, but many patients experience disease recurrence. V940 is an individualized neoantigen therapy that showed improved RFS and DMFS when used in combination with pembrolizumab compared with pembrolizumab alone in patients with stage III/IV melanoma in the randomized phase 2b KEYNOTE-942 study. A randomized, double-blind, phase 3 study has been designed to evaluate the efficacy and safety of adjuvant pembrolizumab plus V940 versus pembrolizumab plus placebo in patients with resected high-risk stage II-IV melanoma.

Methods
Adults with surgically resected stage IIB or IIC (pathologic or clinical), III, or IV cutaneous melanoma per AJCC 8th ed, and have an Eastern Cooperative Oncology Group performance status of 0 or 1 are eligible. Patients will be excluded if they have received any prior systemic therapy, and more than 13 weeks can have elapsed between last surgical resection and first dose of pembrolizumab. Patients with ocular or mucosal melanoma and past or current in-transit metastases or satellitosis are also ineligible. All patients must provide a blood sample and a FFPE tumor sample for sequencing. Patients will be stratified by risk (IIB, IIC, IIIA, and IIIB vs IIIC/D and IV) and age (<65 years vs ≥65 years). Approximately 1089 patients will be randomly assigned 2:1 to receive pembrolizumab 400 mg intravenously every 6 weeks with either V940 1 mg or placebo intramuscularly every 3 weeks for 9 doses or until disease recurrence, unacceptable toxicity, or withdrawal. The primary end point is RFS by investigator review. Secondary end points are DMFS by investigator review, overall survival, safety and tolerability, and quality of life. Hazard ratios and 95% CIs will be estimated using a stratified Cox regression model with the Efron method of handling ties. Between-treatment differences will be evaluated using a stratified log-rank test.

Results
Results are not yet available.

Conclusions
Enrollment is ongoing.

A-322

Ipilimumab and nivolumab in uveal melanoma: report on toxicity and treatment intensity

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Background
Uveal melanoma (UM) is the most common primary ocular malignancy with an incidence of 6-7 per million population per year. Despite of local therapy, majority of the patients develop metastatic UM (MUM) and need systemic therapy. Immune checkpoint inhibitors (ICI) nivolumab and ipilimumab (ipi+nivo) show remarkable responses in cutaneous melanoma (CM), but responses are limited in MUM. This is driven by peculiar biology, but may also be driven by lower exposure to ipi+nivo due to toxicity.

Methods
Patients with MUM, treated with ipi + nivo between 2016 and 2023 at University Hospital Zurich, and with available medical records, were evaluated. Treatment schedule comprised 4 cycles of ipi+nivo, followed by maintenance nivo monotherapy.

Results
Among 39 identified patients (26 male, 13 female), ipi+nivo was first-line therapy in 27 patients (62.9%), and ≥2 line in 12 patients. Adverse events (AE) were reported in 74.4% of the patients, of which grade 3 or 4 toxicity was 56.4%. The most common AE among all patients was hepatitis (35.9 %), followed by colitis (20.5 %) and thyroiditis (12.8%). 25 patients (64.1%) did not finish 4 cycles of ipi+nivo: 19 (48.7%) patients - due to toxicity, four due to death and two due to disease progression. The median number of ipi+nivo cycles was 3: six patients (15.4%) received only one cycle, 12 (30.8%) received two cycles, seven (17.9%) received three cycles and 14 (35.9%) patients received four cycles during induction phase. Of the 19 patients who did not receive full treatment intensity due to toxicity, nine patients were able to continue nivo monotherapy for a median of 6 cycles.

Conclusions
Toxicity is the most common reason for discontinuation of ipi+nivo in MUM. Reduced exposure to the combination may be another factor leading to lower response rates, than seen in CM. Discontinuation of ipi+nivo due to toxicity in CM was reported in 29% of patients (VanderWalde, Nat Med 2023). Our findings suggest dual ICI may be less well tolerated in patients with MUM compared to patients with advanced CM who received full dose of ipilimumab and nivolumab in 53% (Dummer, JCO 2023) respectively in 57% (Larkin, NEJM 2019) of cases.

A-448

Phase 2 Study of aTezolizumab, bevAcizumab, and Cobinetinib (TACo) in patients (pts) with PD1 refractory metastatic brain metastases (MBM)

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Background

While immune checkpoint blockade (ICB) has offered promising results for pts with untreated MBM, no effective systemic txs are available after ICB failure. Preclinical evidence suggests elevated VEGF levels predict poor response to ICB. MEK inhibition can increase MHC I expression and T cell infiltration suggesting potential synergy with PD 1 inhibition. We hypothesized the TACo regimen would demonstrate tolerability and efficacy in pts with MBM.

Methods

In this single-center PhII study in pts with MBM (NCT03175432), primary objectives included safety, efficacy (intracranial response rate (ICRR) by modified RECIST 1.1). Secondary objectives included IC clinical benefit (ICCB), progression free (PFS) and overall survival (OS). Prior PD1 tx and 1 unirradiated, measurable lesion was required, BRAF mutated pts were allowed after BRAF/MEK tx, ≤4m/day dex or equivalent. Tx schedule: atezolizumab 840mgIV q2 wks, bevacizumab 5mg/kgIV q2 wks, cobimetinib 60mgPO for 3 wks on/1 wk off. SRS was allowed to progressing lesions.

Results

20 pts treated, 70% were male, median age 59.5 yrs, median follow up of 8.2 mos (0.4-39.2). 8 pts had 2-4 lesions, 8 had ≥ 5, only 6 had prior SRS. 85% were wildtype BRAF. 18 pts experienced adverse events (AEs). Most common AEs: rash (70%), diarrhea (55%), hypertension (htn) (25%), proteinuria (25%). 35% pts had gr 3/4 AEs: htn (15%), diarrhea (10%) were most common. 2 pts stopped tx due to toxicity. 18 pts were evaluable for IC response: ICRR 39% (1 CR, 6 PR). 3 pts achieved SD resulting in ICCB of 56%. Median PFS was 2.7 mos (95% CI 0.9,7.3) and OS was 9.3 (95% CI 3.8,20.9). 7 (35%) pts continued on tx post progression for ≥ 3 wks (3-55wks) and 4 pts received SRS to progressing lesions and continued on protocol.

Conclusions

In this heavily pretreated MBM population with no available standard systemic therapy options, TACo regimen was tolerable, demonstrated IC clinical benefit and provided clinical benefit beyond progression. Future trial designs for MBM should consider integrating SRS to reflect clinical practice, harnessing the power of multidisciplinary approaches, and evolving endpoints to capture therapeutic benefit.

A-397

Prognostic value of tumor microenvironment molecules in the response to immunotherapy in advanced melanoma

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Background

Dysregulation of TGFβ signaling pathway in melanoma's tumor microenvironment is crucial for its progression by suppressing anti-tumor immunity and promoting fibrosis, epithelial-mesenchymal transition, and angiogenesis. Recently, a TGFβ-induced transcriptomic signature has been described in fibroblasts in various cancers, predicting the failure of PD1-inhibitor immunotherapy. Caldesmon (CALD1) is a TGFβ pathway activation marker, and its immunohistochemical (IHC) expression can be assessed in melanoma paraffin-embedded samples, correlating with increased overall mortality in our experience. The aim of this study is to investigate whether CALD1 expression and tumor inflammatory infiltrate (TII) in patients with advanced melanoma are associated with different response to immunotherapy and progression-free survival (PFS).

Methods

We performed a retrospective, bicentric study (period 2017-2021) including patients with resected stage IIIC/IIID/IV cutaneous melanoma and unresectable stage IV treated with immunotherapy (anti-PD-1 +/- anti-CTLA-4) and exhibiting different therapeutic responses (partial or total response *vs.* no response). We assessed CALD1 expression and characterized TII using CD45, CD8, CD3, and PD1 stains, on paraffin-embedded melanoma samples obtained before immunotherapy initiation. For CALD1, the Histoscore (H-score) (0-300) was calculated. We used *QuPath* for TII analysis calculating the percentage of positive cells for each marker. We used Cox regression to determine distinctive immunotherapy response and PFS based on CALD1 expression and the percentage of positive inflammatory cells for each marker, respectively.

Results

Twenty-eight melanoma samples from 28 patients were included. Fifteen patients were considered responders to immunotherapy, and 13 were non-responders. The mean CALD1 H-score in the non-responder group was significantly higher than in the responder group: 220 (SD 43.9) *vs*. 185 (33.8), HR 0.98 [0.96; 1.00], p=0.044. Progression-free survival was lower in patients with H-score ≥230 (HR 2.99 [1.07;8.38], p=0.037). It was observed that a higher TII was associated with higher response rates to immunotherapy and longer PFS, although statistical significance was not reached.

Conclusions

Patients with melanoma expressing higher levels of CALD1 and eventually lower TII exhibit lower response rates to immunotherapy and shorter PFS. CALD1 could be considered a biomarker for response to immunotherapy in melanoma and may be a determinant for immune evasion.

A-255

Quality-of-Life Assessment in Spanish Stage III Immunotherapy Patients: A Prospective Observational Study

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Background

Cancer immunotherapy has demonstrated an improvement in melanoma treatment. However, there is a lack of knowledge on the quality-of-life (QoL) of those patients outside the controlled environment of randomized clinical trials. We aim to address this gap by gathering real-life data to elucidate the QoL status among a cohort of Spanish melanoma patients receiving immunotherapy. Thus, we investigated whether specific covariates could condition patients' QoL at the start of immunotherapy.

Methods

In this prospective observational study, fifty-four adult melanoma patients undergoing anti-PD1 immunotherapy were enrolled from June 15, 2021, to June 30, 2023 in Hospital Clinic of Barcelona. Clinical data were collected at baseline and during follow-up until December 31, 2023. To evaluate QoL at treatment initiation, participants completed the Functional Assessment of Cancer Therapy – General (FACT-G, v.4) questionnaire, an instrument used worldwide to assess health-related QoL. Higher scores indicate better QoL. Total FACT-G scores and the corresponding four subscales (Physical, Social, Emotional and Functional Well-Being) were calculated for those patients' receiving adjuvant or first-line immunotherapy treatment and who responded to the baseline questionnaire at inclusion (N=31, 57.40 %). Statistical analyses were performed using the R software environment (v.4.2.3) with statistical significance set at a p-value less than 0.05.

Results

Eighteen women (58.06%) and thirteen men (41.94%) completed the questionnaire, yielding a mean FACT-G Total score of 88.01 (SD=14.32) out of 108, without differences to the 80.1 (SD=18.10) reported for the general U.S. population [Webster2003]. Women reported statistically lower Functional Well-Being (p=0.0124) compared to men during the initial assessment, while no significant gender differences were noted in the other subscales or the total score. Moreover, no differences were seen in the quality of life based on melanoma staging upon treatment initiation.

Conclusions

Understanding the QoL of patients at the onset of cancer therapy is essential for effective care. In this study, all 31 patients received adjuvant treatment, indicating they were disease-free. Consequently, it is crucial to monitor their evolution throughout the treatment and investigate whether potential immune-related toxicities could impact their QoL. Further research is needed to evaluate their QoL in real-life settings.

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A-116

Radioimmunotherapy Sequence Impact on Clinical Outcomes of Patients with Melanoma Brain Metastases: A Meta-analysis of Comparative Studies

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Background
The rates of brain metastases in melanoma can approach a high of 50%, which portends an abysmal prognosis. Immunotherapy and radiotherapy have been shown to improve overall survival in patients with melanoma with brain metastases. However, the optimal sequence of immunotherapy and radiotherapy remains unclear. We conducted the following meta-analysis to evaluate the best sequence to improve progression-free and overall survival.

Methods
A review of the medical literature was conducted using online databases. Inclusion criteria consisted of English language, diagnosis of melanoma brain metastases, comparative studies of immune checkpoint inhibitors given before or after radiotherapy, and those that reported overall (OS) and progression-free (PFS) survival. Studies that reported mixed data that included concurrent immune checkpoint inhibitors with radiotherapy were excluded. A meta-analysis using the fixed effects and random effects models was conducted.

Results
Six retrospective comparative studies with a total of 213 patients were included. The median age was 62 years, and the median follow-up was 22 months. Initiating immunotherapy before radiotherapy was associated with worse PFS compared to radiotherapy followed by immunotherapy (HR=1.77, 95%CI 1.21-2.60, p=0.003; I^2=13.5%). Furthermore, starting with immune checkpoint inhibitors followed by radiotherapy was associated with worse OS compared to radiotherapy followed by immunotherapy, but with borderline significance (HR=1.39, 95%CI 0.97-1.99, p=0.07; I^2=0%).

Conclusions
This is the first and largest meta-analysis to date to show that in patients with melanoma brain metastases, the optimal sequence that impacts patients' survival outcomes is to start with radiation therapy followed by immune checkpoint inhibitors.

A-427

Real-World Evaluation of ImmuCare Patient-Reported Outcomes in Melanoma Patients Treated with Immune-Checkpoint Inhibitors

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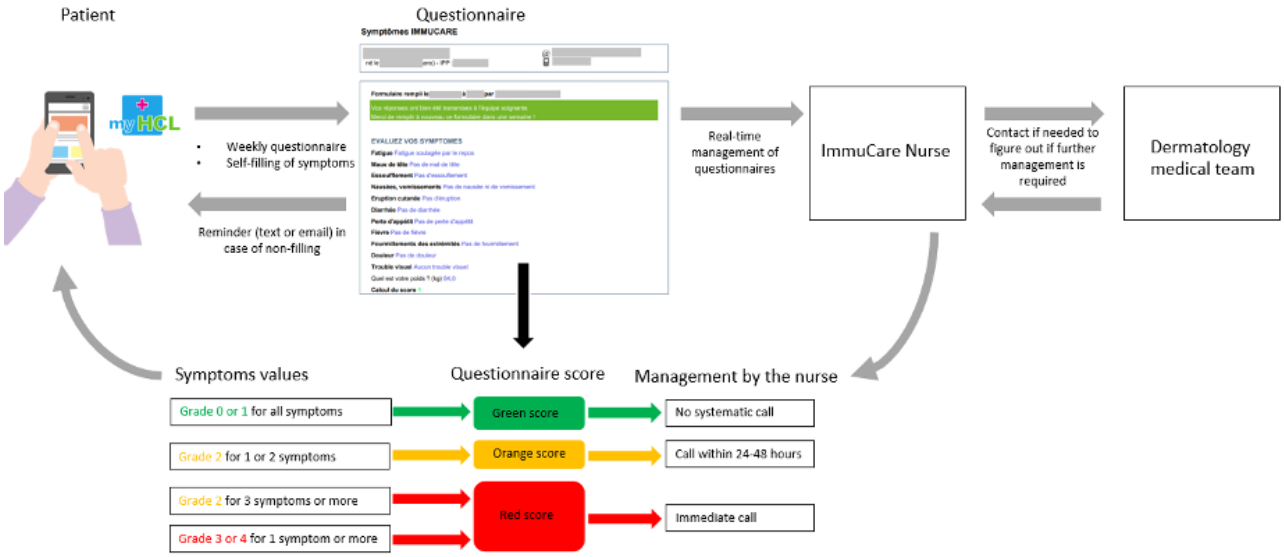
Background

Toxicity profile of immune checkpoint inhibitors (ICI) poses challenges for early detection and management of immune-related adverse events (IrAEs). In oncology, patient-reported outcomes (PRO) programs are reported to have a beneficial effect, however the efficacy for the detection of IrAEs in melanoma patients remains unclear. A PRO program (ImmuCare-PRO) was created in 2018 in our dermatology department; we investigated its real-world impact in detecting grade 2 or above IrAEs occurring during ICI treatment in melanoma patients.

Methods

Patients receiving ICI for a melanoma were followed using a weekly online questionnaire containing 11 symptoms suggestive of IrAE. Moderate/severe symptoms generated an alert score and an intervention by an oncology nurse or physician. The program's performance in detecting grade 2 or above IrAEs, as well as reasons for missed detections, were assessed.



How the ImmuCare-PRO program works

Results

A total of 5202 questionnaires completed by 136 patients led to 783 (15.1%) alert scores; 64 of them were associated with 69 grade 2 or above IrAEs, with 22 (34.4%) questionnaires correctly detecting 27 grade 2 or above IrAEs; saving a mean 4.1 days on the next scheduled visit and leading to only 1 emergency room visit. Forty-two grade 2 or above IrAEs (mainly blood disorders, n=31) were not detected. False alerts often resulted from functional or non-specific symptoms (32.3%), such as fatigue or general pain.

Conclusions

A third of moderate-to-severe IrAEs, and most of those with clinical impact, mainly skin toxicities, colitis and rheumatological IrAEs, were correctly detected by ImmuCare-PRO program, allowing earlier management while avoiding visit to the emergency room.

A-317

Real-world outcomes for advanced melanoma in the adjuvant and unresectable setting: Single-center registry analysis

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Background
Immune checkpoint inhibitors (ICI) and BRAF/MEK-inhibitors (BRAF/MEKi) have significantly improved outcomes of patients with advanced melanoma over the last decade. Registry data can help to validate clinical trial results in the actual real-world setting and point to areas of unmet clinical need.

Methods
Real-world evidence from the melanoma registry of a tertiary cancer center in Switzerland was analyzed in regards to the clinical management and outcomes in both the adjuvant (n=331) and the unresectable (n=375) treatment settings.

Results
Adjuvant therapy showed an overall median relapse-free survival (RFS) of 50 months. The 3-year RFS rate was 53% for anti-PD1, and 67.6% for BRAF/MEKi. Patients who presented with lymph node plus in-transit metastasis or with distant metastasis had a significantly reduced overall survival (OS). Treatment had to be stopped because of toxicity in 10.9% of patients, which did not affect RFS/OS, unless the time on treatment was <3 months. Following a relapse of disease, the median progression-free survival (PFS) dropped to only 6.6 months and was significantly worse for relapses that had occurred within the first 2 months or were unresectable. In patients with a resectable relapse, a second adjuvant therapy retained efficacy (median RFS2 43.7 months).

In the first line therapy of unresectable melanoma, the 5-year OS rates were 46.5% for anti-PD1, 49.2% for anti-CTLA4/PD1 combination, and 52.4% for BRAF/MEKi. Elevated LDH levels or presence of brain metastasis substantially shortened OS in a multivariate analysis (HR>1.78, p<0.035). Anti-CTLA4/PD1 showed a numerical trend for improved survival versus anti-PD1 (HR 0.64, p=0.15). Upon progression, the overall median OS2 was less than two years and was significantly impaired in patients with elevated LDH (HR 4.65, p<0.001) or widespread disease with at least three metastatic sites, particularly bone metastasis (HR 2.62, p=0.026).

Conclusions
The real-world evidence supports the outcomes reported in the pivotal phase 3 trials. There is urgent clinical need for patients experiencing an early adjuvant relapse, as well as those with unresectable melanoma and brain metastasis or who fail first line treatments.

A-271

RESCUE STUDY – International Survey on training of Dermatology Residents in Supportive Oncodermatology

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Background

Dermatologic management of cancer patients with cutaneous adverse events, acquired during and after oncologic treatments, is known as supportive oncodermatology. This subspecialty within dermatology includes the prevention, early identification, and mitigation of dermatologic toxicities affecting the skin, hair, nails, and mucous membranes resulting from chemotherapy, targeted therapies, immunotherapy, endocrine therapies and radiation therapy. Interdisciplinary collaboration between oncologists and dermatologists is becoming increasingly important. A perceived clinical need drives several hospitals to develop specific dermatologic care programs for oncologic patients.

Methods

The European Academy of Dermatology and Venereology (EADV) Task Force “Dermatology for Cancer Patients,” in partnership with the US Oncodermatology Society is conducting this international questionnaire-based survey RESCUE[SV1] (RESIDENTS SURVEY ON TRAINING OF DERMATOLOGY RESIDENTS IN SUPPORTIVE ONCODERMATOLOGY) which aims to evaluate the current state of knowledge and training in supportive oncodermatology for dermatology residents in Dermatology throughout the world, and their expectations for improving their ability/skills to manage these patients with dermatological toxicities More than 25 countries are involved in the RESCUE survey (Europe, USA, South America, Asian countries).

The study consists of an online questionnaire with 30 predefined questions by a panel of experts. The survey is distributed in an anonymised form to dermatology residents via the EADV Task Force Dermatology for Cancer Patients, the US Oncodermatology Society and the national associations of dermatology and dermatology residents.The study takes 5 to 10 minutes to be completed.

Results

To date, 549 dermatology residents have participated in the study. Final results will be obtained in April 2024.

Conclusions

Rhe RESCUE study is designed to improve the training of residents in Dermatology, enabling future generations of dermatologists to take better care of oncologic patients

A-232

Sex differences and its impact on treatment outcomes of advanced melanoma in Germany – a DeCOG study on 2032 patients of the multicenter prospective skin cancer registry ADOREG

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Background

The incidence of melanoma is increasing in patients of both sexes. It is known that women and men have differences in their innate and acquired immune systems. Knowing these differences, it is reasonable to hypothesize that the reagibility of the immune system and hereby the efficacy of tumor therapies might be dependent on sex. This study assessed sex-based differences in the outcome to different treatment strategies in metastatic melanoma.

Methods

Patients with advanced (stage IV, AJCCv8) metastatic melanoma who were first-line treated with either PD-1-based immune checkpoint inhibition (ICI) as monotherapy or combination, or targeted therapy (TT) with BRAF plus MEK inhibitors were identified from the prospective multicenter skin cancer registry ADOREG. The study endpoints were best overall response (BOR), progression-free survival (PFS), and overall survival (OS); all endpoints were evaluated univariately and multivariately with focus on sex differences.

Results

2032 evaluable patients were identified who were treated with ICI or TT. Of those, 1274 (62.7%) were male and 758 (37.3%) were female. Median age was 66 years (range: 20-96) in the ICI cohort, and 60 years (range: 20-90) in the TT cohort. Most patients (n=1484 (73%); m: 941, f: 534) received ICI therapy; 548 patients (27%; m: 333, f: 215) were treated with TT. There were no sex-specific differences in BOR (ICI: p=0.83; TT: p=0.52), PFS (ICI: p=0.46; TT: p=0.21), and OS (ICI: p=0.20; TT: p=0.30). There were also no significant sex-specific differences in OS when patients were separately investigated by serum LDH (normal LDH: p=0.41; elevated LDH: p=0.39) or BRAF status (BRAF wt: p=0.15; BRAF mut: p=0.82). The multivariate analyses likewise showed no sex-specific differences in BOR, PFS and OS. However, LDH and ECOG were confirmed as independent influencing variables in terms of PFS and LDH, ECOG and type of therapy in terms of OS.

Conclusions

There were no sex differences in first-line treatment outcomes in terms of response and survival in patients with advanced metastatic melanoma, irrespective of whether they received ICI or TT. There were also no sex differences in treatment response when BRAF status or LDH levels were measured.

A-267

Title: Survival Analysis of Patients with Non-Cutaneous Metastatic Melanoma Treated in a Reference Center in Northeast Mexico.

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Background/Aim
In 2020, cutaneous melanoma (CM) had an incidence of 324,635 new cases and 57,043 deaths worldwide. Other presentations, such as uveal and mucosal melanoma (NCM), account for 5% and 3.6%, respectively. NCM have atypical anatomical and clinical features, as well as worse prognosis compared to CM. This study aimed to determine differences in overall survival (OS) of metastatic patients diagnosed with NCM (mNCM) compared to patients diagnosed with CM (mCM).

Methods
This retrospective study analyzed the clinical records of patients diagnosed with metastatic melanoma and treated at the Mexican Institute of Social Security, UMAE #25 from June 2020 to October 2023.

Results
We identify 43 patients with metastatic melanoma, 60% with mCM and 40% with mNCM, sites of presentation were head and neck mucosal (35.2%), uveal (23.5%), gastrointestinal mucosal (23.5%), and vulvar mucosal (17.6%). mOS for mCM was 51.7 mo vs 47.4 mo for mNCM (IC 95%, 36.7-72.0; p=0.480). mPFS for mCM was 17.1 mo vs 13.8 mo for mNCM (IC 95%, 11.6-20.8; p=0.330). Most of the patients with mCM have recurrent disease (61.5%), when for those with mNCM most were diagnosed de novo (58.8%). Regarding the sites of metastasis for mCM/mNCM, 32.7%/20.0% were visceral, 18.1%/9.0% lymphatic, 3.6%/1.8% central nervous system, and 9.0%/5.4% other. Only 3 patients (7%) have BRAF determination (1 mutated and 2 wild type). Wide-local excision was performed in 20 patients, 4 patients received adjuvant radiation and only 2 patients received adjuvant immunotherapy (IO) as previous treatment for non-metastatic disease. Thirty-eight patients received first-line treatment, consisting in IO 52.6%, chemotherapy (CT) 44.7%, and targeted therapies 2.6%. OI was used as 2L in 41.2% of patients. Five patients did not receive treatment due to poor functional status.

Conclusions
In our study mNCM was very prevalent, corresponding to a 40% of our overall metastatic melanoma population, showing a 4.3 mo reduction in mOS when compared with mCM; however, it was not statistically significant. Due to barriers of access, we provided 1L CT in 44.7% of patients, BRAF determination was not performed to any patient at our hospital and only 2 patients received adjuvant IO.

A-179

Updated outcomes of AdjuMel study: real-world data in patients with resected stage III-IV melanoma treated with adjuvant nivolumab in France

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Background

Adjuvant nivolumab has become a standard treatment for patients with completely resected stage III-IV melanoma following the results of the phase 3 CheckMate 238 trial (CM238)[1]. A previous interim analysis of the AdjuMel study reported the first safety and efficacy data of adjuvant nivolumab in France in a real-world setting[2]. The aim of the present analysis is to provide updated outcomes for this study with 2 years of follow-up.

Methods

AdjuMel is an observational, prospective, nationwide study evaluating patients treated with adjuvant nivolumab for resected stage III-IV melanoma in France. The study aims to assess effectiveness, safety, and treatment patterns of nivolumab under routine clinical practice in France in the adjuvant setting over a 5-year follow-up. FPFV was on Sept 3rd, 2020 and LPFV on July 21th, 2021. The primary endpoint is Relapse Free Survival (RFS). This interim analysis included patients with ≥1 follow-up visit and took into consideration only data collected up to the 24 months-visit.

Results

343 patients were included in this interim analysis. The median follow-up was 23.4 months (range 2.10-27.33). Median age was 65 years (range: 27-95), 57.4% of patients were male, and 35.8% had a BRAF mutation. At treatment initiation, 86.8% of patients had stage III disease and 13.2% were stage IV. The estimated 2 year-RFS rate was 52.8% (95% CI; 47.0% - 58.2%). An exploratory analysis using Cox Model showed that the risk of recurrence or death was lower in patients with stage IIIA vs IIIB/C/D (HR: 0.43) and in patients < 75 years (HR: 0.56), and higher in patients with ulceration (HR: 1.98). Secondary endpoints (Distant Metastasis Free Survival [DMFS], Overall Survival [OS]) and subsequent treatments received after adjuvant nivolumab will also be presented.

2-years RFS rate	52.8% (95% CI; 47.01%-58.23%)
2-years DMFS rate	67.15% (95% CI; 61.62% - 72.07%)
2-years OS rate	85.67% (95% CI; 81.24% - 89.13%)

2-years Survival data

Conclusions

This interim analysis of the AdjuMel study provides updated insights into the real-world effectiveness of adjuvant nivolumab in patients with resected stage III-IV melanoma in France. The estimated 2-year RFS rate was 52.8% and exploratory analyses revealed potential factors influencing the risk of recurrence or death. These findings shows that outcomes in real life may differ from randomized clinical trials (data to be shown) and underscore the persistence of unmet needs in melanoma.

References:

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A-224

Use of Immune Checkpoint Inhibitor (ICI) Therapy for Cutaneous Melanoma from 2014 to 2021 in Norway: Insights from Real-World Data

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Background
The introduction of immune checkpoint inhibitor (ICI) therapy for cutaneous melanoma (CM), including mono- and combination therapies, took place during 2014–17 in Norway. The initial approval was for patients with localized and metastatic disease. Adjuvant treatment with pembrolizumab or nivolumab for patients with local lymph node metastasis was approved in 2019. There is limited knowledge on patient characteristics and treatment patterns for patients undergoing ICI therapy in real-world clinical practice, and also compared to clinical trial results.

Methods
This population-based cohort study included all adult (≥18) CM patients registered in the Cancer Registry of Norway who were treated with ipilimumab, nivolumab, pembrolizumab, or combination therapy (nivolumab and ipilimumab) during 2014-21 in Norway. Patients were followed until the end of 2021, emigration, or death, whichever occurred first. Descriptive statistics were performed and stratified by year of first ICI treatment period (2014–15, 2016–18, 2019–21).

Results
Among 2083 patients receiving ICI therapy, 1193 (57.3%) initiated treatment between 2019 and 2021. The typical patient receiving first-line ICI treatment was male, had over 11 years of education and had an intermediate to high income. The median age at treatment was 68 and higher than observed in clinical trials such as CheckMate 067 [CheckMate067]. The most frequent tumor location was the trunk. During 2019–21, a higher proportion of treated patients had superficial spreading melanoma (25%) compared to previous years (<8%). There was also a notable rise in the percentage of ulceration from 13% (2016–18) to 30% (2019–21).

Median time from initial diagnosis to first-line ICI therapy decreased over time, reaching under 4 months during 2019–21. Nivolumab monotherapy became the most used treatment over time, with the combination therapy of ipilimumab and nivolumab emerging as the second most frequent during 2019-21. Approximately 10% of first-line ICI therapy users received treatment within 3 months of post-lymph node surgery. Most common second-line treatment were radiotherapy and targeted therapy, except for patients on combination therapy, where nivolumab monotherapy was preferred.

Conclusions
Patients treated in real-world clinical practice differ from patients in clinical trials. This retrospective panorama is pivotal for future studies comparing real-world treatment outcomes with results from clinical studies.
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Melanoma – Surgery

A-245

Clinical characteristics and surgical approach of patient with SAMPUS/ Melanoma and pleomorphic dermal sarcoma on face

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Background
Melanocytic tumors of uncertain malignant potential are pathologic entity which demonstrates pigmented lesions whose evolution, course, diagnosis, classification, terminology and treatment were not determined and their malignant potential is also under further research. Pleomorphic dermal sarcoma is also entity which is under revision classification of Soft tissue tumors since 2013.

Methods
Case presentation:
A patient reported to dermatologist office for pigmented lesion in the right lower eyelid area. Punch biopsy was performed which showed superficial atypical melanocytic proliferation of unknown significance (SAMPUS). Decision was brought to do excision of the lesion together with the excision of the second lesion in immediate proximity (skin of the right cheek area) which had clinical characteristics of squamous cellular carcinoma (SCC).

Results
Pathohistological report of the lesion of right lower eyelid showed atypical junctional melanocytic lesion (peripheral parts) with progression to melanoma (central parts) and lesion of the skin of the right cheek showed pleomorphic dermal sarcoma.

Wide surgical excision for both tumors and reconstruction with full thickness skin graft were our therapy of choice. The aforementioned surgical treatment provided the patients with the tumor free status as well satisfactory aesthetical appearances and quality of life.

Conclusions
SAMPUS/ Melanoma and pleomorphic dermal sarcoma in the same patient with immediate proximity of the lesions was not described in the literature as the best of our knowledge.
We reviewed the literature to find the best surgical options and treatment modalities.

A-378

Does the interval between melanoma diagnosis and surgery have an impact on outcomes? A systematic review and meta-analysis.

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Background
Conflicting studies report the effects of the time interval between cutaneous melanoma diagnosis by an excision biopsy and subsequent surgery in the form of a wide local excision (WLE) and sentinel lymph node biopsy (SLNB). Delays in access to surgery are concerning to patients and physicians, therefore the objective was to conduct a systematic review and meta-analysis to determine whether the time interval from melanoma diagnosis to SLNB affects patient outcomes of overall survival (OS), melanoma-specific survival (MSS) and recurrence-free survival (RFS).

Methods
We screened the public databases for cohort studies and randomised control trials published from January 1997 to August 2023 on the effect of early versus late SLNB on survival outcomes. The study was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. The study protocol was registered in PROSPERO (CRD42021240045). Pooled relative hazard ratio with 95% confidence intervals were calculated for each outcome. Heterogeneity between the studies was assessed with the I^2 statistic using Cochrane RevMan Web v7.4.0.

Results
The initial search yielded 19,740 articles, of which 14 met the inclusion criteria (Figure 1). In the 11 studies selected for quantitative analysis 58,087 patients were identified. The cutoff value to define “early” SLNB in the meta-analysis was up to 43 days, with any comparator cohort included as a “late” SLNB.

MSS and RFS was worse in patients who underwent early SLNB (hazard ratio (HR) of 0.75, 95% CI: 0.61 – 0.94 and 0.87, 95% CI: 0.76 – 0.98, respectively). The early and late groups had similar OS (HR 0.87, 95% CI: 0.75 – 1.02). For SLN positive patients there was no difference in MSS (HR 1.26, 95% CI: 0.79 – 2.01) and RFS (HR 0.98, 95% CI: 0.87 – 1.11) (Figure 2).

Conclusions
Patients undergoing SLNB for melanoma do not have a significant difference in OS but have improved MSS and RFS prognosis in the late group, if SLNB is performed within 3 months after primary excision biopsy. There is no significant outcome difference in SLN positive patients. Clinicians and patients should gain confidence that there is no harm from delaying SLNB up to 3 months.

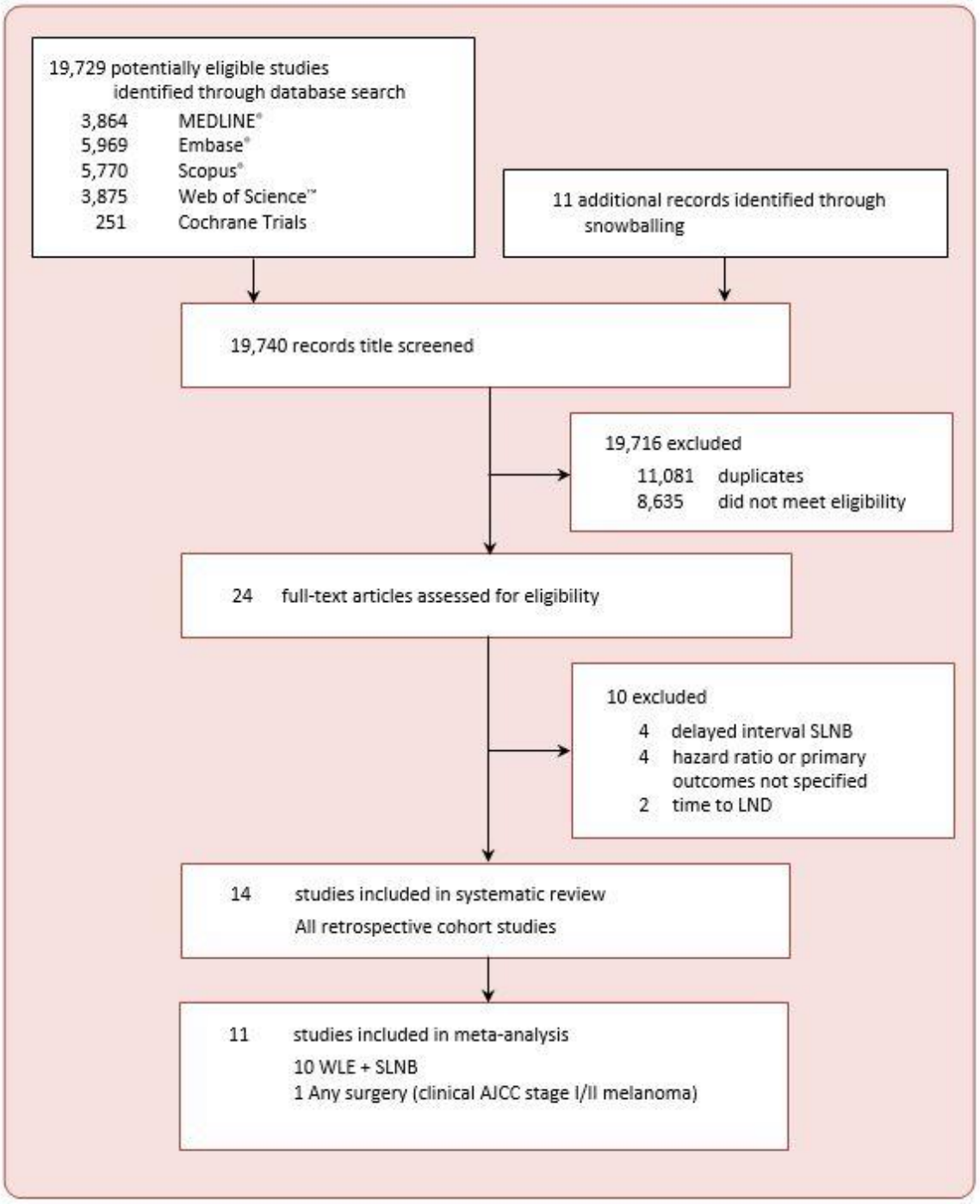
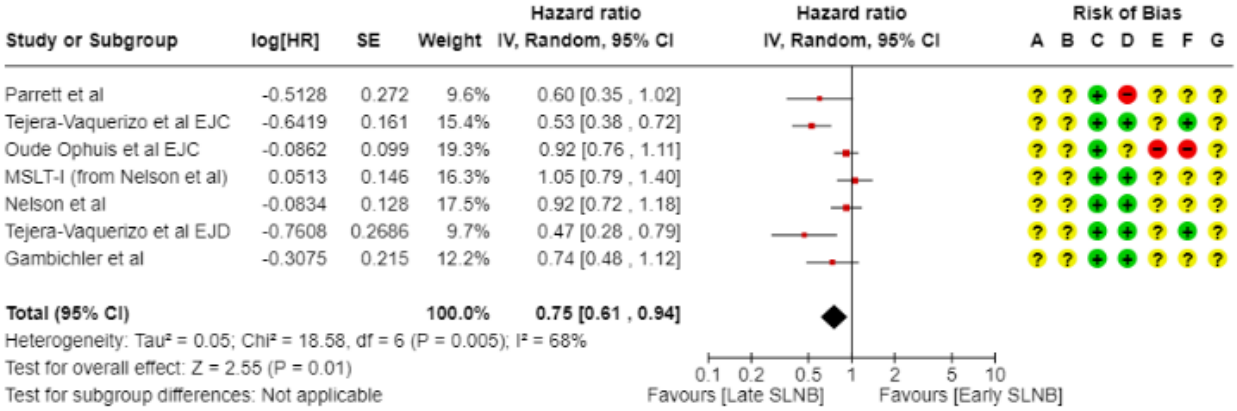
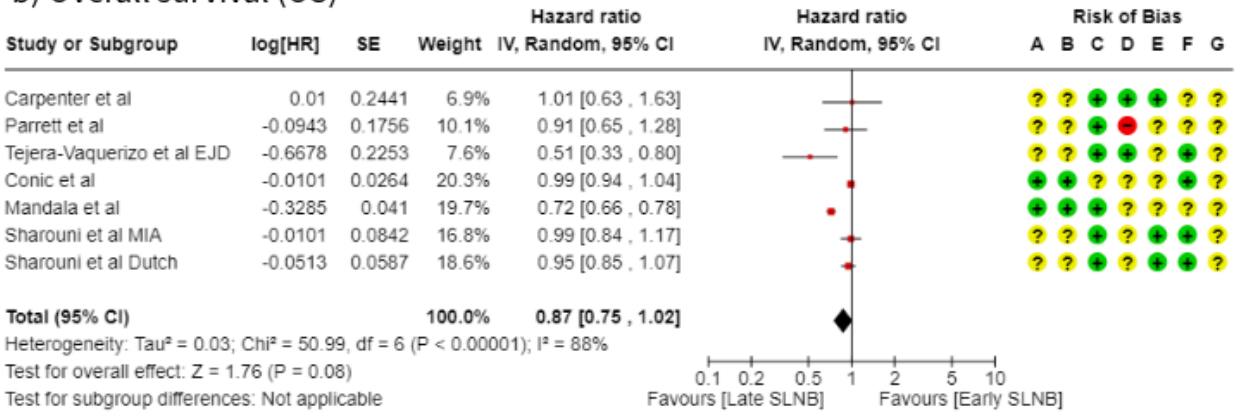


Figure 1: PRISMA flow diagram of the search strategy and literature review process.

a) Melanoma-specific survival (MSS)



b) Overall survival (OS)



c) Recurrence-free survival (RFS)

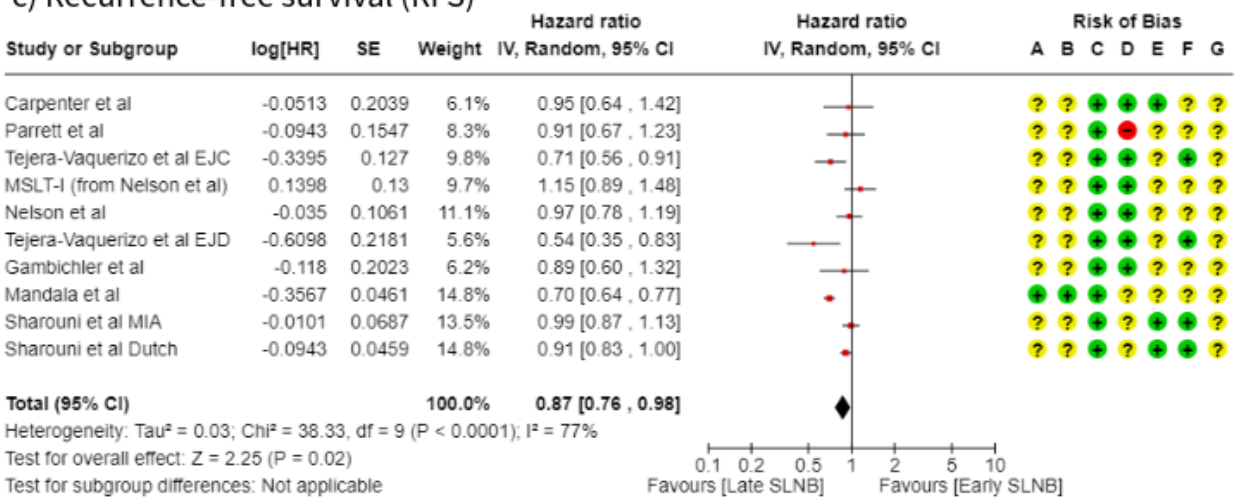


Figure 2: Meta-analysis of outcomes after Early or Late Sentinel Lymph Node Biopsy in patients with primary cutaneous melanoma.

A-315

Higher intraoperative detection rate of suspicious non-palpable lesions using wire marking in skin cancer patients

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Background
Follow-up protocols in patients after complete resection of high-risk cutaneous tumors lead to a discovery of metastases in very early stages, but surgery on non-palpable lesions proves to be challenging.

Methods
In this monocenter retrospective study 39 patients suffering from malignant skin tumors with suspicious non-palpable lesions located in the lymph nodes (90 %) or deep subcutaneously/intramuscularly (10 %) were included. In 21 patients the lesions were excised under ultrasound guidance, and 18 patients received a wire marking before surgery. Both patient groups were compared regarding successful intraoperative finding of the lesion, duration of the procedure, and complications.

Results
Wire marking led to a significantly higher intraoperative detection rate of 100% versus 76% ($p<0.05$). The average time needed for the complete procedure ($p=0.91$) or the rate of complications ($p= 0.70$) did not differ significantly between both groups. The size of the malignant lesions successfully removed by wire marking was significantly smaller ($p<0.05$). Of all 34 detected lesions only 20 (58.8%) were confirmed to be malignant.

Conclusions
Wire marking increases the detection rate of non-palpable suspicious subcutaneous or lymphatic lesions. It leads to earlier diagnosis of metastasis but also allows to avoid unnecessary complete lymph node dissection.

A-300

Lymph Node Operative Experience in the UK – What's Changed?

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Background

The landscape of surgical intervention for melanoma has been transformed in the past decade, influenced by key trials including MSLT-II and DeCOG-SLT, and the emergence of effective adjuvant and neoadjuvant systemic therapies. This study aims to explore the impact of these developments on the surgical training in lymph node surgery in the UK.

Methods

UK-wide data sourced from a prospective, trainee reported, operation logging platform (eLogbook, Joint Committee on Surgical Training). The analysis was structured around three key timeframes to reflect the evolving surgical protocols; the 18 months prior to the MSLT-II findings (July 2015 - December 2016), the 18 months preceding the licensing of NICE adjuvant treatments (January 2017 - June 2018), and the 18 months following these implementations (July 2018 - December 2019).

Results

Across the 54-month study period, plastic surgery trainees logged a total of 36,525 lymph node surgery procedures. There was a trend towards fewer lymph node dissections (Figure 1), with a 14.2% reduction in axillary (n=2,109 to 1,808) and a 11.5% reduction in inguinal (n=944 to 835) lymph node basins, and a 3.8% increase in neck lymph node dissections (n=1,366 to 1,418). Additionally, there was a 33.9% increase in the number of sentinel lymph node biopsies (n=6701 to 8976, Figure 2) performed across all major lymph node basins. We additionally compare data by training grade within Plastic Surgery, and across 4 UK surgical specialties (Breast Surgery, ENT, Plastic Surgery and Maxillofacial Surgery) who report lymph node procedures at completion of training.

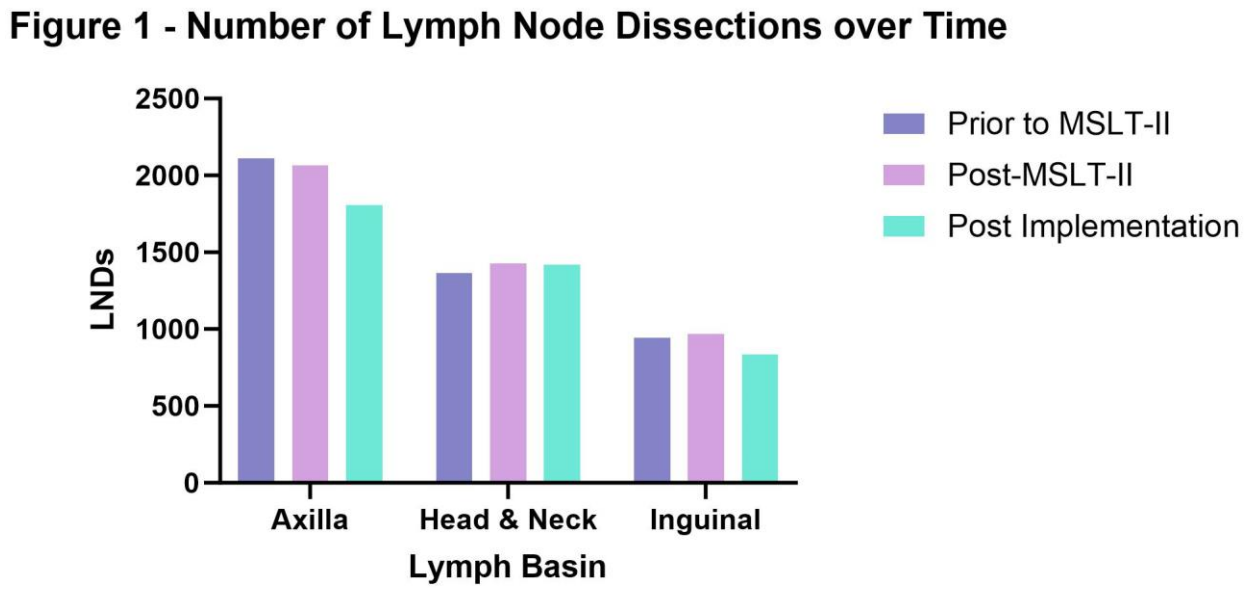

Figure 1 - Change the volume of trainee-reported lymph node dissections over the three time periods

Figure 2 - Number of Sentinel Lymph Node Biopsies over Time

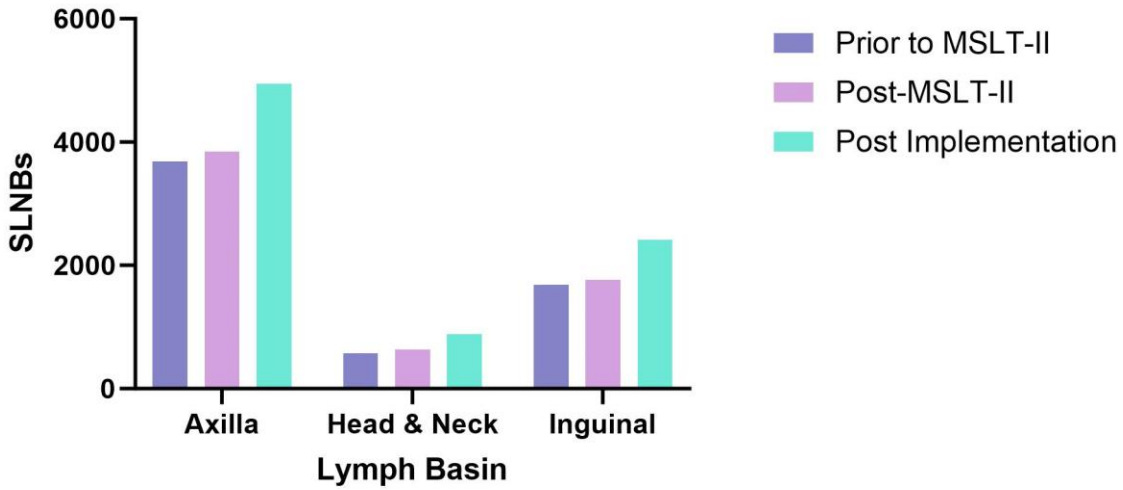

Figure 2 - Change in the volume of trainee-reported sentinel lymph node biopsies over time

Conclusions

The study underscores a significant shift in trainee-reported lymph node surgery within the UK, marked by an increase in sentinel lymph node biopsies and a decline in lymph node dissections, with the exception of procedures involving the head and neck. This reflects the broader changes in melanoma treatment strategies with a reduction in completion lymph node dissections for melanoma, and their implications for surgical training and specialist certification should be considered.

A-262

Patients who forego sentinel lymph node biopsy after 31-GEP testing are not harmed: A prospective, multicenter analysis

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Background
While a positive sentinel lymph node biopsy (SLNB) is a predictor of poor outcomes in patients with cutaneous melanoma (CM), up to 88% of patients undergoing SLNB will have a negative node. Nearly 16% of patients with a negative biopsy will experience tumor recurrence, and 10% risk death from their disease, with risk increasing with increased Breslow thickness. The 31-gene expression profile test is validated to: 1) identify patients at high (Class 2B), intermediate (Class 1B/2A), or low (Class 1A) risk of recurrence who may benefit from increased or decreased management intensity and 2) identify patients with a high or low likelihood of SLNB positivity. The purpose of this study was to demonstrate that patients with a Class 1A 31-GEP who forego SLNB when integrating 31-GEP into clinical decision-making have equivalent outcomes with less surgical complications.

Methods
This prospective, multicenter study included patients with T1-T2 tumors being considered for SLNB. During visit 1, patients provided informed consent, and 31-GEP testing was ordered. During visit 2, 31-GEP results were received. At visit 3, the clinician recorded whether an SLNB was performed, and which clinicopathologic, demographic, and/or GEP factors influenced the SLNB decision. Patients were followed according to established guidelines (e.g., clinical follow-up, imaging) for a median of 2 years (range=0.4–3.6 years). Only those with a Class 1A result are included in this analysis.

Results
Of those with a Class 1A 31-GEP result, 63 (48%) underwent SLNB (3.2% (2/63) SLN positivity); 68 (52%) did not undergo SLNB (T1=59, T2=9), with 94.1% (64/68) citing the 31-GEP as one reason to forgo the procedure. No patient (0% [0/131]) with a Class 1A result had a recurrence, regardless of SLN status, at the last follow-up (100% 3-year RFS).

Conclusions
Patients with T1-T2 CM who forego SLNB, when using 31-GEP testing as part of decision-making, are not harmed, as no patient experienced tumor recurrence (median follow-up=2 years). The 31-GEP identified patients at low risk of SLN positivity who may safely forego SLNB, reducing healthcare costs and procedure complications. Longer follow-up may be needed to further validate this conclusion.

A-298

Predicting sentinel node positivity in patients with primary cutaneous melanoma: an international multicentre study validating and refining the MIA risk calculator

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Background

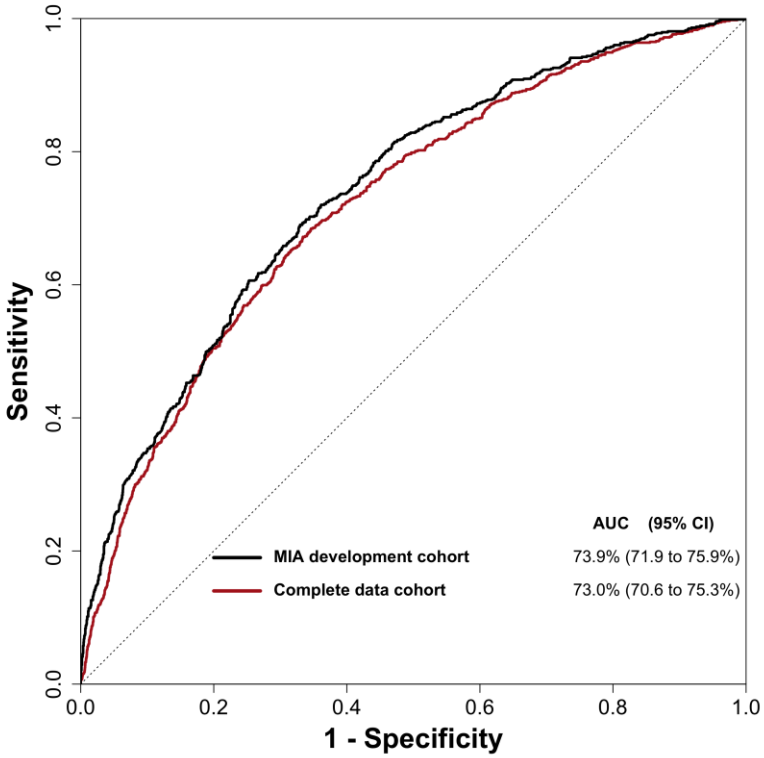
The Melanoma Institute Australia (MIA) sentinel node (SN) metastasis risk-prediction online calculator[Lo2020] is now widely used around the world. The tool comprises eight models that variously use between three and six input parameters. However, the full (six-parameter) model has only been validated in the US population, the model with missing mitoses was validated for the Dutch and Swedish populations. Furthermore, some confidence intervals (CIs) of the tool are large due to uncommon input parameter values. This study further validated the tool in other populations and improved the precision of the risk estimates.

Methods

Validation data were pooled from the Danish national Melanoma Database and eight cancer centres: UK(3), US(2), New Zealand(1), Sweden(1), Brazil(1). CI refinement data were pooled from this and previous validation and development cohorts. All patients had the SN result and the minimum data required for the tool (age, Breslow thickness and melanoma subtype), while the presence of ulceration, lymphovascular invasion or mitoses were included where available. The performance of the tool was assessed using C-statistics for discrimination and via a calibration plot. Re-calculation of CIs for the estimated risks was performed using the combined data from all original risk calculator development and validation cohorts.

Results

The validation cohort consisted of 15,371 patients, 4,989 of whom had all six input parameters for the full model. The C-statistics were 73.0% (95% CI 70.6–75.3%) in the subset with all six parameters available,



Receiver operating characteristic (ROC) curves showing the accuracy (AUC) and confidence intervals (CI) of the Melanoma Institute Australia (MIA) risk calculator to predict sentinel node positivity in the development cohort (black), n=3,477, and the international validation cohort with all six input parameters available (red), n=4,989.

and 70.8%, 71.5% and 70.1% when 1, 2 or 3 optional parameters were missing. Calibration was excellent, with an intercept and calibration slope of 0.01 (95% CI -0.02–0.03) and 1.03 (95% CI 0.90–1.16), respectively. The revised CIs were substantially smaller than in the original tool, with a median reduction of over 75%.

Conclusions

The results demonstrated that the MIA sentinel node risk-prediction tool performance was robust across a wide geographical range of populations. Furthermore, the precision of the models has been substantially improved with updated CIs based on a larger population sample. This study will therefore give users greater confidence in the tool's reliability in predicting the risk of SN positivity.

References:

[Lo2020] Lo, S. N., Ma, J., Scolyer, R. A., Haydu, L. E., Stretch, J. R., Saw, R. P. M., Nieweg, O. E., Shannon, K. F., Spillane, A. J., Ch'ng, S., Mann, G. J., Gershenwald, J. E., Thompson, J. F., Varey, A. H. R., (2020), Improved Risk Prediction Calculator for Sentinel Node Positivity in Patients With Melanoma: The Melanoma Institute Australia Nomogram, Journal of Clinical Oncology, 2719–2727, 38/24, doi: 10.1200/JCO.19.02362

A-219

Prognostic impact of the surgical deep margin distance of invasive acral melanoma of the sole: A multi-institutional retrospective study

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Background
Evidence concerning the optimal deep margins for wide excision (WE) of primary tumors in melanoma surgery is lacking. Despite the importance of preserving plantar subcutaneous fat in the sole for cushioning function, no study has yet investigated the appropriate depth margins for acral melanoma of the sole (sole AM). Herein, we compared the prognosis of different negative deep margins.

Methods
A retrospective review of the clinical records of patients with invasive resectable sole AM who underwent WE of the primary tumor across 40 Japanese institutions was conducted. Patients were divided into two groups: surgical negative deep margin of 3 mm or less (≤3mm-group) and over 3 mm (>3mm-group), and the prognosis was compared. Kaplan—Meier analysis, multivariable Cox proportional hazard models (MCPH models), and propensity-score matching (PSM) were used to estimate survival probabilities.

Results
This study included 425 patients (median age 73 years) who underwent WE based on the peripheral surgical margins recommended in the NCCN guidelines. The median follow-up period was 48 months. The ≤3mm and >3mm groups included 154 and 271 patients, respectively. Baseline characteristics were similar except for Breslow thickness (P <0.05) and presence of in-transit, satellite, and regional nodal metastasis (P <0.05). There was no significant difference in local recurrence-free survival (LRFS), disease-free (DFS), or overall survival (OS) (5-year LRFS, 94% vs 93%; P = 0.58; 5-year DFS, 63% vs. 55%; P = 0.61; 5-year OS, 82% vs. 76%; P = 0.13). MCPH models showed no significant differences in LRFS, DFS, or OS between the two groups (LRFS, P = 0.66; DFS, P = 0.24; OS, P = 0.72). PSM yielded two groups of 153 patients each, while further analysis revealed no statistical significance in LRFS, DFS, or OS (5-year LRFS, 94% vs. 94%; P = 0.78; 5-year DFS, 63% vs. 69%; P = 0.06; 5-year OS, 82% vs. 80%; P = 0.65).

Conclusions
In sole AM, WE with a surgical negative deep margin >3 mm did not improve prognosis and excessive deep margins may be superfluous.

A-185

Surgical treatment of external ear skin melanoma: literature review and one-center experience

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Background
Skin melanoma is a rare condition that affects the external ear, accounting for only 1-4% of all cutaneous melanomas. The helix is the most common location (57%), followed by the lobule (17%). The mean Breslow thickness of skin melanoma is 2.01 mm; the most common histopathological subtype is superficial spreading melanoma (41%), followed by nodular melanoma (22%) and lentigo maligna melanoma (21%). Ulceration is reported in 20% of patients.
According to modern clinical guidelines, the surgical margins from the primary tumor should be from 0.5 mm for melanoma in situ to 2 cm for invasive melanoma with Breslow thickness > 2 mm. However, the peculiarities of the external ear anatomy significantly limit the possibility of tumor resection with such surgical margins. So, in most cases, peripheral resection margins are adjusted to fit individual anatomical or functional considerations.
Our study aims to review the literature and share our surgical experience treating external ear melanoma.

Methods
We analyzed literature published since 1995 on the surgical treatment of external ear melanoma and found a lack of randomized studies on the peripheral margins of resection. Our experience includes five patients with external ear skin melanoma treated surgically in 2023.

Results
The auricle often requires reconstructive surgery due to various types of damage. Some of the most common reconstructive operations performed on the auricle include the retroauricular flap, which is used to repair defects in the helical region that do not involve cartilage; the star modification of wedge excision, which is used for lesions in the helical region; the Antia-Buch flap; the "Revolving door" island flap; coverage of surgical defects with skin grafts; wedge excision; and partial ear amputation.
Among five patients (all women, mean age 48.4 years) with melanoma of the external ear treated at our center in 2023, three had melanoma localized to the helix, one to the lobule, and one to the concha region. The average thickness by Breslow was 2.6 mm; in one case melanoma in situ was diagnosed. The mean surgical margins were 6 mm. For ear reconstruction star-shaped and «Revolving door" island flaps were used.

Conclusions
Boa_Image_Frame wide margins are often challenging to implement during the surgical treatment of melanoma of the external ear; thus, randomized trials are needed to assess the safety of narrower surgical margins.

A-157

The practice of using Vacuum-Assisted Closure in combination with free skin grafts in the treatment of wound defects after removal of malignant skin neoplasms

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Background
One of the most effective methods of malignant skin neoplasms' treatment is surgical removal of the tumor with the achievement of complete cleanliness of the resection edges, which often leads to the problem of closing postoperative defects, especially in complex anatomical areas, such as the distal parts of the limbs and the skin of the head. For treatment of such defects, the method of closing plastic wounds with free skin flaps is used, however, it should be noted that, in anatomically complex areas the engraftment of the donor flap is quite often either incomplete, or there is death of the flap, which is caused by the incomplete fit of the flap. We got the idea of using bandages with negative pressure as a method of fixing free skin flaps arose

Methods
The study included 61 patients, who underwent surgical treatment of malignant skin neoplasms in the clinic of the National Cancer Institute from 2019 to 2023. For closing the wound defects we used the technique of plastic surgery with a free split skin flap. Depending on the tactics of postoperative wound management, patients were divided into two groups. For first group of 41 patients after closing the defect with a dermatome flap the bandage with negative pressure was applied. In second group of 20 patients, the transplanted skin flap was fixed with a conventional ointment bandage

Results
In the group using Vacuum-Assisted Closure, complete engraftment of the flap was observed in 54.4 ± 7.7% of cases, in group 2 this result was achieved in only 5.0 ± 4.8% of patients ($p = 0.002$). It should also be noted the general advantage of group 1 regarding engraftment of > 50% of the graft area, the indicator of which was 85.6 ± 5.4% of patients, while in group 2 it was 70.0 ± 10.2% of patients

Conclusions
The use of a bandage with negative pressure during the transplantation of dermatomal flaps showed an advantage in terms of the number of complete engraftments, as well as the area of engraftment compared to the usual group of ointment bandages. This made it possible to significantly speed up the healing time of the postoperative wound and reduce the rehabilitation period of patients.

A-407

Time interval between Sentinel Lymph Node Biopsy and Excision of Primary Melanoma does not impact long term outcomes in a large UK cohort

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Background
The impact of timing on sentinel lymph node biopsy (SLNB) positivity remains a debated topic in melanoma management, with guidelines recommending SLNB within a three-month window post-diagnosis. Our study sought to identify whether the time interval to perform SLNB affects SLNB positivity in patients with primary cutaneous melanoma. Our secondary aim was to assess whether the time to access SLNB impacts long-term outcomes.

Methods
This large single-centre cohort observational study included all patients over 18 years old with a confirmed diagnosis of primary melanoma undergoing SLNB between December 2009 and December 2022 in Cambridge University Hospital, UK. SLNB patients were categorised into two groups: (i) those who had their SLNB performed ≤42 days, ii) those who had their SLNB performed >42 days. Kaplan-Meier survival analysis was used to compare recurrence-free survival (RFS) and melanoma-specific survival (MSS). The size of the largest metastatic foci was grouped into <0.1 mm, 0.1 – 1.0 mm or >1.0mm. Multiple logistic regression identified independent predictors.

Results
Overall, 1393 patients with primary cutaneous melanoma were included (723 [52%] men, 922 [66%] superficial spreading, median age at diagnosis 60.0 years). 170 patients (12.2%) had their SLNB up to 42 days after their primary melanoma excision. Median follow-up was 4.5 (1.9 – 7.3) years and the median time to SLNB from the primary pathology report was 66 days. The MSS (HR, 1.083; 95% CI, 0.7465 - 1.571), and the RFS (HR, 0.81; 95% CI, 0.43 - 1.53) were no different between the two groups. Within this cohort, 21.1% were SLNB positive, of which 49.8% had a metastatic deposit between 0.1-1.0mm. The presence of ulceration (OR = 1.652, 95% CI: 1.189 to 2.285), mitosis (OR = 4.222, 95% CI: 1.856 to 12.16), and head and neck melanomas (OR = 3.340, 95% CI: 1.974 to 5.908) were independent risks of SLNB positivity.

Conclusions
Time interval to perform SLNB does not affect positivity rate or size of lymph node micrometastasis. Long term follow up does not identify any benefit for SLNB performed within 6 weeks of diagnosis in MSS or RFS.

Supporting Document 1

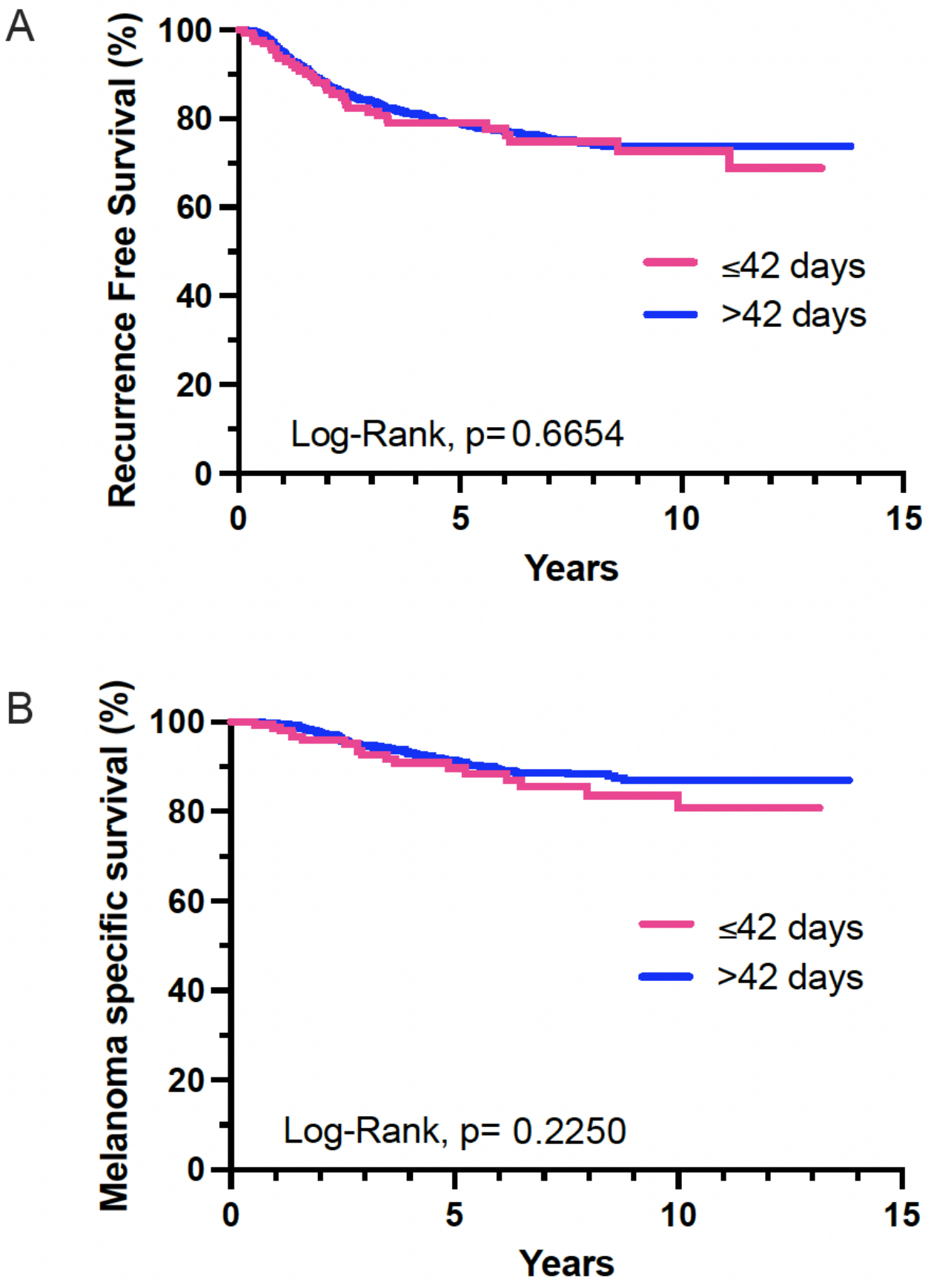

Figure 1 Long term outcome following SLNB for melanoma stratified by time interval between melanoma excision and SLNB. (A) Recurrence free survival, Log-rank p=0.6554 (B) Melanoma specific survival, Log-rank p=0.2250.

A-451

Total skin micrografts with punch for repair of surgical defects in acral skin

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Background

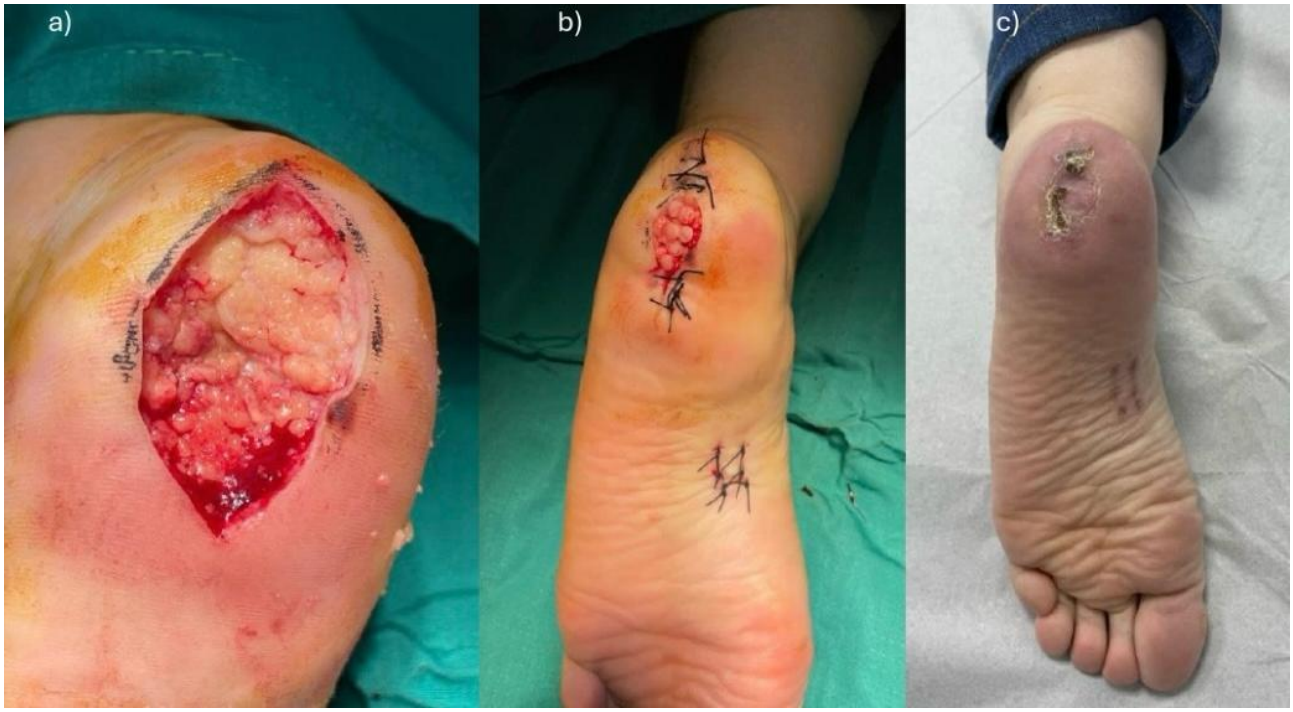
Repairing surgical defects in the foot plantar area represents a surgical challenge due to the limited tissue mobility in that area, poor skin circulation, and the weight-bearing requirement in the zone. Treatment selection considers the size and depth of the defect, as well as the characteristics of each patient. Currently, there are various alternatives that allow for durable, painless, functional, and aesthetically satisfactory coverage. Skin grafts are preferred for small defects (<3 cm) or as temporary coverage, while simple and complex flaps are used for larger defects, although often resulting in longer surgical time, patient morbidity, and increased postoperative care. A reconstruction option is presented for acral foot skin defects, with a simple technique and obtaining an effective and fast result.

Methods

The case of a 61-year-old female patient is presented who during a physical examination revealed a hyperpigmented macule on the left heel. Dermatoscopy revealed a ridge pattern.

Results

A biopsy was performed, and histopathological analysis confirmed acral melanoma in situ. A 5 mm margin expansion was performed from the scar, resulting in a defect measuring 5 x 2.5 cm (Fig 1.a). Primary closure of both edges was performed. Subsequently, 6 micrografts obtained using a No. 4 punch were applied to the central area of the defect. The donor site was the skin from the plantar arch, chosen due to its non-weight-bearing, and closed with simple stitches (Fig 1.b). The patient progressed without complications, with a good and rapid aesthetic and functional outcome at 5 weeks (Fig 1.c).



Conclusions

Optimal reconstruction of any defect aims to achieve the best functional and morphological outcomes while minimizing patient morbidity. Micrografts or punch grafts are a type of full thickness autograft, which in addition to the coverage function, have an angiogenic effect and release growth factors favoring the contraction and epithelialization of the defect. They have been associated with anti-inflammatory and analgesic effects, as well as a shortened healing time. Therefore, this technique allows for defect repair with advantages for both the treating team and the patient. On one hand, it involves a simpler surgical technique, shorter surgical time, and local anesthesia. On the other hand, it avoids adding morbidity, results in better cosmetic outcomes at the donor site, and reduces patient recovery time, with excellent functional and aesthetic results.

Melanoma – Systemic therapy other than ICI therapy

A-211

Adjuvant therapy for Asian patients with resected stage III/IV BRAF V600-mutant melanoma with more than 3 years of follow-up: A multicenter retrospective study in Japan

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Background
Dabrafenib plus trametinib (Dab/Tram) and anti-PD-1 antibodies (anti-PD-1) have been used as adjuvant therapy for resected stage III/IV BRAF V600-mutant melanoma. No randomized trials have directly compared the efficacy of these agents. Some retrospective studies suggest that Dab/Tram is associated with a longer recurrence-free survival (RFS), although longer follow-up is required to evaluate these two different classes of agents as early recurrence is less frequent in Dab/Tram-treated patients, whereas late recurrence is less frequent in anti-PD-1-treated patients. In this study, we aim to evaluate these adjuvant therapies with more than 3 years of follow-up in a real-world setting.

Methods
We retrospectively collected the clinical data of East Asian patients with resected stage III/IV BRAF V600-mutant melanoma treated with adjuvant Dab/Tram or anti-PD1 between July 2018 and June 2020 from 37 institutions in Japan. Kaplan–Meier curves with log-rank tests and multivariable Cox proportional hazard models were used to compare survival outcomes between the two groups.

Results
We identified 145 eligible patients treated with adjuvant Dab/Tram (n=117) and anti-PD1 (n=28). The median follow-up duration (range) was 44.2 (3.2–63.3) months for all patients and 47.9 (36.7–63.3) months for patients who were alive at their last follow-up. At baseline, the median age (range) of patients in the Dab/Tram and anti-PD-1 treatment groups was 59 (22–85) and 62 (20–80), respectively. No statistical difference in baseline characteristics was observed between the two groups; however, all five patients with PS ≥1 were treated with Dab/Tram, and four of six patients with stage IV disease were treated with anti-PD-1. The median RFS of the Dab/Tram treatment group was not reached, whereas that for anti-PD-1 treatment group was 18.4 months ($p = 0.122$). The median overall survival (OS) was not reached in both groups ($p = 0.362$). In a multivariable analysis, the hazard ratios for RFS and OS of Dab/Tram compared with those of anti-PD-1 were 0.51 (95% confidence interval [CI], 0.28–0.92, $p = 0.025$) and 0.67 (95%CI, 0.31–1.43, $p = 0.301$), respectively.

Conclusions
Even with more than 3 years of follow-up, adjuvant Dab/Tram is associated with a longer RFS and equivocal OS compared with anti-PD-1. However, a randomized trial is needed to confirm this owing to the limited number of patients and selection bias in this study.

A-189

Complete remission of malignant lung metastasis of melanoma with stereotacticradiotherapy (Case report)

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Background

The new therapeutic modalities in the treatment of disseminated melanoma malingum, such as immune and targeted therapy, provided a longer progression-free and overall survival. Stereotactic radiotherapy can be mentioned as an additional therapy, and in our case as an alternative treatment.

Methods

In 2014, our patient underwent excision of a Clark IV, 1.5 mm Breslow melanoma from the neck region, followed by re-excision, with negative results. A follow-up CT examination in 2018 described a focus on both sides of the lung, which were also confirmed by a PET/CT examination. CT-guided biopsy confirmed metastasis with BRAF positivity.
We planned BRAF-MEK inhibitor targeted therapy, however, due to Gr.3-4 pancreatic enzyme elevations, therapy was not started. A control CT scan showed minimal progression in the lungs, one 1.6 cm and one 0.8 cm foci, but do not verifeid further dissemination. According to the minimal disease status, we did not start targeted therapy, the lung metastases were treated with Cyberknife in December 2018. During close observation, regression and postirradiation pneumonitis (Gr. 2) appeared around the irradiated foci, which were confirmed by pulmonological examination. The patient received antibiotics with Medrol therapy.

Results

The patient is still being observed, complete remission was still confirmed at the CT scan in December 2023.

Conclusions

In our case, targeted stereotaxic radiotherapy proved to be an effective therapeutic option. The main treatment of patients with disseminated melanoma is systemic therapy, but in special cases, such as the presence of oligometastases or the oligoprogression of the disease, local therapeutic modalities can be successfully used.
Stereotactic radiotherapy and stereotactic radiosurgery can be safe and effective therapeutic modality for the treatment of regional tumors.

A-444

Exceptional response to rechallenge of BRAF/MEK inhibitors in patients with primary acquired resistance to targeted therapy

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Background
The combination of BRAF and MEK inhibitors (BRAF/MEKi) is amongst the standard of care for stage IIIC/IV BRAF-mutated melanoma. However, most patients acquire resistance and develop disease progression. The therapeutic options are limited once a patient has progressed on both targeted therapy and immunotherapy. Nowadays, much data shows that resistance to BRAF/MEK inhibitors is reversible.

Methods
We present two cases with an exceptional response to the rechallenge of anty BRAF/MEK inhibitors in patients who progressed on BRAF/MEKi in the first-line setting and then on immunotherapy in the second-line
The first patient was a 41-year-old male with BRAF-mutated melanoma. with multiple
lymph nodes, bones and muscle metastases at baseline. He had received anty BRAF/MEKi in the first line and progressed after five months. In the second line, the anty-PD-1 antibody was administered with the best response of progression disease confirmed after three months. Then, the rechallenge with BRAF/MEKi was initiated. The therapy lasted for 25 months, with the best response of partial remission. The progression occurred after over two years of therapy in brain metastases.
The second patient was a 40-year-old male with BRAF-mutated melanoma of unknown primary with brain and adrenal gland metastases at baseline. He had received BRA/MEKi in the first-line setting until the progression in the central nervous system (CNS) occurred after 31 months. Once the stereotactic radiosurgery was completed, the immunotherapy with anty-PD-1 antibody was initiated, with a six-month response. Then, the rechallenge with BRAF/MEKi was started. The progression-free survival lasted for 13 months when further progression in CNS occurred

Results
In both cases, the resistance to targeted therapy was overcome.
The progression-free survival (PFS) in the third-line setting lasted for 25 and 13 months, respectively, which significantly exceeded the median PFS known from other reports. The treatment was well tolerated and considerably increased the quality of life.

Conclusions
Rechallenge with BRAF/MEK inhibitors represents a vital treatment option for patients who had previously progressed on both kinase inhibitors and immunotherapy and should be considered whenever available.

A-381

Gastric Melanoma: Primary or Secondary Forms? 2 case reports

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Background

Primary gastrointestinal melanoma, particularly primary gastric melanoma, is a rare entity associated with a poor prognosis due to late diagnosis. Melanoma, lung, and breast cancer are the most commonly implicated cancers in metastatic involvement of the gastrointestinal tract. In 20% of metastatic melanoma cases, the stomach is affected. Distinguishing between primary melanoma and metastatic malignant melanoma of unknown origin presents a significant challenge.

Methods

We reviewing the medical histories of our patients treated for mucosal melanoma and we identified gastric melanoma in the absence of a primary cutaneous tumor in two cases. We compared literature data in terms of epidemiology, possible therapy and expected survival

Results

Our two patients underwent a gastroenterological examination and gastroscopy due to gastrointestinal complaints. The gastroscopy sample from revealed malignant melanoma, suggesting the possibility of both a primary tumor and metastasis, despite the absence of a visible primary tumor on the skin. Mucosal tumor analysis identified a BRAF V600E mutation, leading to the initiation of combined targeted therapy. One of the two patients chest + abdominal-pelvic CT examination revealed disseminated melanoma. Combined targeted therapy was initiated for the patient in bad condition on December 20, 2023. A follow-up PET- CT examination is scheduled for the end of February to assess the treatment's efficacy. The other patient achieved complete remission from melanoma during dabrafenib + trametinib therapy since 2019.

Conclusions

Unfortunately, the majority of upper gastrointestinal (GI) melanomas present as metastatic due to nonspecific symptoms, causing diagnostic delays as indicated by data from the literature. Differentiating between primary and metastatic melanoma in the stomach is particularly complex, where the clinical behavior of the disease, in addition to histological examination, can provide valuable insights. The distinction between primary and secondary melanoma in the stomach relies on clinical behavior. Treating mucosal melanoma of the gastrointestinal tract poses a substantial challenge. Available therapies include surgical resection, targeted therapy, immunotherapy, chemotherapy, or a combination of surgical resection with systemic treatment. Positive BRAF mutation cases show a survival benefit with dabrafenib in combination with trametinib.

A-107

Patient treatment preferences in unresectable/metastatic BRAF-mutated melanoma: a qualitative study

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Background
BRAF V600 mutations occur in ~50% of malignant melanomas. We conducted a qualitative analysis aimed at eliciting treatment preferences of patients with *BRAF*-mutated melanoma.

Methods
Between 2020 and 2021, patients from France, Spain, Italy, and Australia with unresectable/metastatic *BRAF*-mutated melanoma receiving targeted therapy (TT) or immunotherapy (IO) were recruited by their treating healthcare professional (HCP) and participated in a 60-min semi-structured interview (See Table 1).

Results
Data were available for 18 patients (mean age 53 years; 61% male) receiving TT alone (n=10), IO alone (n=7), or both TT + IO (n=1). At treatment initiation, patients' conversations with HCPs focused mostly on efficacy and adverse effects (AEs; Table). Treatment choice was rarely discussed with patients, although patients did not consider this a problem as they trusted their HCPs. Patients expected to discuss how treatment would impact their quality of life (QoL), but this was rarely addressed by HCPs. Fatigue was the most impactful AE for patients. Overall, treatment burden was acceptable for patients. When discussing potential new treatments, patients were less concerned with AEs they deemed manageable or had already experienced. The AEs that most concerned patients were those that impacted their QoL or any that caused treatment discontinuation.

Conclusions
Fatigue is the most impactful AE for patients receiving treatment for unresectable/metastatic *BRAF*-mutated melanoma. Patients want to discuss how treatments will affect their QoL. In the group analysed this was rarely addressed. Tailoring the conversation to each patient, depending on the treatment received, is key.

Table 1. Conversation focus areas

Focus of conversations with HCPs	Patients N=18, (%)
Focus of conversations at treatment initiation	
Efficacy	13 (72)
AEs	11 (61)
Does not want / need to know everything	10 (56)
No / few treatment alternatives discussed	7 (39)
Unsure when treatment will stop	7 (39)
Impact of melanoma on daily life*	
Normal life overall	7 (39)
No sun exposure due to melanoma	6 (33)
Fatigue	5 (28)
Focus of conversations about potential new treatments	
AEs	17 (94)
Efficacy	17 (94)
Pill burden	14 (78)
Impact on QoL	12 (67)
Storage	10 (56)
Non-detailed information on AEs	9 (50)
Administration schedule	8 (44)

*Not necessarily related to treatment

Table 1:Conversation focus areas

A-183

Real-world outcomes of adjuvant therapy in melanoma: an Italian referral center experience.

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Background
In this retrospective study conducted at an Italian referral center for melanoma care, we scrutinized the real-world effectiveness and safety of adjuvant therapy (targeted therapy (TT) or immunotherapy (IT)) for 163 high-risk melanoma patients.

Methods
Melanoma patients treated with adjuvant therapy between September 2017 and April 2023 were collected. Patients' inclusion criteria were age ≥ 18 years, histologically confirmed diagnosis of melanoma, resected stage IIIA-D or IV-NED according to AJCC 2017 (TNM 8th edition), and absence of evidence of distant metastasis before the start of adjuvant therapy according to total-body computed tomography scans. Study endpoints were relapse-free survival (RFS), distant metastasis-free survival (DMFS), overall survival (OS).

Results
82 patients (50.3%) underwent adjuvant treatment with TT, 81 patients (49.7%) with anti-PD-1 (63 patients (38.7%) nivolumab; 18 patients (11%) pembrolizumab). Over a 48-month period, the cumulative RFS rate was recorded at 54.9% (95% CI, 45.0% to 63.7%), the DMFS rate at 58.4% (95% CI, 48.0% to 67.3%), the OS rate at 66.5% (95% CI, 55.5% to 75.3%). No statistically significant differences in RFS, DMFS and OS emerged between the two treatment categories (p=0.532, p=0.761 and p=0.889, respectively) nor among the three different drug types (p=0.754, p=0.666 and p=0.989, respectively).
At a median follow up of 36 months, disease recurrence was observed in 57 patients (35.0%), of whom 29 patients (50.9%) had received TT and 28 (49.1%) IT. 8 patients (14.0%) had a loco-regional recurrence, 38 patients (66.6%) developed only distant metastases, and 11 (19.3%) both local and distant metastasis. 22 TT-treated patients (75.9%) relapsed after the end of the adjuvant cycle, whereas only 7 patients (24.1%) relapsed during adjuvant treatment. Conversely, 19 IT-treated patients (67.9%) recurred during the treatment, whereas only 9 patients (32.1%) relapsed after the end of adjuvant therapy. A higher incidence of brain relapse was noted in the TT cohort (48.3% vs 21.4%, p=0.034), while no significant differences were observed for other sites.

Conclusions
Our research supports the real-world effectiveness of both adjuvant treatment approaches. It sheds light on disparities in recurrence patterns and sites between TT and IT. The lack of influence of completion lymphadenectomy on RFS, DMFS, and OS aligns with existing literature and clinical observations.

A-362

The clinical utility of comprehensive genomic profiling tests for patients with advanced malignant melanoma in a real-world setting: A retrospective analysis from a single cancer center

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Background
The incidence rate of malignant melanoma is increasing, but despite its high mortality rate, there are limited therapeutic options. Significant advances in systemic therapies have been made since the approval of molecularly targeted drugs and immune checkpoint inhibitors (ICIs), but there is still an urgent need to develop new therapies. The comprehensive genomic profiling (CGP) tests based on next-generation sequencing (NGS) assay is becoming a routine in clinical oncology to identify genotype-guided therapies. Several studies, including clinical trials, have reported the utility of CGP testing for solid tumors, but there are few reports discussing its significance for melanoma patients. This study assesses the clinical utility of CGP testing for melanoma patients in a real-world setting in terms of the proportion of patients receiving genotype-matched therapies and patients with actionable and druggable genomic alterations.

Methods
We retrospectively analyzed data from 74 patients with malignant melanoma who underwent one of the CGP tests at the National Cancer Center Hospital, Tokyo between August 2019 and July 2023. All CGP test results were discussed in a molecular tumor board called expert panel consisting of medical oncologists, pathologists, genome researchers, bioinformaticians, and genetic counsellors for treatment recommendations.

Results
All 74 patients had appropriate CGP test results. The median age of the patients was 61, ranging from 9 to 89 years old. There were 27 cases (36.5%) of non-acral cutaneous and mucosal melanoma, 14 cases (18.9%) of acral melanoma and only two cases (2.7%) of uveal melanoma. Four cases (5.4%) were diagnosed as of unknown origin. Actionable genomic alterations and druggable alterations were found in 68 patients (91.9%) and 50 patients (67.6%), respectively. Seventeen patients (23.0%) had access to either genotype-matched therapy, off-label drugs or were enrolled in clinical trials.

Conclusions
The detection rate of actionable and druggable genomic alterations and the proportion of patients who proceeded to another therapy based on the CGP testing after completion of standard treatments were higher than previously reported for other solid tumors. Therefore, CGP tests may be beneficial in daily practice for the treatment of malignant melanoma patients.

A-399

The RoMEO study: a real-world, observational, prospective investigation of dabrafenib and trametinib combination treatment in patients with BRAF V600 unresectable or metastatic cutaneous melanoma.

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Background
Cutaneous melanoma is the most aggressive form of skin cancer, although outcomes have improved markedly with targeted therapies and immune checkpoint inhibitors. The combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib (D+T) administered as first or second-line therapies for locally advanced or metastatic melanoma with BRAF V600 mutation has improved progression free survival (PFS) and overall survival (OS) in randomized trials [1]. The aim of this study, conducted under the auspices of the French National Skin Cancer Task Force, was to further investigate the efficacy and clinical use of D+T in a real-world setting in France.

Methods
We assessed the real-world efficacy of first or second-line D+T at 12 months in 240 patients with BRAF V600 unresectable or distant metastatic cutaneous melanoma from 38 centers. Patient data were collected at baseline and at 3, 6 and 12 months. PFS and OS were computed in the study overall and by treatment line.

Results
Among an assessable population of 224 patients, 101 (45.1%) presented with 3 or more metastatic sites and 75 (33.5%) with a brain metastasis. In addition, 33 (19.1%) had lactate dehydrogenase above twice the upper limit of normal (2xULN). In total, 165 and 59 patients received D+T as first and second-line therapies respectively. PFS rates at 12 months were 29.9% overall (95% CI: 23.8-36.2) and 29.8% (95% CI: 22.7-37.2) and 30.4% (95% CI: 19.1-42.6) for first and second-line treatment groups respectively. The OS rate at 12 months among all patients was 54.8% (95% CI: 47.6-61.3). Of the safety population (n=235), 139 (59.1%) and 40 (17.0%) reported a treatment-related adverse event or serious adverse event respectively. No new safety signals were observed.

Conclusions
Clinical outcomes after treatment of the study population with D+T in France were similar whether deployed as a first or second-line treatment. RoMEO complements the findings from COMBI-d and COMBI-v and provides additional data on patients excluded from these pivotal trials due to brain metastases or following other treatments. Further work is underway to characterize and assess tumor kinetics as a potential predictor of D+T treatment response.

Merkel cell carcinoma

A-394

All-trans retinoic acid activity in Merkel cell carcinoma cells: implication of the retinoid pathway

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Background

Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer. About 80% of MCCs, are linked to oncogenic Merkel cell polyomavirus (MCPyV). The currently available MCC therapeutic options are unsatisfactory, therefore novel therapeutic approaches are required. The biological activity of all-trans retinoic acid (ATRA) is mediated by RAR/RXR receptors that activate genes crucial for cell differentiation. Dysregulations of RAR/RXR receptors lead to carcinogenesis. ATRA displays a strong *in vitro/in vivo* antitumor activity in different carcinoma types, but its effect in MCC is currently unknown. Herein, we investigated cell death effects of ATRA in MCC cells.

Methods

For this purpose, *in vitro* in MCPyV-positive (MCCP), i.e., PeTa and WaGa, and -negative (MCCN), i.e., MCC13 and MCC26, MCC cell lines and control, normal human lung fibroblasts MRC-5 were tested with ATRA. The effect of ATRA was evaluated by testing MCC cell proliferation, migration and colony formation abilities. Apoptosis/cell death were evaluated *via* Annexin-V/P.I. assays. Apoptosis was evaluated by RT^2 Profiler PCR mRNA array and by western blot (WB) analysis. Retinoid pathway was evaluated by RT^2 Profiler PCR mRNA array.

Results

ATRA treatment led to a significant reduction in MCC cell proliferation, migration and clonogenicity, while increasing apoptosis/cell death in MCC cell lines compared to untreated cells. MCCP cells were slightly more ATRA-sensitive compared to MCCN cells. No significant effects have been found in the ATRA-treated control cell line. Gene expression array indicated a significant overexpression of several pro-apoptotic genes in MCC cells. Consistently, high levels of pro-apoptotic proteins have been found following ATRA treatments in MCC cells, while being almost undetectable in untreated cells. Pro-apoptotic markers were almost undetectable in ATRA-treated MRC-5. Numerous retinoic signaling genes were differentially expressed in ATRA-treated MCC cells compared to untreated cells.

Conclusions

Overall, *in vitro* data indicate that ATRA is effective in reducing MCC cell growth, while presenting strong pro-apoptotic effects and favoring cell death, by modulating the retinoic receptor pathway. These results, for the first time, point to ATRA as a potential novel effective antineoplastic drug for the MCC therapy.

A-395

Merkel cell carcinoma cells proliferation is inhibited by the DNA methyltransferases inhibitor guadecitabine via methylome modulation

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Background

Introduction & Objectives. Merkel cell carcinoma (MCC) is a rare, but aggressive skin cancer. Nearly 80% of MCCs are Merkel cell polyomavirus-positive (MCCP), while the remaining cases are UV-induced and virus-negative (MCCN). Currently available MCC therapies are limited. Impaired DNA methylation is common in MCC, making epigenetic-based antitumor therapies feasible approaches in clinical practice. Guadecitabine (gDAC) is a novel DNA methyltransferases inhibitor whose antitumor activity has been demonstrated in skin cancers and could be effective also in MCC. This study aimed to evaluate the efficacy of gDAC on MCC cell death.

Methods

Materials & Methods. gDAC activity was evaluated by testing proliferation, viability, migration, and colony forming abilities in MCCN cells MCC13 and MCC26, and MCCP cells PeTa and WaGa and in the fibroblast control cell line HDFa. Apoptosis was investigated by western blot evaluating the expression of apoptotic markers. Upon gDAC treatment, the methylome profile of each gDAC-treated MCC cell line was evaluated using the Infinium MethylationEPIC v2.0 Kit.

Results

Results indicate that gDAC can significantly reduce MCC cell proliferation, migration, and colony formation abilities, while increasing apoptosis/cell death in MCC cells compared to untreated cells/controls. Increased levels of pro-apoptotic proteins, paralleled to decreased levels of anti-apoptotic proteins, were determined in gDAC-treated MCC cells. An extensive hypomethylation of the genome was detected in treated MCCP and MCCN cells, underlining a similar epigenetic response to the pharmacological treatment with gDAC of both MCC subsets.

Conclusions

gDAC can be considered a novel candidate for MCC antitumor therapy.

A-132

Prognostic significance of sentinel node tumor burden in Merkel Cell Carcinoma.

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Background

A sentinel lymph node biopsy (SLNB) provides important prognostic information in patients with Merkel cell carcinoma (MCC). However, there are no histopathological prognostic factors known to identify high-risk patients amongst those with a positive sentinel lymph node (SLN). In this study we aim to assess the prognostic value of SLN tumor burden and the histological pattern of spread in SLN positive MCC.

Methods

The pathology specimen of all patients with MCC who underwent SLNB procedure between 2005-2022 was reviewed. SLN tumor burden was measured as the largest diameter of the tumor deposit. Additionally, 5 different histological patterns of sentinel node involvement were scored.

Results

A total of 131 patients were included, of whom 46 had a positive SLN. At two years, the overall survival (OS) was significantly higher in patients with a lower than median SLN tumor burden (<0.625 mm) as compared to those with a high SLN tumor burden (90% vs. 63%, p=0.046). The 2-year recurrence-free survival for the respective groups was 61% vs. 37% (p=0.082) and 2-year disease specific survival was 100% and 85% (p=0.078). A trend towards better OS was observed for patients with a non-solid compared with solid pattern of spread (84% vs. 60%, p=0.061).

Conclusions

Sentinel node positive MCC patients with a higher sentinel node tumor burden had a significantly worse 2-year overall survival.

Rare tumors

A-206

A retrospective multicenter study on the real-world efficacy of chemotherapy in 204 Japanese patients with advanced extra-mammary Paget's disease

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Background
Extramammary Paget's disease (EMPD) is a rare skin cancer that develops in the vulva, anus, and axilla. The incidence rate of EMPD is 0.13 per 100,000 population/year in Caucasians and 0.28 in Asians; thus, it is more frequent in Asians. Although distant metastases have been reported to occur in 10%-20% of all cases of EMPD, standard systemic chemotherapy for advanced EMPD has not been established worldwide. To establish a standard treatment for advanced EMPD, prospective clinical trials are necessary. As a pilot study, we investigated a large sample of patients with advanced EMPD and analyzed the efficacy of systemic chemotherapies.

Methods
Patients with advanced EMPD who were treated in 16 Japanese institutions during 2011-2022 were evaluated. The efficacy of each treatment was estimated by determining the objective response rate (ORR) or progression-free survival (PFS) and overall survival (OS) using the Kaplan-Meier analysis. Multivariable analysis was performed to account for potential confounding factors, such as age, sex, and performance status (PS). A total of 204 patients were enrolled, of which 164 (80.4%) patients were treated as follows: Docetaxel hydrate (DOC), n=108 (52.9%); tegafur/ gimeracil/ oteracil potassium (S-1)/DOC, n=16 (7.8%); fluorouracil/cisplatin (FP), n=26 (12.8%); fluorouracil/epirubicin/carboplatin/vincristine/mitomycin C (FECOM), n=3 (1.5%); and other, n=11 (5.4%). Forty (19.6%) patients received the best supportive care.

Results
OS and PFS did not differ significantly among the DOC, S-1/DOC, FP, FECOM, and other groups (p=0.176 and p=0.568, respectively). The ORRs in the S-1/DOC, DOC, FP, and FECOM groups were 75.0%, 51.9%, 38.5%, and 66.7%, respectively. The odds ratio for the ORR of the S-1/DOC group compared with the DOC group estimated by the logistic regression analysis with adjustment for age, sex, and PS was 2.72, (95% CI: 1.09-6.78, p=0.032). S-1/DOC was the only treatment with a significantly higher ORR than that of DOC, which is the most frequently used treatment for advanced EMPD in Japan.

Conclusions
Although there were no significant differences in PFS and OS between the multiple regimens, the S-1/DOC group showed significantly higher ORR compared with the DOC group. Because the high response rate to S-1/DOC greatly improves the quality of life of patients with advanced EMPD, S-1/DOC may be more beneficial than DOC and other regimens for the treatment of advanced EMPD.

A-241

Atypical granular cell tumor - a case for worry?

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Background
Granular cell tumors (GCTs) are uncommon tumors that are thought to arise from Schwann cells. They may occur in patients of all ages, and most commonly occur in the fourth and sixth decades of life, with female predilection. GCTs are rare in childhood.

Methods
A middle-aged lady presented a painful, solitary skin colored nodule on her left abdomen measuring 8mm in diameter. It had persisted for two months. There was no antecedent trauma. She was otherwise well, had no significant comorbidities and does not take any medications. A excisional biopsy of the nodule was performed.

Results
Histopathology was consistent with a dermal proliferation of epithelioid cells that were arranged diffusely and with interstital pattern. The cells contained finely granular, eosinophilic cytoplasm. The cells were S100 and CD68 positive. They were negative for high and low-molecular weight keratins and Mart-1/Melan-A. Focal spindling of the granular cells was seen, with several cells exhibiting variably pleomorphic nuclei. Some of the nuclei were also vesicular with large nucleoli. There were no mitotic figures seen. These findings were consistent with an atypical granular cell tumor (GCT).

GCTs are classified into benign, atypical, and malignant tumours based on histological criteria and immunohistochemistry for S-100 and CD68. Malignant GCTs exhibit three or more of the following features; necrosis, spindling of tumour cells, vesicular nuclei with large nucleoli, mitotic rate (greater than two mitoses/10 high-power fields), high nuclear to cytoplasmic ratio, and pleomorphism. In our case, a diagnosis of atypical GCT was considered as two of these features were present. This lesion did not score sufficient features to be classified as malignant.

Conclusions
Treatment of atypical GCT is challenging, in particular with respect to the extent to which the patient should be investigated. In our patient, shared decision making was performed, and we elected to discuss with the patient a sensible approach of ensuring complete excision via wide local excision to establish negative margins. The patient agreed to be followed up for recurrence and distant metastasis.

A-338

Atypical spitzoid lesions: A molecular and histological analysis of two NTRK driven cases

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Background
Spitzoid lesions exhibit variable malignant potential. Histological features can help classify these lesions. Benign Spitz nevi typically display symmetrical architecture with minimal signs of atypia, while Spitzoid melanomas are characterized by asymmetrical architecture, prominent atypia, and high mitotic activity. While some lesions are easily categorized based on clinical and histological features, others present with ambiguous characteristics indicative of a lesion displaying features between benign and malignant, thus classified as having intermediate biologic potential. Here we present two patients aged twelve and fifteen with atypical spitzoid lesions. Both patients shared similar histological, immunohistochemical, and molecular features, although the suspected lesion had a different clinical appearance. The aim is to investigate these commonalities and to show the difficulties in diagnostic in such lesions.

Methods
In both patients, a suspicious lesion was excised, which was later diagnosed as an atypical spitzoid nevus. Conventional histologic and immunohistological (Melan A, HMB-45, Ki-67, p16, BRAF-V600E, PRAME) analyses were performed. Molecular characterization was carried out by next-generation-sequencing (NGS).

Results
In both lesions a pronounced histological heterogeneity with atypical changes and mitotic activity was found. Immunohistochemistry showed positivity for Melan-A and HMB-45, with partial positivity for p16 and Ki-67. PRAME and BRAF-V600E were negative. In one case, NGS revealed a fusion driven activation of NTRK3 which was due to translocation of MYO5A-NTRK3. Additionally, heterogenous deletions on chromosome 6 were detected. In the other case the analysis showed an activation of NTRK1 caused by fusion of LMNA-NTRK1. Furthermore, heterogeneous deletions on chromosome 9 were found.

Conclusions
Histologically and immunohistochemically, no reliable indications could be made regarding the dignity of the lesions. In the NGS a translocation resulting in the activation of NTRK1 and NTRK3 was found, which can lead to uncontrolled cell growth and survival. Noteworthy these fusions have been identified as oncogenic drivers in spitz nevi, atypical spitzoid lesions and spitzoid melanoma. Further, NGS showed chromosomal changes; however, mutations were not identified in pivotal regulatory mechanisms commonly implicated in melanoma, including telomerase, p53, NRAS, BRAF or p16. These findings uncovered an atypical Spitz nevus with intermediate biologic potential.

A-270

Autoimmune Bullous Disorders induced by Cyclin-Dependent Kinase 4/6 inhibitors – first case series from the EADV Task Force "Dermatology for Cancer Patients"

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Background

Cyclin-Dependent Kinase 4/6 inhibitors have revolutionized the standard of care in women with hormone-receptor positive, locally advanced or metastatic breast cancer. Cutaneous adverse events have been reported in about 15 % of patients treated, the most common being pruritus, alopecia, and eczema-like lesions. More characteristic dermatological toxicities have been also described including vitiligo and lupus erythematosus. However, autoimmune bullous disorders have been exceptionally reported so far with CDK4/6 inhibitors.

Methods

We conducted with the EADV Task Force "Dermatology for Cancer Patients" a retrospective review of patients exposed to CDK 4/6 inhibitors and developing an autoimmune bullous disorder.

Results

Ten patients from 6 European institutions were included. Five patients were treated with palbociclib, four with ribociclib, and one patient with abemaciclib. Time between the initiation of CDK4/6 inhibitors and the onset of autoimmune bullous disorders ranged from 3 to 46 weeks, with a mean time of 24 weeks. They mostly presented with bullous pemphigoid (90%), often preceded by pruritus or maculopapular eruptions. Lesions were mostly mild to moderate in severity, with one patient developing mucous membrane pemphigoid with severe lesions. Histopathology and direct immunofluorescence was conducted in all cases, with positive direct immunofluorescence in 9 cases with linear IgG and C3 deposits at the basal membrane zone. Screening for BP180/230 antibodies with ELISA was positive in 7 patients. Management included topical and/or oral corticosteroids. Discontinuation of CDK4/6 inhibitors was required in 5 patients (50%).

Conclusions

We report, to the best of our knowledge, the largest case series of CDK4/6 inhibitor-related autoimmune bullous disorders, as well as the first case associated with abemaciclib, suggesting a class-effect. Oncologists should be aware of this toxicity, which should be managed quickly, in order to minimize treatment discontinuation, considering drug rotation.

A-242

BRCA1-associated-protein 1 tumour predisposition syndrome (BAP1-TPDS) presenting with multiple BAP1-inactivated melanocytic tumours – a rare hereditary tumour syndrome

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Background
BRCA1 associated-protein 1 tumour predisposition syndrome (BAP1-TPDS) is a rare inherited cancer predisposition syndrome associated with germline BAP1 mutation. Those affected have a higher risk of developing BAP1-inactivated melanocytic tumours (BIMTs), malignant mesothelioma, uveal and cutaneous melanoma. The main cutaneous manifestation is the development of distinct type of melanocytic tumours on the scalp, trunk, and limbs from the second decade of life.

Methods
A 28-year-old Chinese female presented with a gradually enlarging red-brown firm nodule over the right chin, present for the past 15 - 20 years. She also reported having developed an erythematous papule over the right zygoma for the past 2 years. She has no past medical history and no previous history of malignancies. Her sister had a history of thyroid cancer. On examination, there was a 17x13 mm skin-coloured firm nodule with central brown pigmentation over the right chin, and a 6x5 mm erythematous papule over the right zygoma.

Results
Excision biopsies of both the right chin nodule and right zygoma papule showed a dermal-centred combined melanocytic proliferation with two cell populations; large epithelioid melanocytes with large pleomorphic nuclei and abundant cytoplasm, associated with common acquired nevus at its periphery. The tumor was positive on Melan-A, negative for PRAME and showed a low proliferative index of less than 5% on Ki-67 stain. p16 expression was preserved. BRAF V600E staining was positive in both populations while BAP1 expression was lost in the large epithelioid melanocytes. Both lesions were diagnosed as BAP1-inactivated low grade melanocytomas.

Conclusions
The occurrence of a single BIMT can be a sporadic event, but the presence of two BAP-1 inactivated melanocytomas raises the possibility of a germline BAP1 mutation and BAP1-TPDS should be considered clinically. Diagnosis is established with detection of loss-of-function germline BAP1 mutation. There are no evidence-based guidelines on the optimal management of BIMTs. Affected patients have an increased susceptibility to other cutaneous and solid-organ malignancies, hence cancer surveillance with annual dermatologic and ophthalmological reviews, urinalysis, and appropriate abdominal imaging is required.

A-357

Clinical and dermatoscopic features of multiple piloleiomyomas - a case report

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Background
Piloleiomyomas, rare benign tumors originating from smooth muscle tissue, often manifest as tender nodules primarily on the trunk and head. Dermatoscopy has become pivotal in characterizing these lesions and facilitating diagnosis. This study aims to present a case of multiple piloleiomyomas in a female patient over 50 years old, elucidating their clinical and dermatoscopic features, including an unusual vascular pattern.

Methods
A female patient over 50 years old with numerous tender nodules on her trunk and upper extremities underwent clinical examination and dermatoscopy. Histopathological examination post-surgical excision confirmed the diagnosis of piloleiomyoma. The study assessed clinical, dermatoscopic, and histopathological findings to characterize piloleiomyomas comprehensively.

Results
Clinical examination revealed firm, subcutaneous nodules consistent with piloleiomyoma. Dermatoscopy depicted a yellowish homogenous background with pigmented networks and a rare vascular pattern characterized by branching and linear vessels surrounding the nodules. Surgical excision of symptomatic lesions led to resolution of discomfort and cosmetic enhancement.

Conclusions
This case underscores the significance of integrating dermatoscopy into the diagnostic evaluation of cutaneous nodules, particularly in the context of piloleiomyomas. The identification of a rare vascular pattern through dermatoscopy contributes to the limited existing literature on the dermoscopic features of piloleiomyomas.

A-280

Evaluation of anticancer therapy- related dermatologic adverse events: insights from fda's faers dataset

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Background

Anticancer treatments are effective for treating cancer but can be associated with significant skin toxicities (adverse events [AEs]). These AEs can cause discomfort and may lead to discontinuation of therapies. A comprehensive estimation of associations between the use of cancer drugs and skin AEs is currently lacking.

Methods

This study utilized the FDA's Adverse Event Reporting System (FAERS) database, focusing on health professional reports from January 2013 to September 2022. The database includes 3,399,830 reports involving 3,084 drugs across all therapeutic areas and 16,348 different AEs. A matching model using the nearest neighbor technique to identify 10 control reports for each case report based on cosine similarity of demographic and AE severity factors was used to minimize false positives and negatives. Bonferroni correction was used to handle false positives due to multiple comparisons.

Results

Anticancer drugs were identified in the database (n=212). There were 10,698 unique anticancer drug-skin AE pairs, of which 676 had significant Reporting Odds Ratios (ROR) >1, comprising 113 drugs and 144 AEs. The minimum ROR was 1.25, and 50% of associations displayed a ROR >10. Rash was significantly associated with 51 drugs and dry skin with 28 drugs. Methotrexate was associated with 34 different AEs (among the 34 AEs, 7 are also statistically considered an indication of treatment), mechlorethamine with 33, and the anti-BRAF vemurafenib with 24 AEs. Targeted therapies were present in 49% of the pairs, chemotherapies in 35.9%, and immunotherapies in 11%. Multikinase inhibitors were present in 21.8% of the pairs involving a targeted therapy, and antimetabolites were present in 33.3% of the pairs involving chemotherapy. Considering the relative weight of skin AEs on the tolerance profile of drugs, these AEs were present on average in 11% of the reports, with a maximum of 51% for mechlorethamine.

Conclusions

In this study, 113 anticancer drugs were identified as significantly associated with skin AEs, most frequently rash and dry skin. These data do not allow for assessing the incidence of skin AEs with anticancer drugs as they are likely underreported but enable quick identification of skin toxicity signals after the introduction of new treatments.

A-414

First description of atypical fibroxanthoma in Line-Field Confocal Optical Coherence Tomography and comparison with Reflectance Confocal Microscopy

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Background

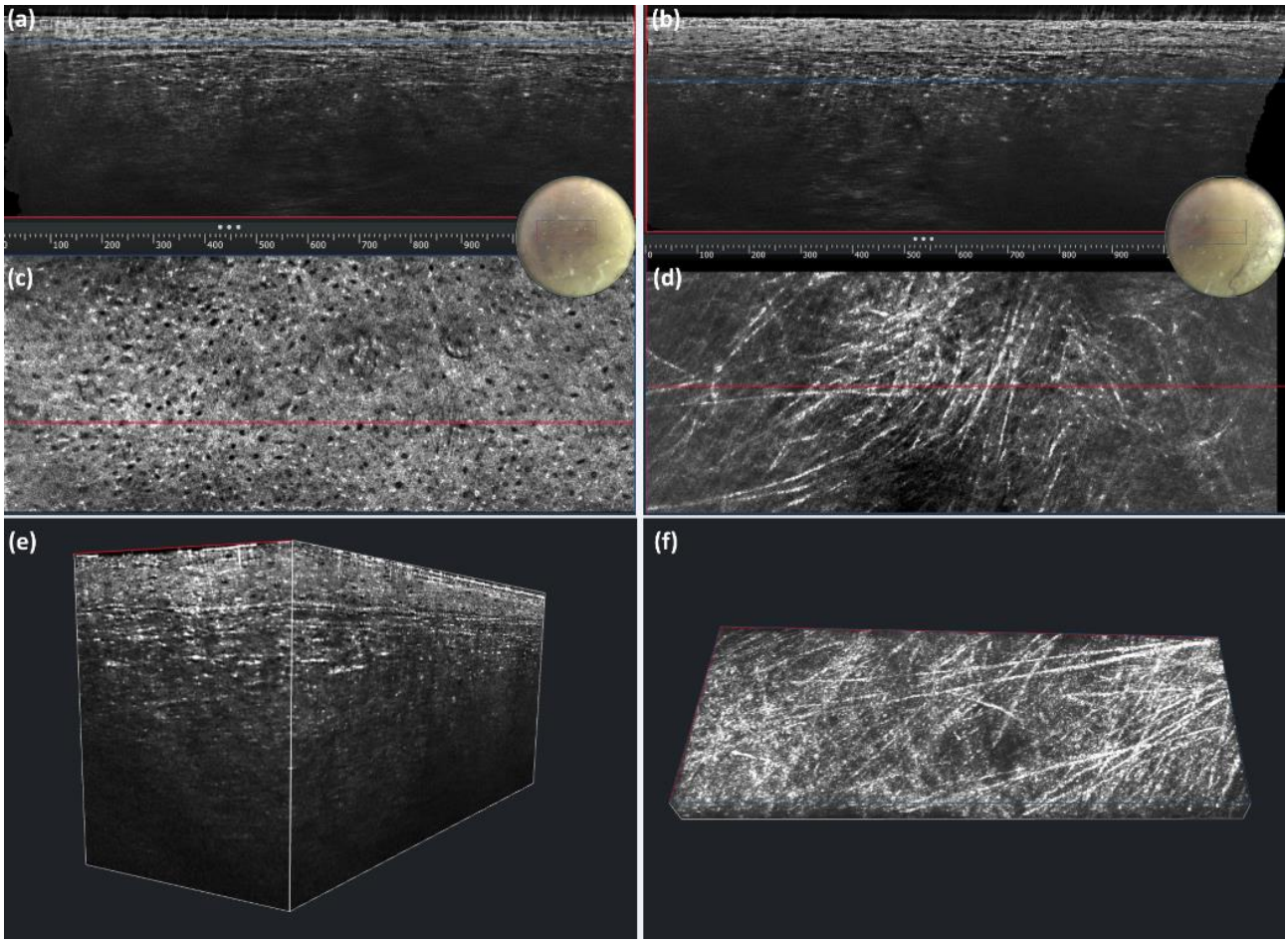
Atypical fibroxanthoma (AFX) is a rare mesenchymal skin tumor that typically presents as solitary, rapid-growing, dome-shaped nodules, which can be clinically and dermoscopically difficult to distinguish from other non-pigmented skin lesions. We report a histopathologically confirmed case of atypical fibroxanthoma (AFX) and the first description of its features in Line-Field Confocal Optical Coherence Tomography (LC-OCT) and we compared it with Reflectance Confocal Microscopy (RCM).

Methods

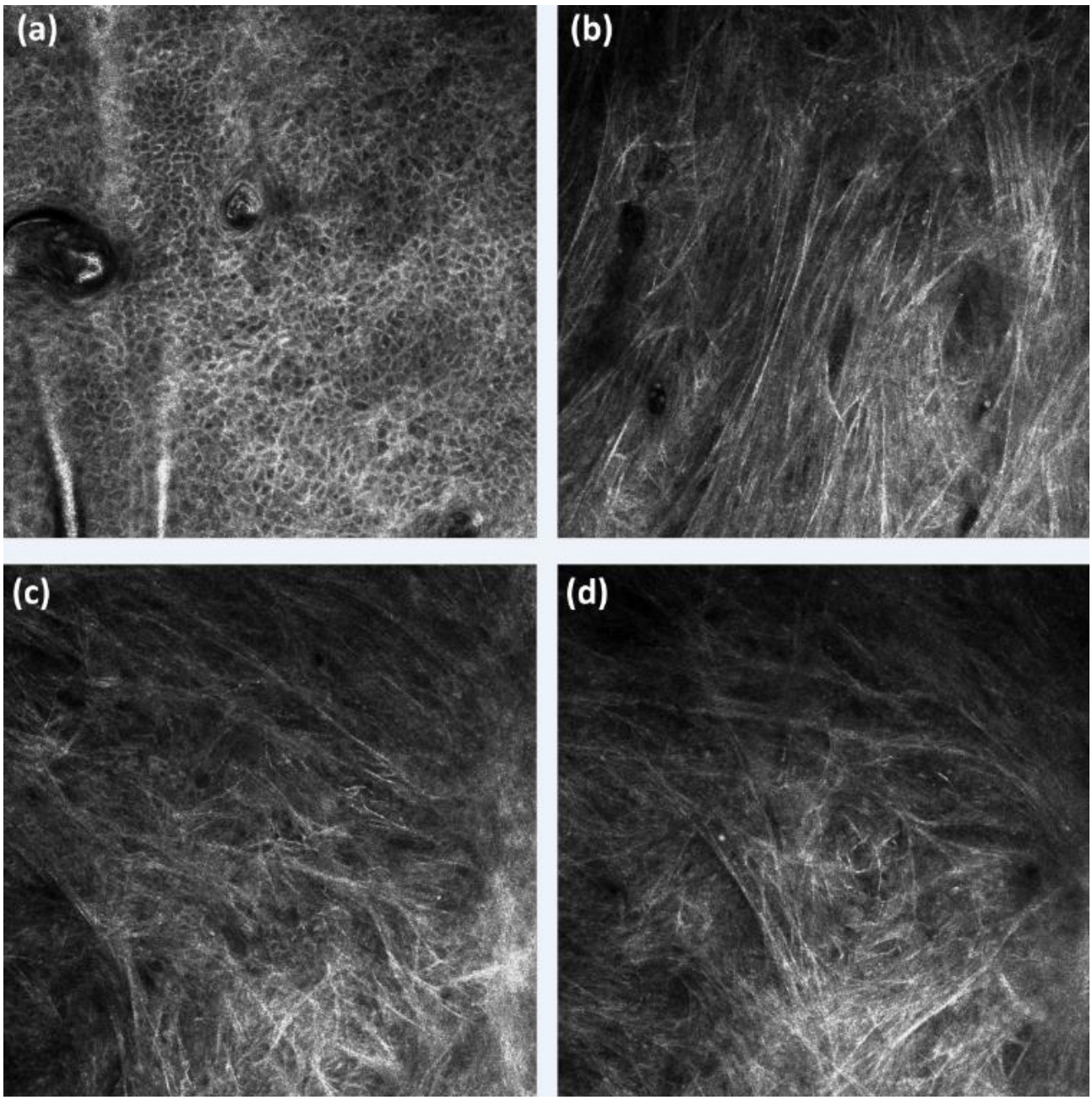
A 70-year-old female patient presented with rapidly growing suspected recurrence of a histologically confirmed AFX in the left ear canal. The lesion was evaluated using Line-field LC-OCT and RCM to characterize its morphological features. Comprehensive imaging analysis relied on identifying specific morphologic criteria associated with this pathology based on established literature in histopathology and the few existing reports of AFX examined with RCM. The acquisitions from these two imaging techniques were then morphologically compared.

Results

LC-OCT provided high-resolution, horizontal and vertical images as well as tridimensional reconstructions of the nodular lesion. It showed a proliferation of large hyporeflective roundish cells among a very dense dermal matrix characterized by thick, elongated and disorganized collagen fibers.



RCM examination revealed the same stretched and thick collagen fibers intertwined around large roundish cells in the dermis but with less penetration depth and finer contrast in the horizontal plane than in LC-OCT.



The normal epidermis was clearly identified by a regular honeycomb pattern on both imaging modalities. No sign of other possible neoplasm like fast-growing basal cell and spinal cell carcinoma or melanoma were observed in either techniques.

Conclusions

The recent introduction of LC-OCT as a non-invasive diagnostic tool after the emergence of RCM represents a significant advancement in dermatologic oncology and has already been proven valuable for the management of frequent and less frequent skin lesions. LC-OCT has the advantage of providing vertical and tridimensional visualization with similar resolution as RCM but deeper penetration, potentially valuable in the case of dermal lesions like AFX. Further reports and performance studies are required to assess the accuracy of these new techniques in such tumors.

A-332

Genetic sequencing and Novel Therapeutic Targets in Perianal Extramammary Paget Disease

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Background
Molecular drivers of Extramammary Paget Disease (EMPD) are poorly understood. Targeted treatment options for invasive and metastatic EMPD are limited. There has been no large study of perianal EMPD genetics. This study aimed to identify genomic alterations as potential therapeutic targets in perianal EMPD.

Methods
This observational, retrospective study investigated strength of associations between genetic profiling and clinical course of 26 biopsy-confirmed perianal EMPD cases at Memorial Sloan Kettering Cancer Center (MSKCC) with primary or secondary perianal EMPD treated at least once from 2000 to 2022. Clinical disease was described by recurrence after primary treatment, tumor invasiveness, metastases, and death from disease. Genetic data were measured using paired tumor-normal parallel sequencing of 410-468 cancer-related genes (MSKCC-IMPACT test) and clinically relevant mutations were identified via OncoKB, a precision oncology knowledge base of genomic alterations in cancer.

Results
TP53 mutation was the most frequent mutation (53.8%) followed by ERBB2 (26.9%), ERBB3 (19.2%), and PI3KCA (15.3%) mutations. Recurrence or non-response following primary treatment occurred in 11 patients (42.3%). MYC gene amplification was positively associated with disease metastases (OR = 12.8, p = 0.03). ERBB3 mutation gene was significantly associated with disease recurrence after primary treatment (OR = 13.3, p = 0.04).

Conclusions
Perianal EMPD has a chronic, locally recurring course that may lead to mortality. There are few effective treatments outside of surgery and high rates of recurrence. We identified MYC amplification and ERBB3 as possible predictors of disease metastases and recurrence. Additional research regarding targetable MYC and ERBB3 therapies are warranted.

A-307

Kissing lesions on penis – a very rare case report

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Background

Introduction & Objectives: Kissing or divided nevi are a very rare clinical variant of melanocytic nevi developing in adjacent areas of the skin. Penile kissing lesions are extremely rare, with only few cases described in the literature. Typically, they present as two opposing darkly pigmented macular or papular lesions on the glans and prepuce, exhibiting a mirror-image symmetry relative to the coronal sulcus.

Methods

Materials & Methods: In this short report we would like to present a case of a 57-year-old male patient who initially consulted a dermatologist due to glans erythema. However, upon examination, two acquired atypical, brown-bluish pigmented, kissing lesions on glans and prepuce were observed.

Results

Due to their striking dermoscopical features, a biopsy was performed, and the lesions were histopathologically and immunohistochemically diagnosed as kissing epithelioid blue nevi.

Conclusions

Due to the rarity of acquired kissing lesions on the penis and only a few cases of kissing blue nevi in such a location described in the literature, we would like to emphasize the possibility of occurrence of such interesting lesions and additionally give a brief review of the literature of all genital kissing lesions and possible pathophysiology of such changes.

A-229

Localized multiple spiradenomas are caused by somatic mosaicism in ALPK1 hotspot mutation

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Background
Malignant eccrine spiradenoma (MES) is a rare skin adnexal tumor, mostly arising from a benign precursor eccrine spiradenoma (ES). While localized multiple ESs are exceptionally rare, one of these ESs may undergo malignant transformation into MES. A previous report suggested that multiple ESs result from somatic mosaicism because of their Blaschkoid hemicorporal distribution. Recurrent *ALPK1* p.V1092A mutation has been reported in MES, ES, and adjacent morphologically normal skin, implying the possibility of field cancerization. Here, we present an aggressive case of MES arising from localized multiple ESs. Our objective is to better understand the mutation profile and evolutionary trajectories of MES and ES through exome-sequencing of multiple tumors.

Methods
Whole exome-sequencing was performed on one sample (T1) from MES and four samples (T2-T5) from surrounding ESs. As *ALPK1* p.V1092A mutation was identified in all samples, we analyzed adjacent normal epidermis (T6-8) and dermis (T9-10) with amplicon-sequencing targeting the *ALPK1* mutation hotspot.

Results
We identified 42, 17, 11, 10, and 17 mutations in samples T1-5, respectively. Only *ALPK1* p.V1092A mutation was shared between all MES and ES samples (T1-5). A *TP53* mutation was exclusively detected in the MES sample (T1). Amplicon-sequencing of adjacent epidermis and dermis (T6-10) did not identify the *ALPK1* mutation.

Conclusions
We present compelling evidence that somatic mosaicism in *ALPK1* p.V1092A mutation leads to localized multiple ESs. A *TP53* mutation is the likely driver of malignant transformation to MES, as seen in other malignancies. Clonal expansion of normal-appearing tissue carrying the *ALPK1* mutation was not detected in our case. Given the potential for malignant transformation, excision of all multiple ESs is recommended.

A-418

Paediatric Spitzoid Neoplasms : a 10-year retrospective study

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Background
Spitzoid lesions are a wide tumour class comprising Spitz nevus (SN), atypical Spitz tumour (AST) and Spitz melanoma (SM). These are all histologically characterized by spindle cell and epithelioid cell melanocytic proliferations, but while SN display benign histological features and SM display malignant histological features, AST present some atypical histological features in between SN and SM, yet insufficient to make a diagnosis of melanoma.
We present a large series of paediatric-specific spitzoid neoplasms from a single centre with the aim of analysing the epidemiological, morphological and genetic aspects of paediatric spitzoid lesions.

Methods
We conducted a single-centre-based retrospective survey on all histologically diagnosed spitzoid lesions of paediatric patients (1-18 years) of the last 10 years (2012-2022). Histopathological reports and electronic records of patients were used to retrieve relevant data regarding patients' features, clinical and dermatoscopical aspects of lesions when recorded, and FISH tests when present.

Results
Of 255 studied lesions, 82% were histologically benign, 17% atypical, 1% malignant. Clinically, all the malignant lesions and most of the atypical ones were large (≥6 mm) and raised, while benign lesions were more likely to be small (≤5 mm), flat, and pigmented ($p < 0.0001$).
Dermatoscopical patterns, analyzed in 100 patients, further aided diagnosis: a starburst pattern suggested benignity (26% SN ($p = 0.004$)), while a multicomponent pattern pointed towards atypicality or cancer (56% AST, 50% SM ($p = 0.0052$)).
Eighty-five lesions were subjected to fluorescence in situ hybridization (FISH): positive results were more likely in atypical lesions (FISH-positive:71% AST; 29% SN vs FISH-negative:63% SN; 37% AST) ($p = 0.0038$).

Conclusions
This study on pediatric spitzoid lesions disclosed that most (82%) were indeed harmless, but a concerning number (17%) showed unclear features (atypical), requiring careful evaluation, and 1% showed even malignancy. This highlights the importance of caution when dealing with spitzoid lesions in children, as some may appear harmless but have the potential to be cancerous. While clinical size, appearance, and dermoscopic features offer valuable clues to lesion type, histological analysis and genetic tests remain essential for achieving the highest diagnostic accuracy, particularly in children, where underestimating their importance can have significant consequences

A-411

Pembrolizumab treatment for advanced pleomorphic dermal sarcoma, a three-case series in a spanish tertiary-level hospital

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Background
Pleomorphic dermal sarcoma (PDS) is a rare skin tumour, associated with a high mutational burden (TMB). In locally advanced or metastatic cases, recent reports have proposed anti-PD-1 immunotherapy as an effective alternative.

Methods
We present a three patient case series of locally-advanced or metastatic PDS treated with pembrolizumab in our service. Outcomes were evaluated using RECIST v1.1 criteria.

Results
Case 1:
An 80-year-old woman consulted with a 4,5 cm mass at her right cheek. After wide excision, PDS was confirmed. Ki-67 rate was 85% and PD-L1 expression on tumoral cells (TPS) was 20%. After a first local recurrence was treated with Mohs surgery, a second one was deemed irresectable. We started off-label pembrolizumab at 2mg/kg every three weeks. After the first dose, a dramatic complete response was observed. She continues in treatment with a relapse free survival of 6 months.

Case 2:
A 94-year-old man consulted with a 4 cm mass in his right ear and a pathological right submandibular lymphadenopathy. Biopsies were compatible with PDS. TPS was 0%. The tumours were considered irresectable and we started pembrolizumab at a 4mg/kg (optimised) dose every 6 weeks. After 4 doses, partial response was obtained. He remains in active treatment.

Case 3:
A 67-year-old woman consulted with a 14 cm ulcerated tumour on her right ankle and a gigantic right inguinal pathological lymphadenopathy. Biopsies were also compatible with PDS. TPS was 10%. A chest CT-Scan revealed nodules in both lungs, highly suggestive of metastasis. We initiated pembrolizumab at an optimised dose. She remains in active treatment pending re-evaluation.

No immune-related adverse effects were observed.

Conclusions
PDS is considered an immunogenic tumour, presenting a high number of CD8+ tumour-infiltrating lymphocytes, expression of diverse checkpoint molecules (PD-L1, CTLA-4 and others) and a particularly high TMB. Tumours with both elevated TMB or TPS rates are usually related with a better response-rate to immunotherapy in other cancers. Recently, at least 4 cases of locally advanced or metastatic PDS treated with pembrolizumab have been published. We propose to consider immunotherapy as a first or second line option in advanced PDS.

A-372

Skin adnexal carcinomas DNA genomic profiling uncovers oncogenic pathways and potential therapeutic targets.

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Background

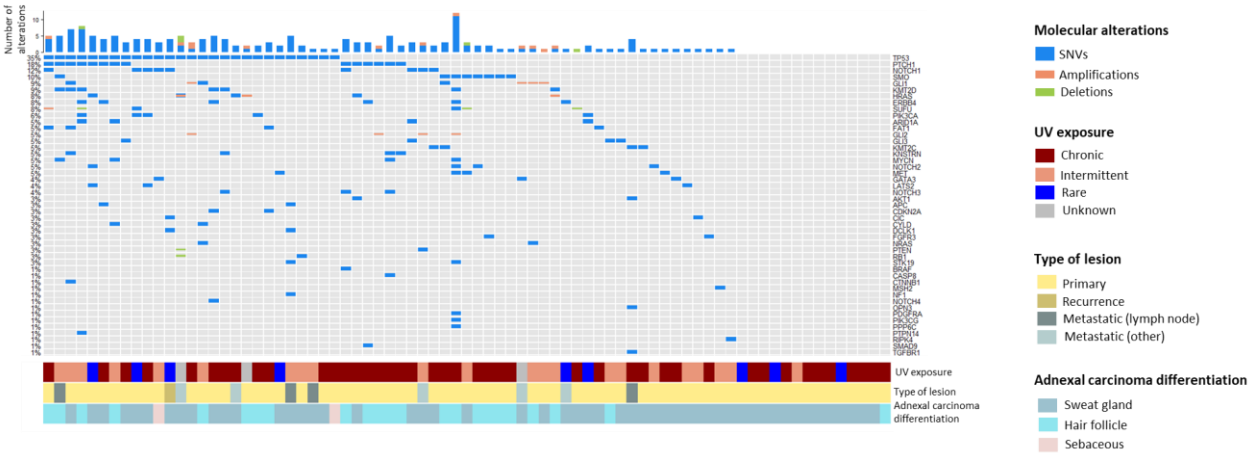
To date, proposing a genomic landscape of skin adnexal carcinomas (SAC), which can emerge from a wide range of skin appendage structures, remains challenging. However, due to their low incidence, it is highly needed to differentiate entities and identify molecular alterations driving oncogenesis [1].
Here, we conducted a comprehensive molecular characterization of a SAC cohort to identify genomic profiles for tumorigenesis comprehension, classification and therapeutic applications.

Methods

Patients with cutaneous carcinoma followed at Saint-Louis hospital or reviewed through the CARADERM network [2] with somatic tumor molecular profiling performed as part of routine care from 2017 to 2020 were included in this retrospective study approved by an IRB (IRB00003888). Clinico-pathologic data were collected from review of patients' medical records. DNA sequencing was performed on FFPE samples with a NGS panel targeting 95 genes involved in pathways related to skin carcinoma tumorigenesis. Single nucleotide variants (SNV), copy number variations (CNV) and UV profile analyses were proposed.

Results

Our cohort was composed of 77 SAC including 52 (68%) sweat gland, 23 (30%) hair follicle and 2 (2%) sebaceous carcinomas. Sixty-seven (87%) specimens were primary tumors and 10 (13%) were metastases.
An average of 2.3 mutations per case was retrieved and 42 (55%) presented concurrent alterations with *TP53, PTCH1*, *NOTCH1*, *SMO*, *KMT2D* and *GLI1* as the six most altered genes (



Landscape of prioritized SNVs and CNVs in the series of 77 adnexal carcinomas. Each column represents a sample and each row a gene. SNV: single nucleotide variant

). Hair follicle and sebaceous carcinomas displayed a significantly higher number of SNVs than sweat gland carcinomas (2.9 *vs* 1.7, p<0.05). No UV profile enrichment nor association with SAC entity was detected. SNVs and CNVs comprehensive analysis identified recurrent altered pathways, notably MAPK and Shh pathways. Hair follicle carcinomas mutational profile was similar to basal cell carcinomas and differentiated from sweat gland and sebaceous adnexal entities. Moreover, we identified theragnostic evidence for 32 (42%) cases including 14 with *PTCH1* truncating mutations and 5 with *SMO* oncogenic variants that may be sensitive to hedgehog inhibitors.

Conclusions

We propose a genomic characterization of a large series of SAC. Besides providing insights regarding classification, tumorigenesis processes and therapeutic options, our data emphasize the importance of wide molecular profiling in routine practice management of these rare skin tumors.

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A-364

Slow Mohs Micrographic Surgery in the management of Extramammary Paget's Disease

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Background
Extramammary Paget's Disease (EMPD), a slow growing skin condition, is often associated with an internal malignancy. Primary EMPD presents in the absence of other malignancy. We present 4 cases of primary EMPD, managed with slow Mohs margin control.

Methods
Patients were identified using the EPIC® record of patients who received Mohs surgery between 20-April-2017 and 20-July-2022. 4 male patients received slow Mohs surgery for EMPD of the groin.

Results
The average diameter of the EMPD primary lesion was 60mm (range: 30-100mm). After complete excision, the average margin removed was 46mm (range: 5-117mm). 3 patients required >1 excision to completely remove EMPD; the average number required was 4. Patients waited on average 27 days between subsequent excisions. One patient required 9 excisions to completely excise EMPD [figure 1]. Procedures were either under general (n=2) or local (n=2) anaesthesia. Patients attended hospital on average 21 times (range: 9-41). Regarding reconstruction, 1 patient received a split skin graft, and 3 patients had primary closure. After a minimum follow-up period of 18-months, 0 patients experienced recurrence following complete excision.

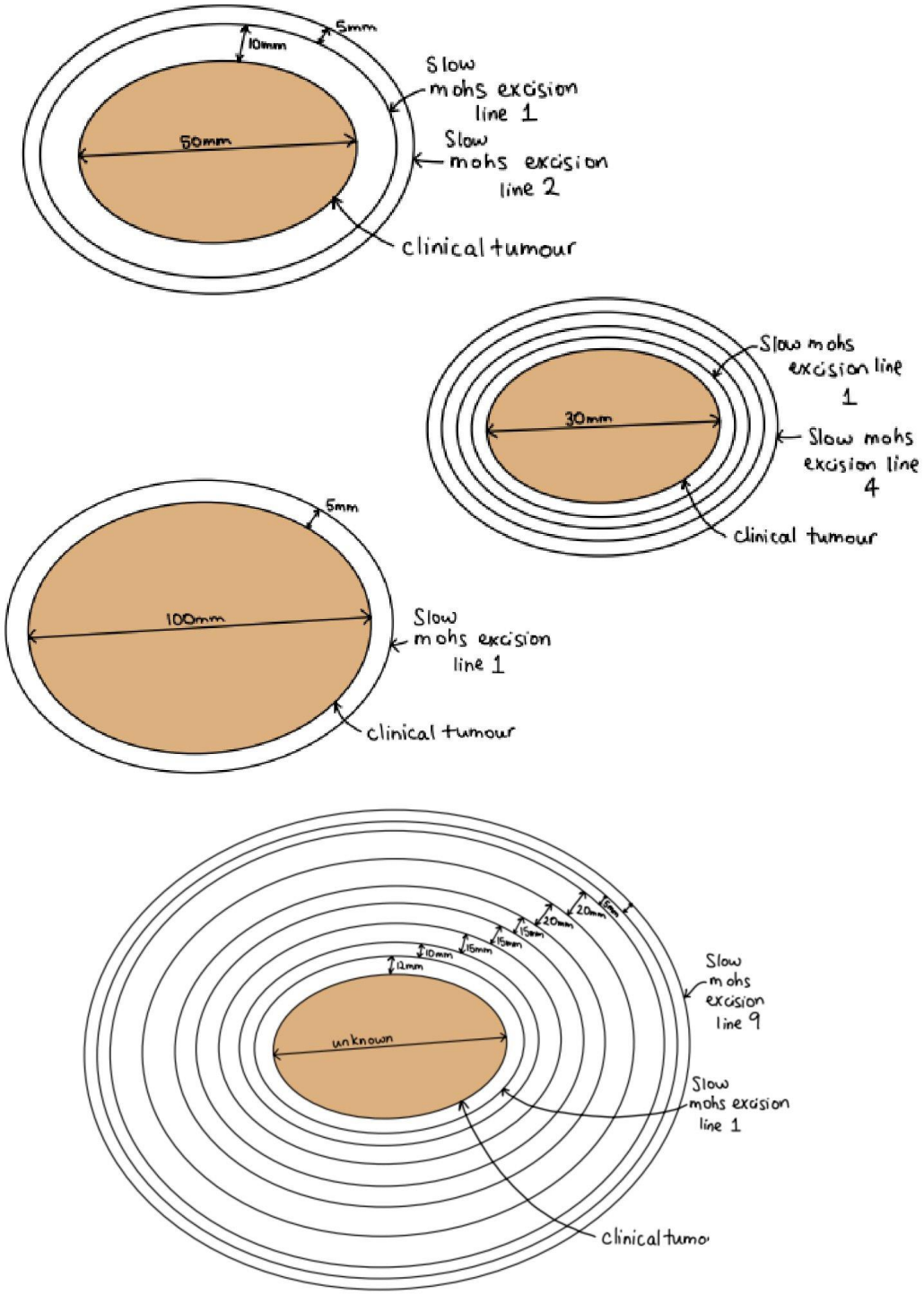

Figure 1: Diagrammatic representation of number of slow Mohs excisions for each patient

Conclusions

EMPD commonly has ill-defined margins which poses a challenge for complete excision. Slow Mohs overcomes this by allowing accurate margin analysis, facilitating exact locations of residual disease, so further excisions can be focused and tissue preserving. Slow Mohs provides reassurance that all EMPD is removed, evidenced by the 0% recurrence rate. These patients demonstrate the complexity of removing all EMPD, as after the first excision there is no surface indication of the disease.

A-410

Squamoid Eccrine Ductal Carcinoma: A Case Series of Three Patients

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Background

Squamoid eccrine ductal carcinoma (SEDC) is a rare cutaneous adnexal tumor originating from the eccrine apparatus, characterized by a biphasic differentiation pattern on histopathology. Its superficial component resembles well-differentiated squamous cell carcinoma (cSCC), while the deeper component exhibits infiltrative features with prominent ductal differentiation. Despite its rarity, accurate diagnosis is critical due to SEDC's aggressive behavior, including local invasion, perineural and intravascular spread, and high potential for recurrence and metastasis. Unfortunately, nearly half of reported cases are initially misdiagnosed, often confused with squamous cell carcinoma (SCC).

Clinically, SEDC typically presents as solitary nodules or plaques, occasionally ulcerated, predominantly located in the head and neck region, though extremity involvement is also reported. It primarily affects elderly individuals, particularly males, and is more prevalent in immunocompromised patients.

Methods

Here, we present three cases of SEDC observed at our Dermatology Clinic, all in elderly males (age 60, 84, and 90 years) with a history of actinic keratosis and prior excisions of basal cell and squamous cell carcinomas. Clinically, two cases manifested as ulcerated plaques, while one presented as a dyskeratotic nodule on the head.

Results

The preferred therapeutic approach involved radical surgical excision in two cases, while radiotherapy was performed in the third case due to the patient's age, medical history, and preference. In this last case, subsequent surgical intervention was necessary due to incomplete response to the treatment.

It is noteworthy that none of the cases showed evidence of regional or distant metastases. However, vigilance is essential due to the potential for recurrence and dissemination, necessitating long-term follow-up.

Conclusions

The lack of a standardized treatment protocol for SEDC underscores the need for further research into its biological behavior and optimal therapeutic strategies. While excision and Mohs surgery have shown efficacy, Mohs surgery appears superior in reducing recurrence rates compared to wide local excision.

In summary, SEDC poses diagnostic challenges due to its rarity and histopathological complexity. Early and accurate diagnosis, coupled with appropriate management strategies, is crucial for optimizing patient outcomes and minimizing the risk of recurrence and metastasis.

A-195

The risk of subsequent skin cancer in patients with atypical fibroxanthoma or pleomorphic dermal sarcoma compared to the general population: a retrospective cohort study

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Background
Atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS) enhance a rare skin cancer (SC) continuum. UV-exposure is assumed to be the main risk factor. Consequently, patients with AFX/PDS may have an increased risk to develop subsequent SC. This study's objective was to determine the risk for subsequent SC in patients with AFX/PDS relative to the general population.

Methods
Retrospective cohort study on multiple SC in patients diagnosed with AFX/PDS. Boa_Image_Frameized incidence ratios (SIRs) were calculated by using age-, sex, and year of diagnosis matched incidence data from the Netherlands Cancer Registry.

Results
Of all 132 patients, 71 (53.8%) were diagnosed with at least one subsequent SC after the AFX/PDS diagnosis. Squamous cell carcinoma (SCC; 40,9%) was most frequently diagnosed, followed by basal cell carcinoma (BCC; 40,3%). Compared to the general population, patients with AFX/PDS had a statistically significant increased risk for subsequent SC including SCC (SIR 11.9; 95%CI 8.4-16.3), Bowen's disease (BD; SIR 11.6; 95%CI 4.2-25.2) and BCC (SIR 5.6; 95%CI 3.0-9.6).

Conclusions
Patients with AFX/PDS have an increased risk of developing subsequent SC, especially SCC and BD. Therefore, proper instruction on UV-protection, self-examination and routine follow-up with total body skin examination is recommended.

A-210

Ultrasonography for the diagnosis and follow-up of extramammary Paget's disease (EMPD). A case-report.

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Background

Extramammary Paget's disease (EMPD) is an intraepidermal adenocarcinoma that typically arises in areas rich in apocrine glands. It is a rare disease and more prevalent in older adults, especially in Caucasian women and Asian men. The most common localizations are the vulva, followed by penoscrotal, perianal, inguinal, perineal, and axillary regions. Clinically, it appears in the form of ill-defined erythematous plaques. The assessment of tumor margins is equally challenging as tumors have a propensity to spread beyond clinically visible boundaries.

Most cases of EMPD are limited within epidermis, resulting in a 100% survival rate over 10 years. However, when invasion of the underlying dermis occurs, survival rates decreases significantly. Thus, the most important prognostic factors are related to the degree of dermal infiltration.

As the surgical treatment in these areas can be very aggressive, intraepidermal lesions can be treated non-surgically with photodynamic therapy or topical imiquimod. However, these methods carry a high rate of recurrences. Therefore, it is important to monitor those patients so recurrences or infiltrative foci can be detected, as surgery would be indicated then.

A good correlation has been reported between US and histologic assessment. Moreover, a US examination has the advantages of wide availability, noninvasiveness, low cost, ease of use, and real-time scanning.

Methods

We reviewed the literature, searching in during 2023 in Pubmed and Google scholar for the terms in Spanish and English: "Ultrasounds", "extramammary Paget's disease", "EMPD", "ecography".

Results

We present the case of a 72-year-old woman with perianal in situ EMPD. She was treated with multiple courses of imiquimod and photodynamic therapy associated with calcipotriol, with improvement but persistence of the disease. The extension of the lesion and its evolutionary course could be monitored by ultrasound.

In addition, we review all the ultrasound signs described for this disease and discuss their histological translation as well as their sensitivity and specificity.

Conclusions

Although histology continues to be the gold standard test, ultrasound can be very useful to choose the area to biopsy, screening for possible infiltration foci and delimiting the extent of the lesion for its evolutionary control during medical treatment or prior to surgery.

A-145

Unresectable endocrine mucin-producing sweat gland carcinoma revealing an actionable somatic CHEK2 gene mutation

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Background

Endocrine mucin producing sweat gland carcinoma (EMPSGC) is a rare adnexal carcinoma of the skin with neuroendocrine differentiation. Less than 200 cases have been reported to date. Information regarding their molecular profile is limited. Herein, we present a case of unresectable axillary EMPSGC, revealing a pathogenic, actionable *CHEK2* gene mutation, with clinical benefit from palbociclib (CDK4/6-inhibitor), letrozole and goserelin (LHRH-analog) combination therapy.

Methods

A 60-year-old man was referred for a right-axillary tumor, with marked homolateral lymphoedema (Fig1a). Baseline PET-CT scan revealed a hypermetabolic right axillary mass (115mm72mm, SUV_{max}11.9) with locoregional lymph nodes (SUV_{max}2.8-3.1) (Fig1b). Breast MRI was normal. Histopathological examination (H&E) revealed an intradermal tumoral proliferation containing solid aggregates of cells with eosinophilic cytoplasm and anisokaryotic nuclei (Fig2a). Immunohistochemistry showed positivity for chromogranin, synaptophysin (Fig2b), cytokeratin7, estrogen, progesterone and androgen receptors. P40 and cytokeratin20 stains were negative. This pattern was consistent with EMPSGC. The patient was started on carboplatin+paclitaxel, without response. Subsequently, the treatment was switched to carboplatin+5-FU+radiotherapy, but was stopped due to radiodermatitis and anemia. At this point, high-throughput DNA-sequencing revealed a pathogenic mutation in exon 11 of the *CHEK2* gene (c.1116_1117delinsTG, p.Lys373Glu*3–VAF3%–K373E) (Fig2c). A third-line treatment with palbociclib+letrozole+goserelin was initiated, by analogy to HR+/HER2- breast cancer treatment. The patient presented a partial response at 3M of follow-up (PET-CT: tumor=43cm3–SUVmax3.1, LN=SUVmax2.8) (Figure1c), peristant at 12M of follow-up (tumor=25vs93cm3–SUVmax1.9,LN=SUVmax1.9) (Fig1d).

Results

The identification of an actionable pathogenic *CHEK2* gene mutation, allowed us to introduce an unconventional treatment consisting of palbociclib-letrozole-goserelin, with a prolonged clinical benefit. Despite a low rate of mutated tumor cells (3%), possibly related to a subclone-emergence, targeted treatment had a significant therapeutic effect. This subclone may have a possible role in the sustained tumoral growth before targeted treatment.

Conclusions

This is the first observation reporting the potential involvement of *CHEK2* gene variants in EMPSGC. However, further epidemiological and functional studies are needed to confirm the link between these variants and EMPSGC.

A-367

Whole transcriptome sequencing: Optimizing molecular classification and management of rare skin cancers.

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Background

Molecular characterization is now a cornerstone of diagnostic and theranostic management in cancer. These last few years, sequencing technologies have significantly move forward and whole transcriptome sequencing (WTS) constitutes a key step allowing a wide exploratory analysis to detect relevant molecular alterations. Along with networks of pathology expertise, such molecular screening is of great interest to optimize patients' clinical management.

Methods

In our hospital, we have developed and implemented WTS in routine practice on FFPE or fresh frozen samples. After RNA extraction and library preparation with the RNAseq SureSelect XTHS2 RNA System® kit (Agilent®), sequencing was performed on a Nextseq 2000 platform (Illumina®). Inhouse bioinformatic pipelines were developed in collaboration with the bioinformatic MOABI platform and allowed the screening of molecular alterations including wide detection of fusion transcripts as well as targeted single nucleotide variants and mRNA expression signatures analyses.

Results

From 2021 to 2023, 300 cases have been addressed for WTS based on the following indication: "Diagnostic: tumor difficult to classify" (80%) or "Theranostic: therapeutic target identification" (20%).

Most frequent included tumor subtypes were skin carcinomas, sarcomas, melanomas and lymphomas notably addressed in the context of national expert network (NETSARC, CARADERM, and GFELC).

Molecular alterations were detected in 142/300 (47%) cases and this included 68 (23%) harboring alterations of high relevance in oncology after comprehensive analysis. Among analyzed cases, we identified *PAK* fusions allowing to classify lesions as poromas. *PRKCA* and *EWSR1* rearrangements also oriented diagnostic of atypical melanocytic lesions. *GRHL2* fusions, which have been recently described in trichogerminomas, were detected in 4 cases and *MF2C::SS18* were detected in 2 cases further classified as microsecretory adenocarcinomas. Moreover, targeted SNV analysis identified 2 spiradenocarcinomas thanks to *ALPK1* p.V1092A detection.

Conclusions

Whole transcriptome sequencing in clinical practice plays a key role to orient diagnosis, particularly in situations of uncertainty in tumor classification. The application of our approach on FFPE tumor samples facilitates its implementation and clinical access in the management of rare skin cancers.

Squamous cell carcinoma

A-305

A Phase 1 study of fianlimab in combination with cemiplimab in patients with anti–PD-1/L1-experienced cutaneous squamous cell carcinoma

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Background
Concurrent blockade of LAG-3 may enhance efficacy of anti–PD-1 therapies. We present safety and clinical activity data from a Phase 1 study in patients with cutaneous squamous cell carcinoma (CSCC) treated with anti–LAG-3 (fianlimab) + anti–PD-1 (cemiplimab).

Methods
Adult patients with locally advanced/metastatic CSCC who were anti–PD-1/L1-experienced with most recent dose within 3 months prior to screening were enrolled. All patients received fianlimab 1600 mg + cemiplimab 350 mg intravenously every 3 weeks for up to 24 months. Tumor measurements were performed every 6 weeks for 24 weeks, then every 9 weeks.

Results
As of 04 October 2023 data-cutoff, 15 patients (median age: 62 years) were treated. 80% of patients were male and White. All patients had prior cancer-related systemic therapy. 60% (9/15) of patients had ≥2 lines of prior therapies. Most patients (12/15) experienced progressive disease while on prior anti–PD-1 treatment.

Median treatment duration and median follow-up was 12 weeks and 9 months, respectively. Grade ≥3 treatment-emergent AEs (TEAEs) occurred in 47% of patients. Serious TEAEs and immune-related AEs each occurred in 27% of patients. Treatment-related AEs (TRAEs) were reported in 47% of patients. The most common TRAE (grade 1/2) was infusion-related reaction (13%). Grade ≥3 TRAEs occurred in 7% of patients. There were 2 fatal TEAEs, unrelated to study drugs: 1 sudden death in a heavily pre-treated patient and 1 death due to failure to thrive in a patient who was in a palliative care facility after disease progression on study.

RECIST 1.1-based investigator-assessed ORR, KM estimation of median PFS, and disease control rate were 20% (2 CRs, 1 PR), 3 months (95% CI, 1–4), and 47%, respectively. Duration of responses were 11, 13, and 16 months in 3 responders. 2 responders (1 CR, 1 PR) experienced disease progression while on prior anti–PD-1 and 1 responder who achieved CR had an ongoing PR on previous anti–PD-L1 therapy before joining the study.

Conclusions
Treatment with fianlimab + cemiplimab in anti–PD-1/L1-experienced patients with CSCC had encouraging clinical benefit with durable responses, and an acceptable safety profile warranting further investigation.

A-456

A Randomized, Double-Blind, Phase 2 Study of Perioperative MK-4280A (Coformulation of Favezelimab and Pembrolizumab) vs Pembrolizumab in Patients With Resectable Cutaneous Squamous Cell Carcinoma

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Background
The immune checkpoint receptor lymphocyte-activation gene 3 (LAG3) is upregulated in many tumor types including cutaneous squamous cell carcinoma (cSCC) and frequently coexpressed with PD-L1. In the RELATIVITY-047 study, relatlimab (anti–LAG3 antibody) + nivolumab (anti–PD-1 antibody) prolonged PFS vs nivolumab in unresectable advanced melanoma; a phase 2 study additionally showed high pathological complete response (pCR) rate in resectable disease. Studies have also demonstrated antitumor activity and manageable safety with favezelimab (anti–LAG3 antibody) + pembrolizumab (anti–PD-1 antibody). Cohort A of the basket study MK-4280A-010 (NCT06036836) is evaluating MK-4280A (fixed-dose coformulation of favezelimab + pembrolizumab) vs pembrolizumab for resectable cSCC.

Methods
Cohort A of this randomized, double-blind, phase 2 study will enroll patients aged ≥18 yrs with histologically confirmed stage II–IV resectable cSCC as the primary malignancy (without M1; staging per AJCC 8th ed. for head/neck tumors or UICC 8th ed. for other tumor sites) and no prior systemic therapy or radiotherapy to the index lesion. Patients must have ECOG PS 0/1 and a tumor sample for biomarker analysis. Approximately 40 patients per arm will be randomized 1:1 (stratified by non-nodal vs nodal disease and head/neck vs other tumor site) to MK-4280A (favezelimab 800 mg + pembrolizumab 200 mg) or pembrolizumab 200 mg IV Q3W for ≤3 cycles in the neoadjuvant period, followed by surgical resection; then MK-4280A or pembrolizumab, as allocated, Q3W for ≤14 cycles in the adjuvant period (adjuvant radiotherapy per investigator discretion is permitted if no pCR by local assessment). Total treatment duration will be approximately ≤1 yr or until PD/recurrence or intolerable AEs. Imaging occurs after the last neoadjuvant cycle before surgery, then Q12W during the adjuvant period through ≤1 yr. AEs are assessed throughout the study and graded per NCI CTCAE v5.0. Primary endpoint is pCR (no viable tumor in resected sample) by blinded central pathology review (BCPR). Secondary endpoints are pCR or clinical CR (no residual tumor per clinical exam/imaging) with negative biopsy, EFS and ORR (before surgery) per RECIST v1.1 by investigator review, major pathological response (≤10% viable tumor in resected sample) by BCPR, OS, and safety. Enrollment began in Sep 2023.

Results
Pending

Conclusions
Pending

A-296

A successful treatment of locally advanced squamous cell carcinoma with cemiplimab in a patient with multiple myeloma

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Background

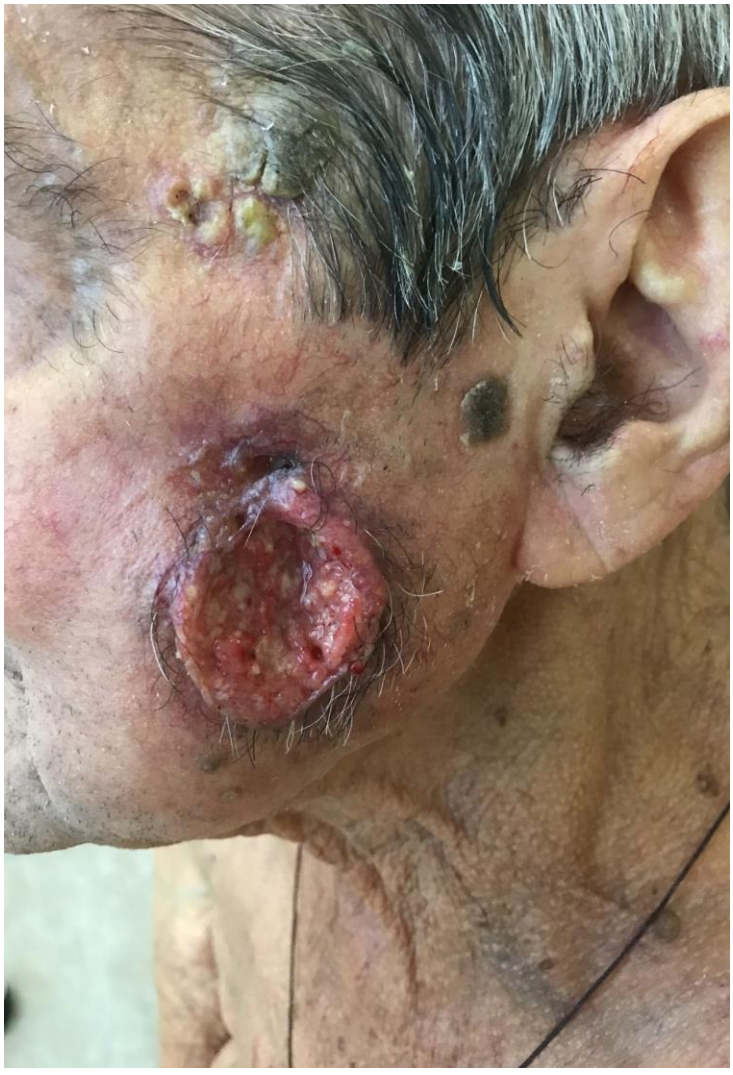
Cutaneous squamous cell carcinoma (cSCC) accounts for approximately 20% of cutaneous malignancies. Although surgical excision is the main treatment in 95% of cases, there is a group of patients who develop advanced cSCC. Cemiplimab, a programmed cell death (PD- 1) inhibitor, was approved for advanced cSCC, with a 50% overall response rate[1]. However, these studies excluded patients with immunosuppressed disease states such as multiple myeloma (MM). The efficacy and safety of PD-1 inhibitors in treating cSCC in MM patients are currently unclear. It is crucial to investigate the advantages and risks associated with this treatment, as MM patients have a significantly higher risk of developing cSCC, with an incidence rate 2.44 times greater than those without MM[2].
We report a case of complete response of a locally advanced cSCC in a patient with MM, with sustained response after a 3-year follow-up period.

Methods

Review of 2023 medical records from the Oncology Department of Hospital BP, examination slides from Laboratório Bacchi for anatomopathological evaluation, as well as computed tomography (CT) scans.

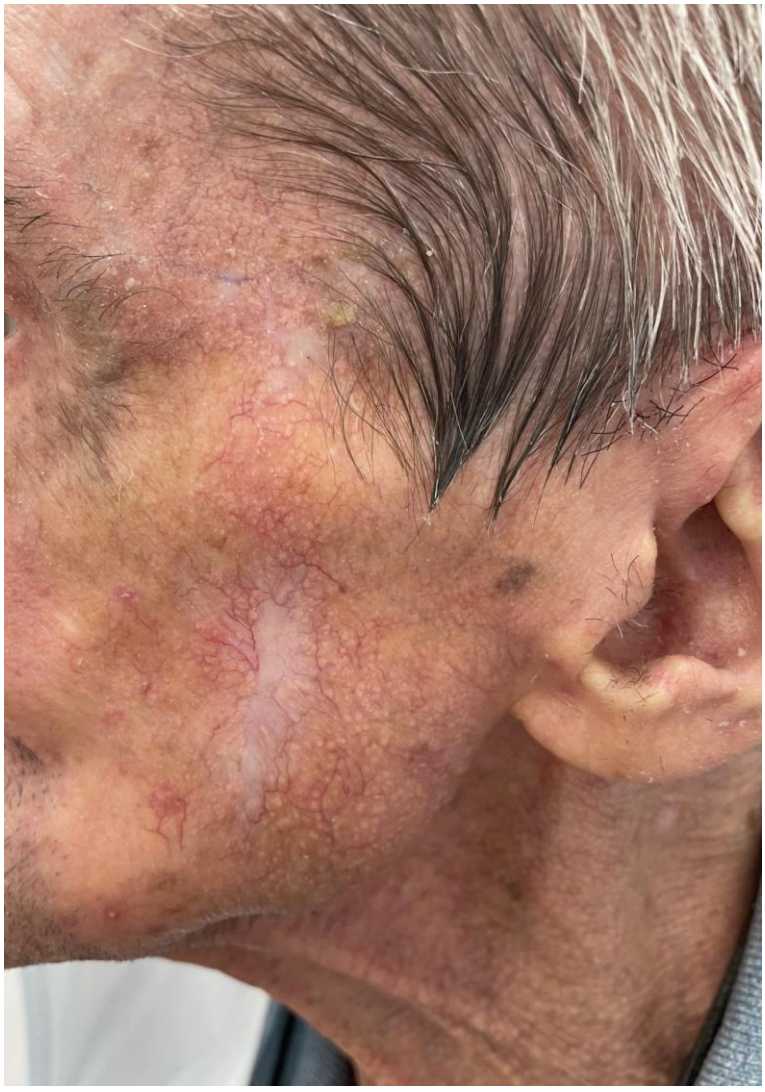
Results

A 76-year-old man with a 13-year history of Smoldering MM treated with thalidomide presented to the dermatology clinic with a rapidly growing ulcerated pre-auricular lesion (Fig 1). A biopsy confirmed the suspicion of cSCC and CT revealed close proximity to the parotid gland.



Ulcerate tumor in the left preauricular region in December 2020

After multidisciplinary discussions, it was agreed to discontinue the MM therapy, and start cemiplimab.
The patient started cemiplimab 350mg intravenously, every 3 weeks, with significant clinical (Fig 2) and radiological improvement after 15 cycles. As a consolidation strategy, he received radiotherapy. He tolerated the treatment well, requiring only one interruption after the second cycle due to skin rash on the lower limbs.
The patient remains under continuous observation, exhibiting a sustained complete response even after a follow-up period of three years.



Complete clinical response in January 2024

Conclusions

This case exemplifies a successful treatment of locally advanced SCC in an MM patient with cemiplimab, showing the medication's effectiveness and safety in this specific patient population. And also provides insights as duration of response seen in this patient exceeded the previously established duration of response (24,2 months) noted in previous cemiplimab trials for locally advanced cSCC.

References:

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A-228

Age over 90 years is an unfavorable prognostic factor for resectable cutaneous squamous cell carcinoma

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Background
Surgery is the gold standard treatment for cutaneous squamous cell carcinoma (cSCC). However, dementia and other complications experienced by older patients can create surgical challenges.

Methods
During this retrospective study, we analyzed 316 patients with cSCC who underwent surgery at Kagoshima Medical Center from October 2014 to September 2022.

Results
Patients were separated into two groups based on age: those aged < 90 years (104 patients; 40 [38.5%] men and 64 [61.5%] women) and those aged 90 years or older (212 patients; 130 [61.3%] men and 82 [38.7%] women) ($p<0.001$). A comparison of the groups indicated that more patients in the age < 90 years group had immunosuppression ($p=0.031$). Regarding the National Comprehensive Cancer Network risk classification, there was no difference between groups. A univariate analysis, multivariate analysis, and Cox analysis of relapse-free survival of patients in both groups indicated that the recurrence risk was significantly higher among those in the 90 years or older group.

Conclusions
Patients 90 years or older were at higher risk for recurrence, suggesting that extremely old individuals have some immunological differences compared with individuals aged < 90 years.

A-336

Analysis of risk factors in melanoma survivors for the development of non-melanoma skin cancer

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Background
The increasing global incidence of skin cancers such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma highlights the need to understand their interrelationships. This study focuses on non-melanoma skin cancer (NMSC) in patients previously diagnosed with melanoma.

Methods
Objective: to explore the state of immunosuppression, analyze the relationship between melanoma and other types of NMSC including basal cell and squamous cell skin cancers as well as less common types, and examine the association between MC1R gene variants and NMSC. Design: a retrospective analysis of 1,888 melanoma patients from the Hospital Clínic de Barcelona between 2011 and 2018 was conducted. Data collection included information on NMSC, immunosuppression, MC1R gene mutations, and demographic factors. Advanced statistical methods such as Fine and Gray model for competitive risk analysis and Chi-square and Wilcoxon tests for descriptive analysis were applied.

Results
Of the 1,888 melanoma patients included in this study, 397 developed NMSC resulting in a total of 991 tumours. BCC was the most prevalent tumour, diagnosed in 723 cases (73%), while squamous cell carcinoma in situ (Bowen's disease) was identified in 145 cases (15%), and squamous cell carcinoma in 106 (11%). Other less common types accounted for a total of 11 cases (1.1%). A significantly higher proportion of men (60.5%) was observed in the NMSC group compared to the non-NMSC group (45.6%). A higher prevalence of immunosuppression was found in the NMSC group (27.6%) compared to the non-NMSC group (21.8%). The study revealed no statistically significant differences in the presence of MC1R gene variants between patients with and without NMSC. The median age in the NMSC group was notably higher (69.4 years) compared to the non-NMSC group (54.9 years).

Conclusions
The high incidence of NMSC in our cohort of patients with MM (21%) underscores the need for specific follow-up regimes in these patients, specially in older men and those with immunosuppression.

A-388

Anhidrotic ectodermal dysplasia with multiple cutaneous squamous cell carcinomas in sun-exposed areas

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Background
Anhidrotic (Hypohidrotic) ectodermal dysplasia（AED）is a genetic disorder characterized by dysplasia of the hair, teeth, nails and sweat glands. Although many different forms have been described, only one case of skin cancer in this disease was reported.Here we present a case of multiple cSCC in the sun-exposed areas, in which a definitive diagnosis of AED was obtained by genetic testing.

Methods
Case: 51 years old, male. Occupation: Truck driver. Family history: none.
Since infancy, the patient had poor sweating and often exhibited heat retention. He had hair and eyebrow defects and had tooth dysplasia. Although he had been pointed out to be the possibility of AED by several medical institutions, but definitive diagnosis had not been made. Over time from around age 38, he developed multiple cutaneous squamous cell carcinomas (cSCC) on the face,and which were resected at several medical facilities. At the age of 48, a tumor developed on the left mandibular skin. Histopathology of biopsied specimen revealed a suspected cSCC, and he was referred to our institute. At the time of the admission, a 3 × 2 cm diameter pale red tumor was observed. The head and neck skin showed dryness with a mixture of depigmentation and hyperpigmentation. The FDG-PET/CT showed an accumulation in the left cervical lymph nodes as well as in the skin tumor. Under general anesthesia, the mandibular mass was resected, and selective lymph node dissection of the left neck was added.

Results
Histopathologic examinations of the resected skin mass and lymph nodes revealed cSCC and its lymph node metastases. The Genetic testing was negative for Rothmund-Thomson syndrome and a diagnosis of AED was made.

Conclusions
A case of AED with multiple occurrences of cSCC in sun-exposed areas is reported. Genetic testing ruled out Rothmund-Thomson syndrome and allowed a definitive diagnosis of AED. In this patient, the skin barrier damage due to concomitant atopic dermatitis and overexposure to sunlight due to his occupation could affect on the carcinogenesis of cSCC.

A-441

Beyond tropical verrucose syndrome: new associations of skin cancer and verrucous lesions.

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Background

Chromoblastomycosis is defined as mycosis of the skin and subcutaneous cellular tissue. It belongs to the group of tropical verrucous syndrome diseases. It is mainly caused by dematiaceous fungi such as F. pedrosoi and C. carrionii. Normally, it occurs after a penetrating trauma to the skin with plant objects, and that's why it is more common in farmers or peasants in the tropic. Different complications have been described with malignant transformation, mainly squamous cell carcinoma being the most serious complication [1][2].

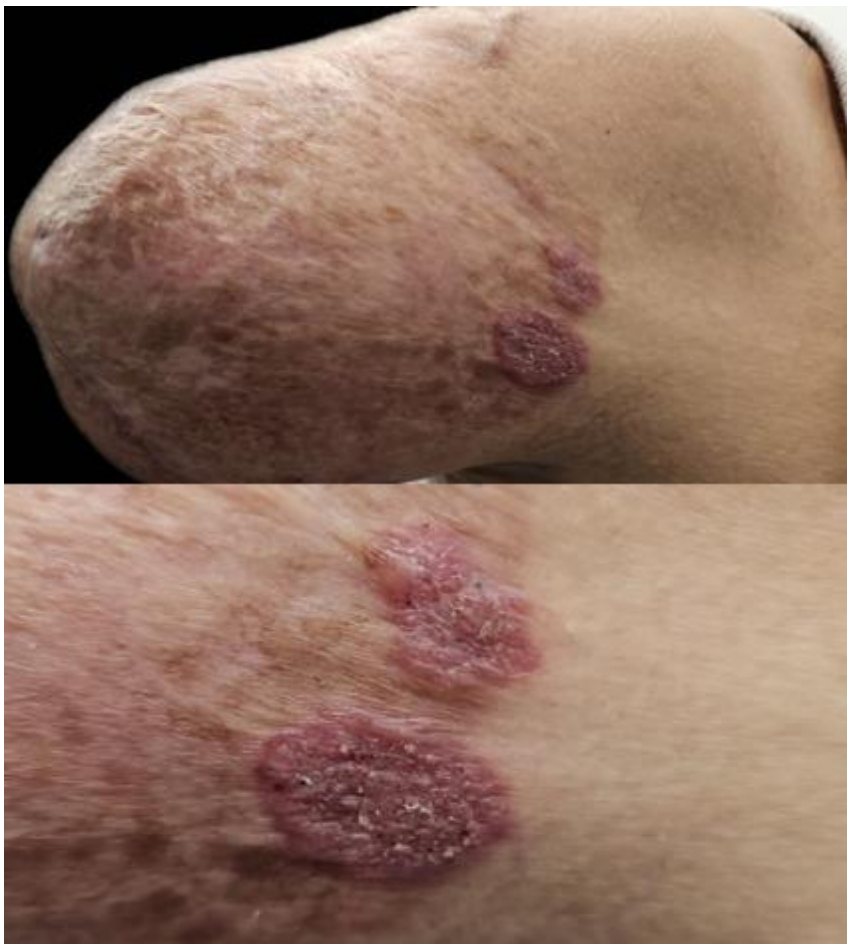
we present the case of a patient diagnosed with chronic chromoblastomycosis and associated squamous cell carcinoma

This is the case of a 70-year-old male patient, from Mosquera Cundinamarca in Colombia, with diagnosis of Chromoblastomycosis since 2016 made by skin biopsy, which reported a pseudoepitheliomatous and irregular epidermal hyperplasia, lymphohistioplasmacytic infiltrate and presence of pigmented yeasts evident with hematoxylin eosin staining.

On physician examination

Yellowish brown tumor plaque, with a warty surface with black dots located on the back of the hand with extension to the proximal third of the forearm

He received treatment with Terbinafine 500 mg every 12 hours and Itraconazole 200 mg every 12 hours for 1 year without obtaining clinical improvement, hence left transhumeral amputation was performed with evidence of well-differentiated squamous cell carcinoma, keratinizing and infiltrating soft tissues and in contact with bone. Three months after surgical management, he presented new lesions in the stump suggestive of chromoblastomycosis, for which extension of the stump amputation was indicated



Nummular erythematous and scaly plaques with black dots on the surface in the proximal third of the left arm

Methods

Descriptive observational case report type.

Results

In cases of long-term infection caused mainly by Fonsecaea pedrosoi, poor response to treatment, extensive lesions and associated ulcerations predispose to malignant transformation to melanoma or squamous cell carcinoma, these being the most serious risk factors for malignancy bad prognosis [1].

Conclusions

Chromoblastomycosis is a chronic deep mycosis, which can present different complications. Therefore, taking these into account will help provide a timely diagnosis, taking into account these possible association [1][2].

References:

[1] Rojas OC, (2015), Chromoblastomycosis by Cladophialophora carrionii Associated with Squamous Cell Carcinoma and Review of Published Reports.

[2] Azevedo CMPS, (2015), . Squamous Cell Carcinoma Derived From Chronic Chromoblastomycosis in Brazil. Clinical Infectious Diseases

A-253

Cemiplimab Immunotherapy in the Treatment of Cutaneous Squamous Cell Carcinoma

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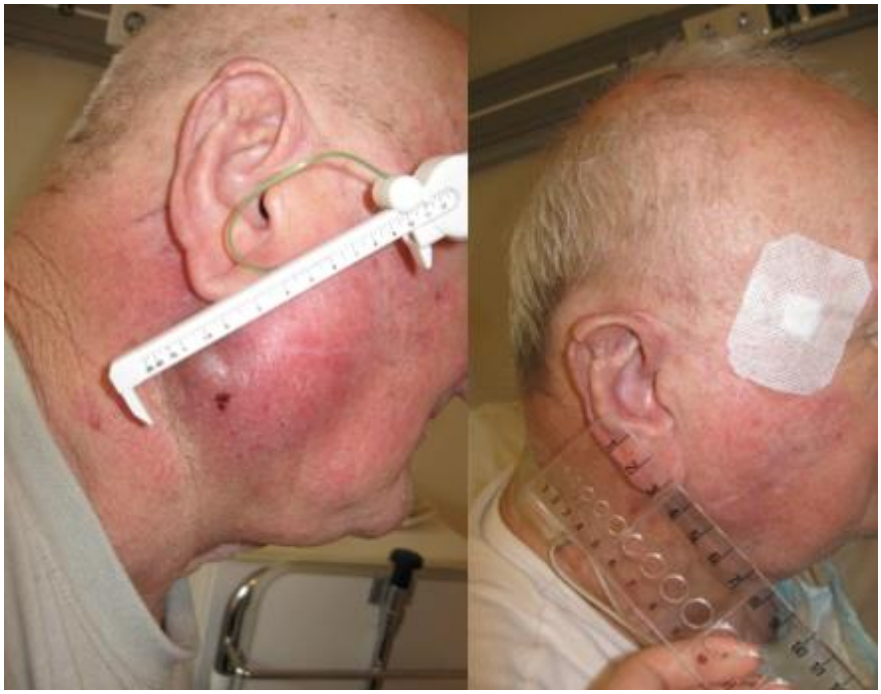
Background

[REFERENCE01]In the treatment of locally advanced and metastatic cutaneous squamous cell carcinoma (cSCC), the first-line systemic therapy is the anti-PD-1 (programmed cell death protein-1) immunotherapy cemiplimab, which was approved in 2019. The aim of our study was to evaluate the efficacy and safety of cemiplimab in our own patients.

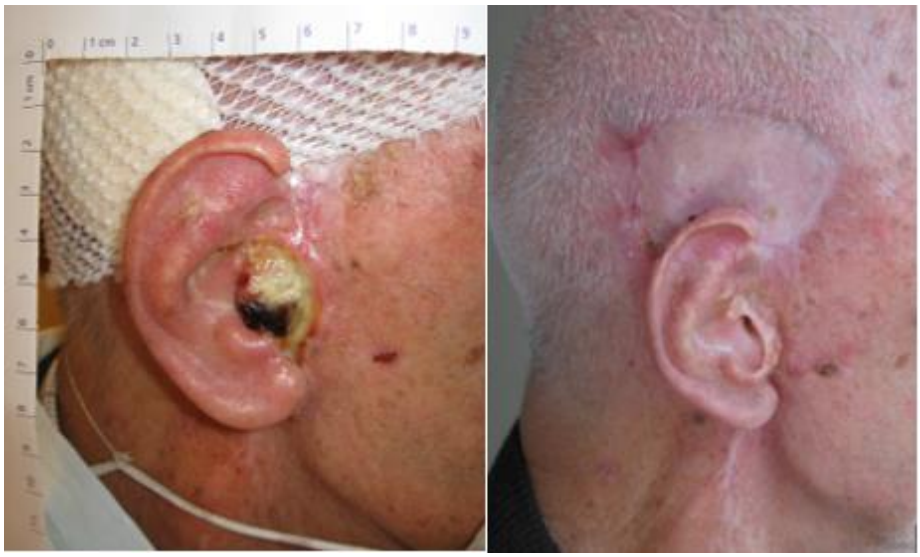
Methods

Between January 2021 and May 2023, we retrospectively evaluated the efficacy and safety of cemiplimab immunotherapy in 18 patients diagnosed with locally advanced or disseminated cSCC. Patients received immunotherapy in three-week cycles at a fixed dose of 350 mg. The safety of the therapy was analyzed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Results



Squamous cell carcinoma metastasizing to the parotid gland.



Squamous cell carcinoma infiltrating the tragus

Our study included 13 males (78%) and 5 females (28%), with a mean age of 78 years (range 64-91). Locally advanced cSCC was present in 3 patients (16.6%), metastatic cSCC in 15 patients (83.3%), and the primary tumor was unknown in 1 patient (5.5%). Patients received cemiplimab immunotherapy for an average of 10 cycles, with a median follow-up time of 10 months (range 2.4-33.2 months), and achieved an objective tumor response rate (ORR) of 50%. Complete remission (CR) was observed in two patients (11.1%), partial remission (PR) in seven patients (39%), stable disease (SD) in five patients (27.8%), and progression disease (PD) in four patients (22.2%). The six-month progression-free survival rate was 88.8%, and all patients were alive six months after the start of therapy. Drug-related adverse events occurred in half of the treated patients (50%), with Grade 1 adverse events in 22.2% of cases and Grade 2 adverse events in 11.1% of cases. As a side effect of immunotherapy, second primary skin tumors, cSCC, or basal cell carcinoma (Grade 3 adverse events) developed in approximately 33% of patients, all of which were surgically removed.

Conclusions

In our study, cemiplimab proved to be an effective therapeutic modality in patients with locally advanced or disseminated cutaneous squamous cell carcinoma, with tolerable side effects.

References:

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A-284

Cemiplimab in the treatment of locally advanced cutaneous squamous cell carcinoma: a case series study.

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Background
Cutaneous squamous cell carcinoma poses significant challenges, especially in advanced stages on the face or scalp, representing the most common skin cancer in Caucasians worldwide. Excision with histologic margin review remains the gold standard, but the management of locally advanced cases becomes complicated when surgery is not feasible, given the associated perioperative morbidity and the impact of aesthetic trauma on quality of life. Cemiplimab, a PD-1 inhibitor, is emerging as the preferred option for locally advanced and metastatic cases when surgery is not feasible, demonstrating efficacy in both the palliative and recently the neoadjuvant setting.

Methods
We present a case series study of four immunocompetent patients with locally advanced cutaneous squamous cell carcinoma (stage III to IV) who received cemiplimab 350mg intravenously every three weeks, with re-evaluation every 12 weeks for possible surgery. Prior to cemiplimab therapy and at 12-week intervals, comprehensive assessments were performed using whole-body computed tomography and magnetic resonance imaging of the head to evaluate tumor extension.

Results
Within 12 weeks, all patients demonstrated a significant clinical response based on clinical inspection and MRI results, with no high-grade adverse events (CTCAE III and IV).
Two patients achieved a complete clinical response within one year and remained relapse-free at 3 and 6 months.
The remaining two patients experienced clinical tumor shrinkage at 6 and 4 months, respectively, before the patients voluntarily discontinued therapy. At a recent follow-up visit, one of the patients developed a growing lesion at the site of the primary tumor, necessitating a biopsy to rule out recurrence.

Conclusions
This case series highlights (neoadjuvant) cemiplimab as a favorable alternative to extensive surgery, especially in the elderly, with a safe treatment profile. However, further studies are imperative to establish long-term efficacy and to assess its impact on overall disease-free survival.

A-285

Clinical response to immune checkpoint inhibitors in immunocompromised patient with metastatic non-melanoma skin cancer.

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Background

Treatment with immune checkpoint inhibitors (ICI) has shown promising results in patients with locally advanced and/or metastatic cutaneous squamous cell carcinoma (cSCC), but data regarding their efficacy and safety in patients with concurrent hematological disorders are limited. We present a case of metastatic cSCC treated with pembrolizumab with a good response in a patient with T-cell prolymphocytic leukemia (T-PLL).

Methods

An 82-year-old male presented with a left parietal tumoral lesion compatible with poorly differentiated cSCC, invading up to the subcutaneous tissue and perineural invasion) in contact with the deep margin, undergoing contact radiotherapy for 1 month. After 4 months, recurrence of the parietal lesion with an adjacent subcutaneous nodule was detected, biopsied with results of cSCC with vascular invasion and satellite lesions, respectively. Surgical rescue was decided, without achieving clear margins. In the following weeks, multiple nodules appeared on the flap edges and ipsilateral hemiface, along with a 3 cm cervical mass evidenced on CT scan. At that moment, it was considered not curable with surgery or radiotherapy, a candidate for immunotherapy. Initial blood work showed leukocytosis with a blood smear compatible with chronic lymphoproliferative syndrome. After consensus with Hematology, pembrolizumab 200 mg every 3 weeks was initiated. Cutaneous lesions and cervical mass regressed after five infusions, but with progression of leukocytosis. Prior to the sixth cycle, the patient was admitted due to clinical deterioration in Hematology completing the study. He was diagnosed with T-PLL and died within a month.

Results

Advanced CSCC presents a high mutational burden, with ICI being effective in its management, achieving overall response rates of up to 52% and complete remission after 4-6 cycles. However, patients with hematological disorders present worse outcomes (26.7%) due to greater tumor aggressiveness and dysfunctional immune system. The relationship between ICI and the development of hematological neoplasms is debated, although the loss of T-cell suppression by PD1 could play a role. The aggressiveness and lethality of T-PLL make it difficult to determine the influence of ICI on this condition.

Conclusions

Immune checkpoint inhibitors have shown to be an effective treatment for inoperable cSCC, but further studies are needed to evaluate efficacy and safety in patients with hematologic conditions.

References:

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A-457

Complete regression of Bowen's disease after incisional biopsy: case report

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Background

Bowen's disease is a squamous cell carcinoma in situ that generally presents as an erythematous, well-demarcated, squamous plaque located on photo-exposed areas such as the head, neck, and extremities, with glomerular vessels and scales on the surface on dermoscopy. Histologically, it shows dysplasia of keratinocytes throughout the epidermis without dermal infiltration. Given the risk of progression to local invasive disease or metastasis, it requires timely treatment, including surgery, cryotherapy, radiotherapy, among others.

Methods

We present the case of a 72-year-old man with no medical history who consulted for an asymptomatic erythematous lesion of 1 year's evolution of slow growth in the left lumbar region. On examination, he presented with a 7x5 cm erythematous scaly plaque composed of confluent papuloplaques of smaller size

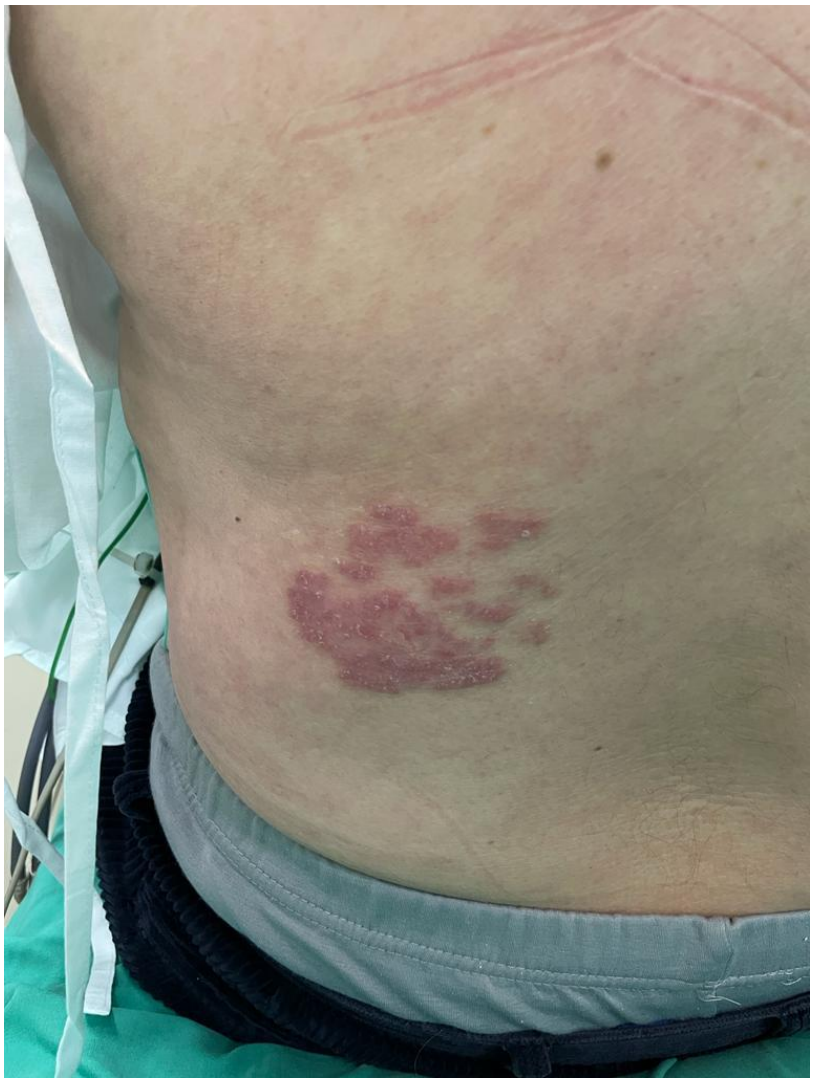

Figure 1. Initial clinical picture showing an erythematous-squamous plaque in the left lumbar region.
. Dermoscopy showed glomerular vessels grouped in clusters and whitish scales on a pink background. Diagnostic punch biopsy was performed and Bowen's disease was confirmed. The patient was scheduled for surgical resection in 4 weeks, clinical and dermoscopic involution of the lesion was noted, visualizing only faint erythema of smaller size. A new biopsy was performed at 3 different sites of the remaining lesion, showing a lymphocytic infiltrate without malignant neoplasm.

Results

At the 1-year follow-up, the clinical remission of the original lesion persisted

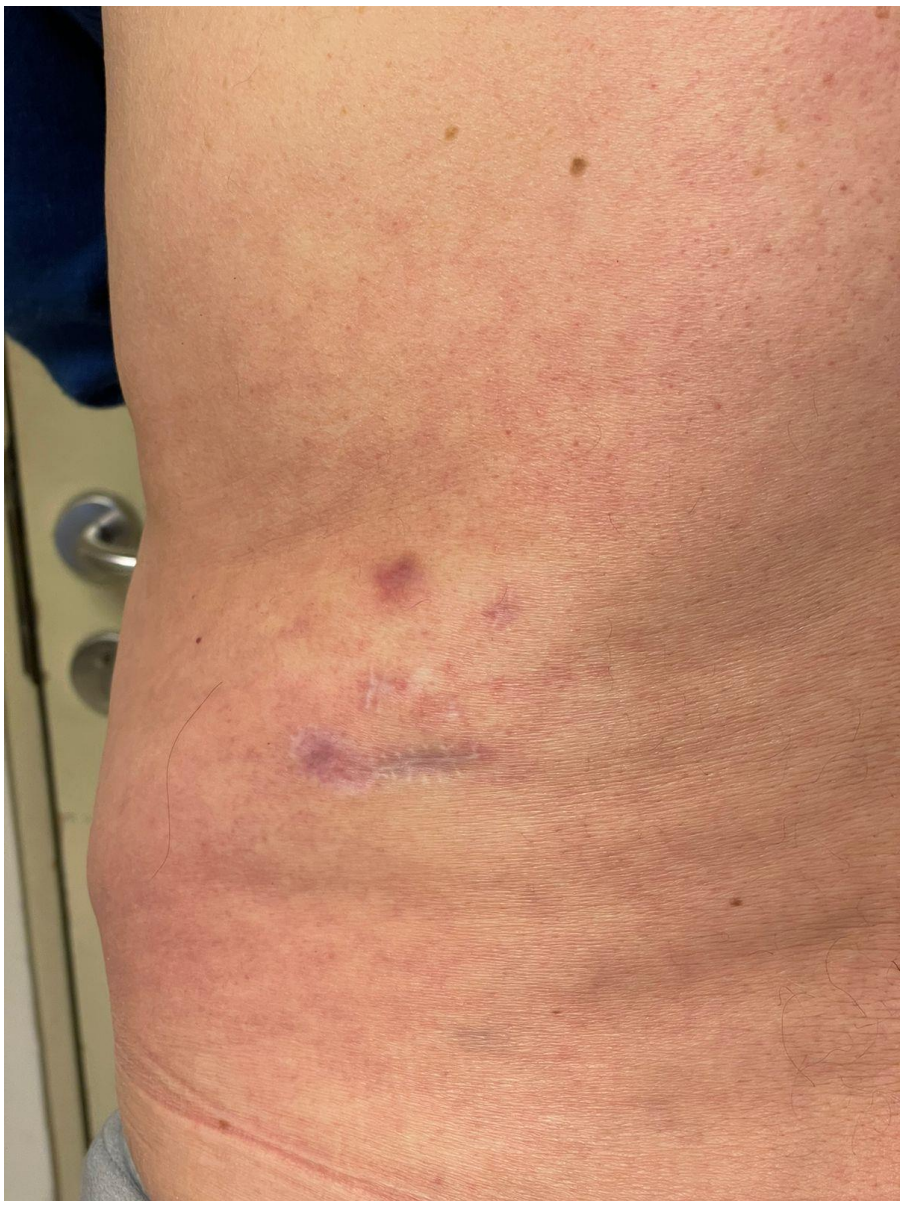

Figure 2. Clinical image showing complete regression of the initial lesion.

Conclusions

The case of Bowen's disease of unusual location and with an atypical evolution, with complete spontaneous regression in less than 1 month after diagnostic biopsy, maintained at 1-year follow-up is presented. We highlight the infrequency of this evolution, with only 2 cases reported with complete regression [1][2], one in the left thigh at 6 weeks and the other at 8 weeks in the interdigital space of the left foot, the case presented being the one with the earliest complete regression. It is believed that local T-cell-mediated immune responses and apoptosis play a role in the spontaneous regression of malignant skin tumors, which would explain the prominent lymphocytic infiltrate in the remaining lesion. The role of the previous biopsy remains unknown, in part due to the paucity of similar reports.

References:

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A-439

Cost -effectiveness of Surgical Excision versus Photodynamic Therapy and 5-Fluorouracil Cream in Treatment of Bowen's Disease: a trial based economic evaluation

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Background
Given the increasing incidence of Bowen's disease, treatment leads to a substantial economic burden for healthcare services. It is important to justify treatment costs, particularly when less expensive, but equally effective treatment alternatives exist. Health economic evaluations for different treatments of Bowen's disease are currently lacking.
To determine which treatment is cost-effective when comparing surgical excision, methylaminolevulinate photodynamic therapy (MAL-PDT) and 5% 5-fluorouracil cream for Bowen's disease. To determine which treatment is cost-effective when comparing surgical excision, methylaminolevulinate photodynamic therapy (MAL-PDT) and 5% 5-fluorouracil cream for Bowen's disease.

Methods
Data were collected alongside a randomized controlled trial with 250 patients in the Netherlands. All health care resource use was assessed. A cost-utility analysis (CUA) was performed from a health care perspective. The primary outcome was expressed as the incremental costs per Quality Adjusted Life Years (QALYs) gained at 12 months. The QALY combines life expectancy with health related quality of life, the latter measured with the EQ-5D-5L questionnaire. Bootstrap analysis and sensitivity analysis were performed to address uncertainty. This trial is registered with ClinicalTrials.gov number, NCT03909646.

Results
At 12 months after treatment, the costs made for 5-fluorouracil cream were substantially lower (- €309) and the costs for MAL-PDT were higher (€49) compared to excision. The observed difference in QALY between the treatments was 0.02 in favor of 5-fluorouracil and 0.01 in favor of MAL-PDT when compared to surgical excision. Our results showed that 5-fluorouracil has the highest probability of being cost-effective compared to MAL-PDT and surgical excision.

Conclusions
5-fluorouracil cream is a dominant cost-effective treatment when compared to surgical excision and MAL-PDT. Therefore, also from a cost-effectiveness point of view, 5-fluorouracil is considered the first-choice treatment option for Bowen's disease.

A-147

Delphi Consensus of Tumor Stage Based Treatment Approach to High-Risk Cutaneous Squamous Cell Carcinoma

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Background
Staging systems for cutaneous squamous cell carcinoma (CSCC) have improved remarkable in the last decade. Despite improvements in the clinician's ability to counsel patients on prognosis, significant gaps remain in the utilization of staging systems and stage-based treatment algorithms for CSCC. There are no current guidelines based on tumor stage; moreover, there is no distinction of the impact between different individual or combination risk factors. The small subset of tumors that have a substantial risk for recurrence and metastasis is becoming more defined, but how to use radiologic or invasive (e.g. sentinel lymph node biopsy (SLNB)) staging modalities or when to consider potential adjuvant therapies remains unclear. To address this practice gap, a multi-specialty expert panel will perform a multiple round Delphi study using various clinical scenarios in CSCC care. Our findings will help develop a systematic management algorithm for CSCC that follows staging systems as well as identify specific areas that need future clarification.

Methods
75 multi-specialty CSCC experts from dermatology, dermatologic surgery, radiation oncology, medical oncology, head & neck surgery, and surgical oncology were recruited and surveyed on their management approach in high-risk CSCC (see Table 1). A Delphi consensus process utilized a series of 3 iterative surveys sent to the expert panelists. Each survey round included clinical questions regarding a healthy, immunocompetent 65-year-old white male with a surgically resectable tumor located in the head and neck region. Tumor stages were defined based on the 8th American Joint Committee on Cancer criteria for CSCC.

Table 1. Demographics of Panelists (N = 70)

Characteristic		N (%) of panelists
Length of experience (years)		
	1-5	8 (11.4)
	6-10	18 (25.7)
	11-20	34 (48.6)
	21+	10 (14.3)
Specialty		
	Dermatologic Surgery	15 (21.4)
	Medical Dermatology	15 (21.4)
	Head & Neck Surgery	18 (25.7)
	Radiation Oncology	12 (17.1)
	Medical Oncology	10 (14.3)
Country of Practice		
	US	40 (57.1)
	Europe	14 (20.0)
	UK	4 (5.7)
	Australia	12 (17.1)
Practice Type		
	Community Practice	6 (8.6)
	Academic Practice	66 (94.3)
	VA (Veterans Affairs)	3 (4.3)
	Other	2 (2.9)

Demographics of Panelists

Results

70 panelists participated in the first round of the Delphi survey. 66 of those panelists completed the second and third rounds of the survey, with an overall completion rate of 94.3%. The panelists, including the steering committee, were 15 dermatologic surgeons, 15 medical dermatologists, 18 head & neck surgeons, 12 radiation oncologists, and 10 medical oncologists. The survey results are listed in Table 2.

Table 2. AJCC8 Stage Based Consensus Recommendations

AJCC8 T1N0M0	%
Areas of Strong Consensus	
Surgery is recommended as first line therapy	100
Do **NOT** recommend additional therapy if inked surgical margins are clear	100
Do **NOT** recommend pre-operative imaging to detect distant	98.6
Do **NOT** recommend SLNBx to detect subclinical lymph node metastasis	95.7
Do recommend additional therapy if inked surgical margins are positive and surgical re-resection is not possible	91.3
(a) Consensus treatment of choice is radiation therapy	85.2
Do **NOT** recommend pre-operative imaging to assess tumor extension	88.4
Do **NOT** recommend pre-operative imaging to detect lymph node metastasis	87.0
No consensus	
• Split between CCPDMA or Mohs Surgery (54.3%) vs Standard surgical excision with standard margin evaluation (45.7%) as first line surgical therapy • No preferred treatment for a T1N0M0 patient that is not a surgical candidate	

AJCC8 T2N0M0	%
Areas of Strong Consensus	
Surgery is recommended as first line therapy	100
Do **NOT** recommend additional therapy if inked surgical margins are clear	97.1
Do recommend additional therapy if inked surgical margins are positive and surgical re-resection is not possible	96.6
(a) Consensus treatment of choice is radiation therapy	92.3
Do **NOT** recommend pre-operative imaging to assess tumor extension	94.1
Do **NOT** recommend SLNBx to detect subclinical lymph node metastasis	86.8
Do recommend radiation therapy as preferred treatment for a T2N0M0 patient that is not a surgical candidate	84.3
No consensus	
• Do NOT recommend (58.8%) vs. recommend (41.2%) pre-operative radiologic imaging to detect lymph node metastasis	

AJCC8 T3N0M0	%
Areas of Strong Consensus	
Do recommend additional therapy if inked surgical margins are positive and surgical re-resection is not possible	98.5
(a) Consensus to recommend post-operative adjuvant radiation therapy	98.9
Surgery is recommended as first line therapy	92.6
Do recommend MRI as preferred imaging modality to evaluate concerning PNI	88.6
Do **NOT** recommend pre-operative imaging to detect lymph node metastasis	86.8
Do recommend salvage post-operative radiation therapy as adjuvant treatment modality for s/p surgery and margins are reported as **POSITIVE**	84.3
Areas of Weak Consensus	
Radiation therapy is the preferred treatment for a not a surgical candidate	68.6
Recommend performing sentinel lymph node biopsy	65.7
Perform additional radiologic imaging in a patient with PNI of ≥0.1mm diameter	65.7
CCPDMA or Mohs Surgery as first line surgical therapy for a T3N0M0 tumor	64.3
Do NOT recommend pre-operative imaging to detect distant metastasis	61.8
CT preferred imaging modality to evaluate for potential lymph node metastasis	60.0
No consensus	
• Recommend additional therapy if inked surgical margins are clear (57.4%) vs. do not recommend additional therapy (42.6%)	

AJCC8 T4N0M0	%
Areas of Strong Consensus	
Do recommend additional therapy if inked surgical margins are POSITIVE	100
(a) Recommend post-operative adjuvant radiation therapy in this situation	93.9
Do recommend pre-operative imaging to detect lymph node metastasis	96.9
Do recommend additional therapy if inked surgical margins are **CLEAR**	86.2
(a) Recommend adjuvant post-operative radiation therapy for patient post surgery with CLEAR margins	91.4
Surgery is recommended as first line therapy	84.6
No consensus	
• Split between CCPDMA or Mohs Surgery (40.0%) vs Standard surgical excision with standard margin evaluation (60.0%) as first line surgical therapy • Preferred radiologic imaging modality to evaluate for potential lymph node metastasis • No preferred treatment for a T4N0M0 patient that is not a surgical candidate	

Resectable Nodal Disease	%
Area of Strong Consensus	
Do recommend pre-operative imaging to detect lymph node metastasis	100
Do recommend post-operative radiation therapy to nodal basin after surgery	98.4
Surgery is recommended first line therapy	93.7
Do recommend pre-operative radiologic imaging to detect distant metastasis	93.7
Do **NOT** recommend post-operative systemic therapy if surgery performed	93.7
Do recommend radiologic imaging surveillance	90.5
Area of Weak Consensus	
Recommend post-operative nodal radiation if multiple positive nodes or extranodal extension	77.1
PET+CT is preferred radiologic imaging modality for to detect distant metastasis	68.6
Do **NOT** recommend post-operative elective nodal radiation in a patient with no clinical or radiologic signs of lymph node metastasis	61.4
No consensus	
• Preferred radiologic imaging modality to assess the nodal basin • Preferred radiologic imaging modality or frequency for surveillance after surgery	

AJCC8 Stage Based Consensus Recommendations

Conclusions

The results of this Delphi panel show there are number of areas of strong consensus among multi-specialty experts establishing a framework for a stage based systematic management algorithm for CSCC. This study also highlights specific issues and questions that need future clarification especially in higher stage tumors, particularly the role of radiologic imaging, the use of SLNB, and optimal surgical techniques.

A-313

Desmoplasia, a risk factor for recurrence and metastasis in cutaneous squamous cell carcinoma: an interobserver agreement study among dermatopathologists.

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Background
Desmoplasia has emerged as a significant risk factor for local recurrence and metastasis in cutaneous squamous cell carcinoma (cSCC). However, a universally accepted definition for desmoplasia is lacking and its inclusion in clinical guidelines is inconsistent, which raises concerns about the reliability of its assessment by dermatopathologists. This study aimed to investigate the interobserver agreement among dermatopathologists in the assessment of desmoplasia in cSCC, and to examine differences in interobserver agreement based on work experience (i.e. ≤5 years versus >5 years) and work setting (i.e. non-academic versus academic centers).

Methods
In this prospective multicenter study cSCCs were randomly selected from a retrospective database of patients with cSCCs. For each selected tumor, only the most representative sections were selected, with a maximum of four sections per tumor. Dermatopathologists from non-academic and academic centers assessed the histopathologic sections for the presence of desmoplasia according to the following definition by Brantsch et al., 2008: “the presence of fine branches of tumor cells at the periphery and a surrounding stromal reaction”. To determine the interobserver agreement, the proportion of agreement (%) and the Fleiss’ kappa coefficient (κ) were calculated. Kappa values were interpreted using the Criteria by Landis and Koch. Based on existing evidence, a kappa value below 0.60 was considered inadequate agreement.

Results
Nine dermatopathologists completed the assessment of histopathological slides of 50 cSCCs. The proportion of agreement was 71.8% (95% CI, 66.5-77.1) and Fleiss’ kappa coefficient was 0.34 (95% CI, 0.22- 0.47), corresponding to a fair interobserver agreement. The kappa for dermatopathologists with ≤5 years of work experience was higher compared to dermatopathologists with >5 years of experience (κ=0.47 and κ=0.175, respectively; p<0.001). Interobserver agreement was higher among dermatopathologists from non-academic centers (κ=0.44) compared to dermatopathologists from academic centers (κ=0.29; p=0.141).

Conclusions
The assessment of desmoplasia in cSCC is challenging and our results show an inadequate interobserver agreement among dermatopathologists. In our opinion, the current used definition is therefore not suitable for reliable risk assessment in cSCC. Future research should focus on achieving a clear and uniform definition of desmoplasia to increase interobserver agreement and refine risk stratification in cSCC.

A-286

Examining the Association Between Ruxolitinib and Aggressive Cutaneous Squamous Cell Carcinoma: Is There a Justified Need for Screening Programs?

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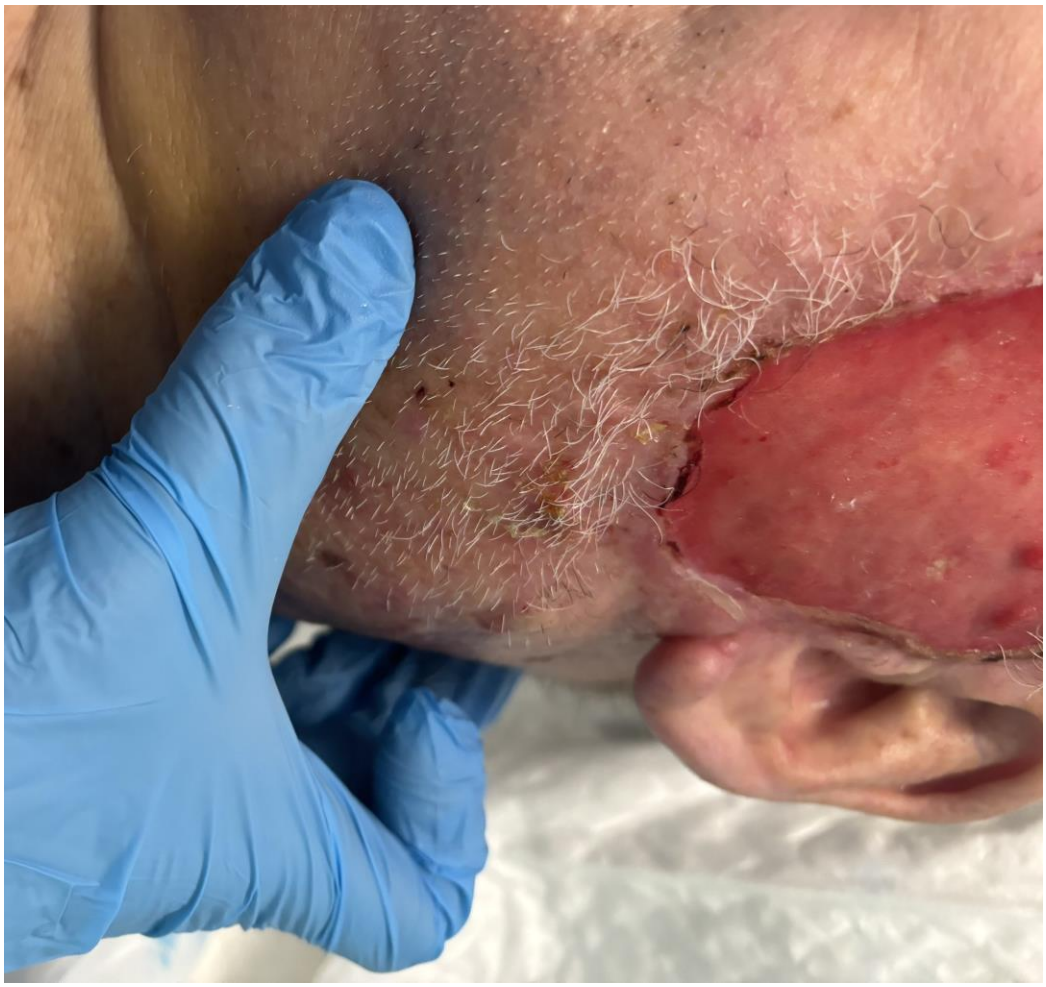
Background

Ruxolitinib is an anti Janus kinase (JAK) inhibitor that selectively inhibits JAK 1 and 2. It is approved to treat myelofibrosis, polycythemia vera and refractory graft versus host disease.

Methods

We present the case of a 76-year-old male under surveillance for high-risk cutaneous squamous cell carcinoma (SCC) on the right cheek, which required surgical treatment along with adjuvant radiotherapy. Past medical history included polycythemia vera treated with ruxolitinib for a two-year period. During follow-up, an erythematous scaly plaque was observed in the left preauricular region, for which a six-week topical imiquimod treatment course was prescribed. Subsequent evaluations revealed persistent ulceration and worsening of the plaque, extending over an area of 5 cm. Biopsy confirmed the diagnosis of invasive SCC. A surgical excision along with a two-stage reconstruction using artificial dermis was performed. Histopathological analysis demonstrated involvement of the lateral medial margin and proximity to the lateral inferior margin.

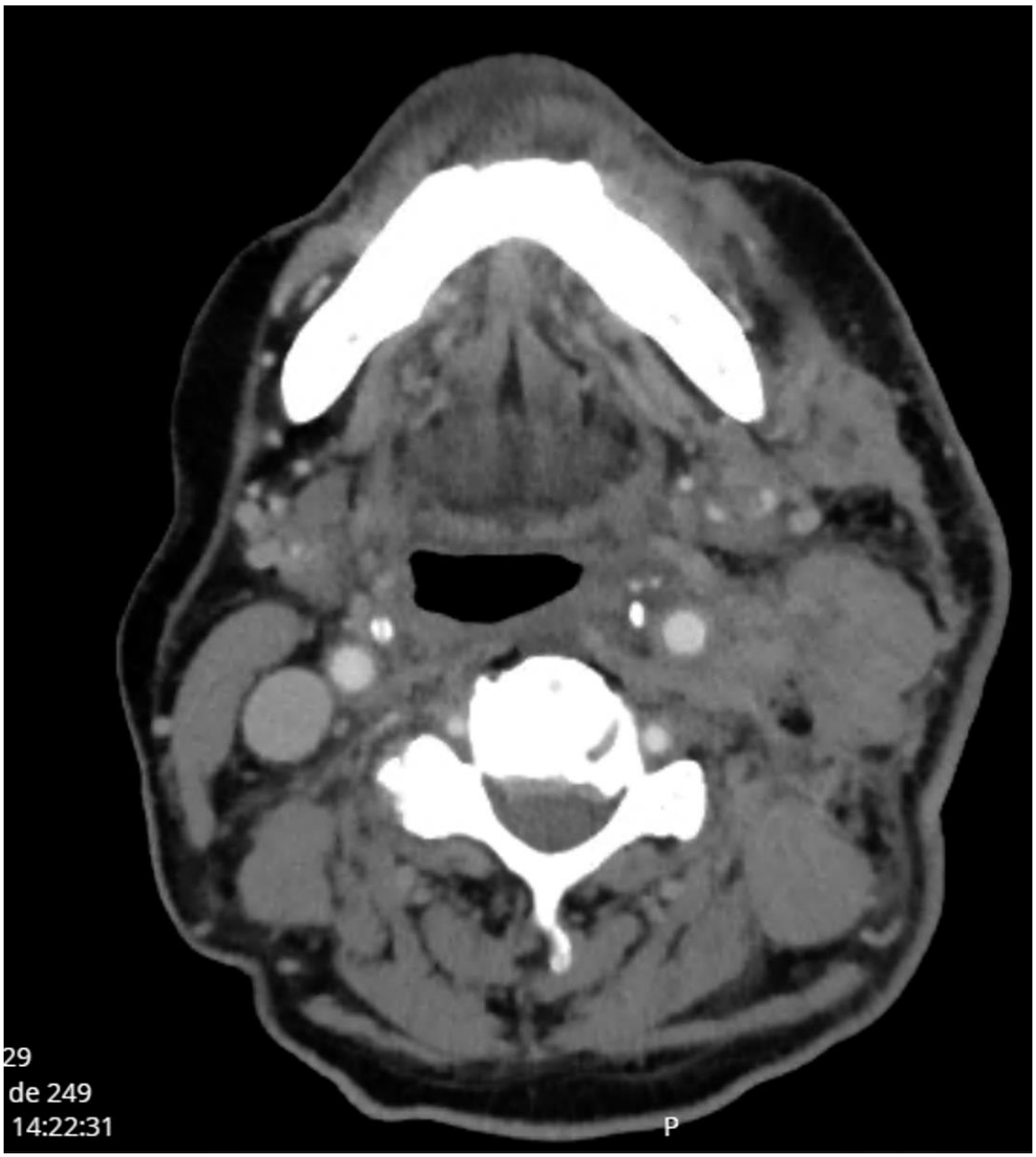
One-month post-surgery, the patient presented to the emergency department with edema and erythema located in the left laterocervical region.



Cervical mass along with induration and non-painful cutaneous edema ipsilateral to the squamous cell carcinoma excision surgery.

Biopsy results consistent with SCC

Computed tomography scan showed a diffuse infiltrate in the subcutaneous and muscular tissues of the neck, consistent with infectious involvement



Computed tomography reveals diffuse infiltration of the neck muscles and subcutaneous tissue affecting multiple cervical spaces and the epiglottis. Additionally, thrombosis of the left jugular vein is also observed
. Following the lack of improvement after antibiotic treatment, a biopsy of the neck was performed. Histopathological findings were consistent with SCC. The patient was diagnosed with metastatic advanced SCC. A multidisciplinary committee opted to initiate cemiplimab and radiotherapy while discontinuing ruxolitinib therapy.

Results

Multiple studies have shown the augmented risk of cutaneous SCC in patients that take ruxolitinib, although the precise mechanisms remain unknown. These pathways may include a distorted host immune response, direct oncogenic targeting through JAK2 inhibition, or enhanced long-term photosensitivity. Further reviews suggest that patients with SCC who take ruxolitinib may have a higher risk of developing more aggressive tumors and may have worse response rates to immunotherapy. A formal screening program of patients taking ruxolitinib has not been established in clinical practice.

Conclusions

Patients with an active treatment with ruxolitinib may be at an increased risk of developing aggressive SCC. Given the observed association between ruxolitinib therapy and SCC,here is a need to assess the necessity of implementing a formal screening program.

A-391

Factors Influencing the Risk of Involved and Close Squamous Cell Carcinoma Excision and Recurrence: A Comprehensive Analysis over a 7-Year Period.

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Background
This study collected data on patient management and outcomes following involved or close primary squamous cell carcinoma (SCC) excision, to determine what factors impacted the risk of involved or close excision and recurrence.

Methods
6694 histology reports identifying SCCs at Cambridge University Hospital (CUH) between 2015 and 2022 were collected. Following filtering and applying inclusion criteria, 252 involved SCCs and 481 close SCCs were identified for data collection, after which 90 involved and 288 close margin primary SCCs were included for analysis. Multiple variables were analysed to determine what factors contribute to an increased risk of involved or close margin excision, and recurrences. Patients who were managed conservatively who did not reach 2 years of follow up could not have recurrence determined.

Results
The average age was 81.0 (SD – 9.61) in the involved group, with 80.7% male patients and 80.1 (SD – 9.08) in the close group, with 74.7% male patients. 92.2% of involved margin and 78.8% of close margin excisions occurred in the head and neck region. In the involved group, 19 (21.1%) were poorly differentiated, 19 (21.1%) invaded beyond subcutaneous fat, 24 (26.7%) showed perineural invasion, and 11 (12.2%) showed lymphovascular invasion. In the close group, 33 (11.5%) were poorly differentiated, 41 (14.2%) invaded beyond subcutaneous fat, 22 (7.6%) showed perineural invasion and 2 (0.7%) showed lymphovascular invasion. Involved SCCs were further managed by follow-up in 14 cases (15.6%), radiotherapy in 25 cases (27.8%), and re-excision in 48 cases (53.3.%). In the close group, 152 patients (52.8%) were followed up in clinic, 52 (18.1%) received radiotherapy, and 69 (24.0%) underwent re-excision.

20 patients in the involved group and 61 patients in the close group could not have recurrence determined. The recurrence rate was notably higher in the involved group (19 recurrences - 27.1%) compared to the close group (9 recurrences - 3.96%). 2 involved margin group recurences were managed conservativly after the initial excison comapred to 5 close margin recurrences.

Conclusions
This relatively large study highlights factors that may increase the risk of involved or close margin excision, in addition to recurrence. These findings raise questions around what optimal management should involve post involved or close margin SCC excision and may help in making data backed choices when offering further management to this patient group.

A-319

Flow cytometry-based strategy to characterize the microenvironment of skin tumors as a tool for preclinical research

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Background

Introduction: The tumor microenvironment (TME) plays an essential role in tumor progression. Its characterization allows to anticipate recurrences and responses to treatments and provides opportunities for the discovering of novel therapies.

Objectives: Aiming to generate a preclinical tool for cancer research, we have developed two multicolor flow cytometry panels for characterizing TME changes across progression in a melanoma and two squamous cell carcinomas (SCCs) mouse models, representing three different immune landscapes and sensitivity degrees to immune checkpoint inhibitors (ICIs).

Methods

Materials and Methods: The B16F10 melanoma and the SCC cell lines PDVC57B and KLN205, were isografted in the C57Bl6/J and DBA/2 immunocompetent mouse strains. The resulting tumors and the draining lymph nodes (DLNs) were immunophenotyped at the onset of tumor growth and 10 days later by using two spectral flow cytometry panels.

Results

A detailed characterization of these tumors revealed the existence of different immune scenarios: Whereas the B16F10 melanomas displayed a very poor immune infiltrate, the two SCCs showed a high infiltration of myeloid cells, being predominant the pro-inflammatory M1 Tumor Associated Macrophages (TAMs) in PDVC57B-derived tumors and the anti-inflammatory M2 TAMs in KL205-derived tumors. Moreover, the PDVC57B tumors displayed the highest content in NK, CD4+ and CD8+ T cells compared to the other tumors.

Accordingly, the DLNs of PDVC57B tumors showed an overall increase in lymphoid and myeloid cells, thus suggesting a higher immunogenic capacity.

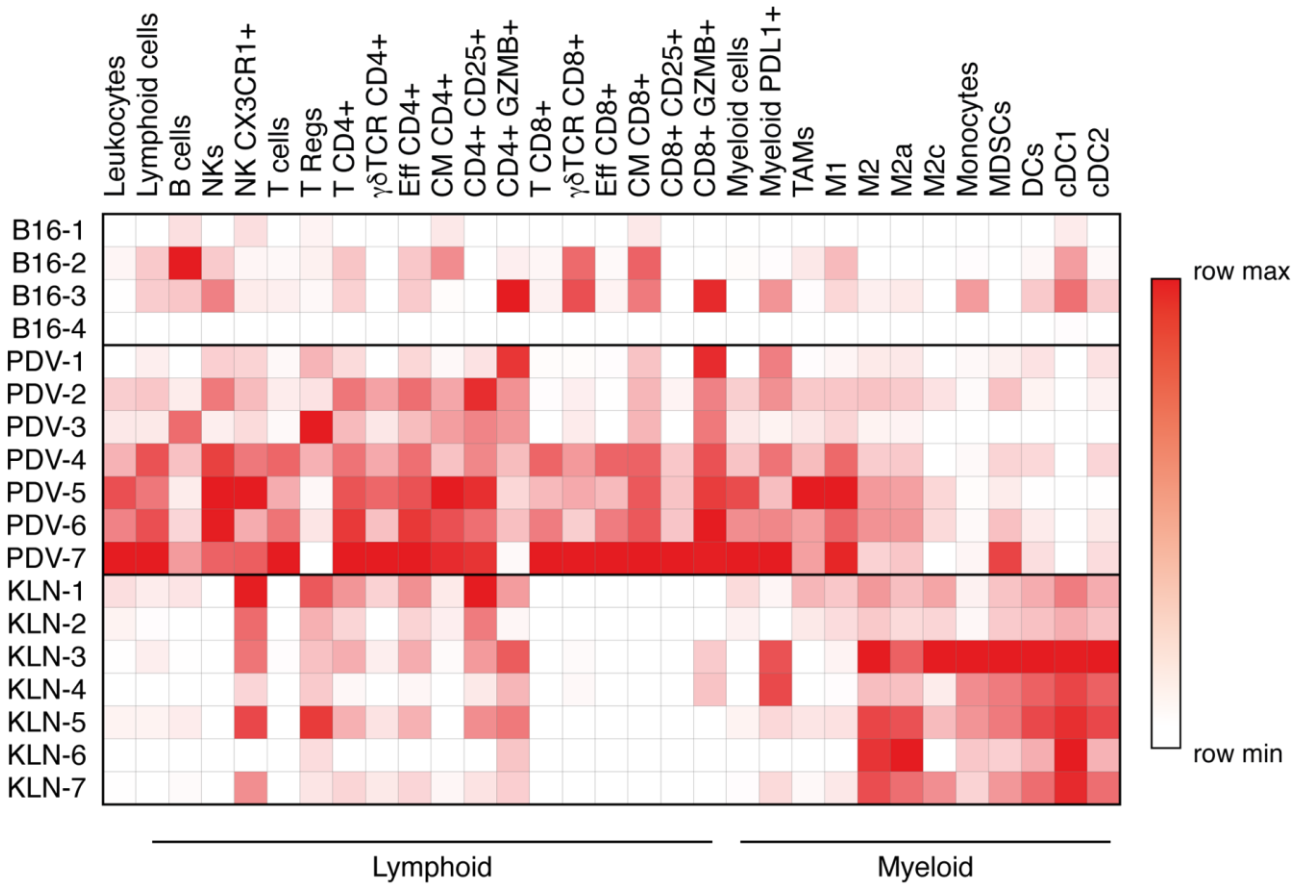
Regarding the changes occurring in the TME across progression, PDVC57B tumors reduced the proportion of NK cells, monocytes, and TAMs, and increased the content of Myeloid-Derived Suppressor Cells (MDSCs), suggesting a transition to a more aggressive phenotype.

By the contrary, despite their low leukocytic infiltration, B16F10 tumors increased their T cell content and decreased infiltration of myeloid cells across progression.

Finally, KLN205 tumors increased in NK, CD8+ T cells and MDSCs and reduced the infiltration of TAMs and dendritic cells (DCs), suggesting a maintenance of a TME refractory to ICIs.

Conclusions

The immunophenotyping strategy herein presented, provides a detailed overview of the changes in the TME across tumor growth that can be applied to other **murine models** used to evaluate immuno-**oncology** therapeutic agents.



Heatmap representing the content of each assessed immune cell population (nº cells/mg of tumor, relative to maximum number of cells within each population) for B16F10, PDVC57B and KL205-derived tumors.

A-288

HPV vaccination practices among organ transplant recipients in France.

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Background

Infection with Human Papilloma Virus (HPV) leads to frequent cutaneous and mucous complications in organ transplant patients. The availability of an HPV-directed vaccine in France used since 2007 should have a positive impact on this situation. While the serological benefit of the vaccine has been proposed in this population, no study has reported its clinical relevance. The aim of this work was to study vaccination practices in transplantation centers in France, first step in the study about the interest of this strategy for these patients.

Methods

A questionnaire was sent by email to physicians in organ transplant centers regarding: place of practice, transplanted organ, annual number of transplantations in the center, patient age, administration of an HPV vaccine pre-transplant, number of injections, sex and age of vaccine recipients if applicable, and willingness to participate in a registry to monitor HPV-related events.

Results

Twenty-three transplantation centers answered from the 58 existing centers representing 1347 transplants per year (5897 organ transplants performed in France in 2019). Twelve pediatric centers were represented, performing 169 transplants per year (242 pediatric transplantation performed in 2016). All pediatric centers reported vaccinating against HPV pre-transplant (9 always, 3 sometimes), 9/12 starting from 9 years old, 3/12 starting from 11 years old, and 6 of them maintaining a database of their recipients' vaccination schedule. 3 centers administer 3 doses, while 9 centers administer 2 doses. Eleven adult centers were represented, totaling 1178 transplants per year; 3 centers out of 11 reported vaccinating their young patients up to 19 or even 26 years old for 1 center, and 1 center vaccinated only females. All centers agreed to participate in a cohort study to collect data on HPV-related events.

Conclusions

This study shows global good adherence to vaccination recommendations in pediatric centers. For adult, situation is not clear, no vaccination recommendations have been validated yet outside of extending vaccination up to 26 years old for homosexual men. Ongoing studies are expected to change this approach. These initial results confirm the implementation of recommendations in pediatric organ transplant centers and the willingness of all centers to establish a registry study to assess the clinical relevance of HPV vaccination throughout the follow-up of organ transplant patients.

A-164

IL-17 mediates angiogenesis in Basal Cell Carcinomas and Squamous Cell Carcinomas

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Background
In cancer, the emergence of the angiogenic switch heralds increased tumour aggressiveness. IL-17 has recently emerged as a relevant player in the tumour microenvironment (TME), possibly due to its angiogenic effects on stromal cells. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common skin cancers, and the angiogenic action of IL-17 in these tumours is poorly understood.

Methods
In this work we tested whether the IL-17/IL-23 axis mediates the expression of angiogenic mediators in cancer cells derived from BCCs (M77015 cell line) and SCCs (CAL27 cell line), and in cancer-associated fibroblast (CAFs) and macrophages.
We used quantitative reverse-transcriptase PCR (qRT-PCR) to assess the expression of VEGF-A, VEGF-C, bFGF, EGF, MMP9, CXCL1, CXCL2, IL-8, PF4, CXCL9 and CXCL11, after in vitro stimulation with increasing concentrations of IL-17 and/or IL-23.

Results
CAFs were the cell-type most responsive to either IL-17 and IL-23 stimulation, whilst macrophages and CAL27 SCC cells were less responsive, and M77015 BCC cells were non-responsive to these stimuli.
The most striking results were observed in IL-17-stimulated SCC- and BCC-derived CAFs. In both cell lines, exposure to IL-17 led to a more than 50-fold increase in the expression of the angiogenic chemokines CXCL1 and IL-8 and a more than 5-fold increase in the expression of CXCL2. In contrast, the expression of the angiostatic chemokines CXCL9 and CXCL11 remained unchanged (SCC-derived CAFs) or was abolished (BCC-derived CAFs). The expression of VEGF-A, VEGF-C, bFGF and EGF was slightly increased (~2-fold increase) in BCC-derived CAFs and SCC-derived CAFs (<2-fold change). Within SCC cells, both IL-17 and IL-23 stimulation resulted in decreased expression of CXCL9 and CXCL11, with slight effects on the expression of pro-angiogenic mediators. After stimulation with IL-23, the expression of both angiogenic and angiostatic mediators remained unchanged in M1-polarised macrophages, whereas a subtle suppression of the expression of CXCL1, CXCL2, CXCL9 and CXCL11 was observed in M2-polarised macrophages.

Conclusions
In conclusion, the IL-17/IL-23 axis plays a role in the expression of angiogenic mediators in the TME of BCCs and SCCs, mainly through the induction of CXCL1, CXCL2 and IL8. CAFs are thus the most likely key players in IL-17/IL-23 mediated angiogenesis. The IL-17/IL-23 axis emerges as a potential target for the development of innovative strategies for the drug treatment of BCCs and SCCs.

A-276

Incidence and surgical treatment trends of non-melanoma skin cancer in Denmark 2002-2021

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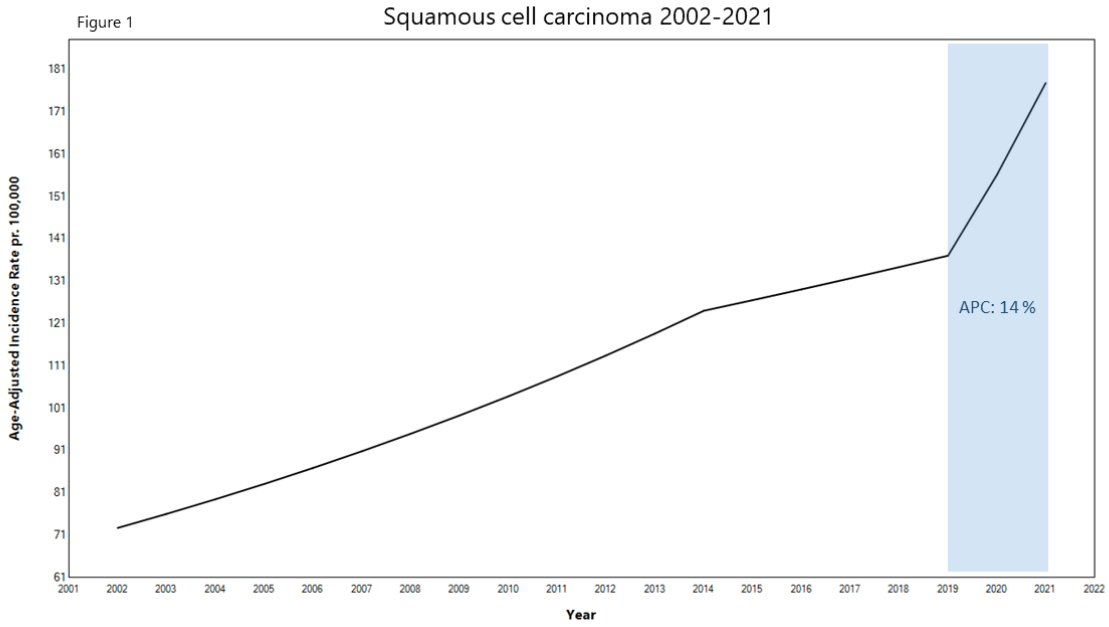
Background
As the most common malignant disease in Denmark, non-melanoma skin cancer (NMSC) causes a significant burden on healthcare resources. While many cases are managed within primary care settings, surgical treatment in a secondary setting is necessary for NMSC of certain subtypes and anatomical locations. Knowledge on recent incidence trends is crucial to improve the care and management of specifically basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in the future. Understanding the current trends in treatment is imperative to plan the specialized care of NMSC. The objective of this study is to assess incidence rates and development in hospital management of BCC and SCC with special attention to surgical treatment.

Methods
This is a nationwide cohort study. Information on all incident cases of BCC and SCC in Denmark from 2002-2021 were extracted from Danish health registries. Age-adjusted incidence rates were calculated, standardized to the 2013 European Boa_Image_Frame Population. The annual percentage change (APC) for BCC and SCC cases were estimated using Joinpoint regression models. Likewise, we analyzed trends in surgical treatment, including reconstructive procedures.

Results
We found 457,080 cases of BCC and 89,054 cases of SCC in the 20-year period. The incidence rates increased from 380 to 620 per 100,000 for BCC and from 72 to 175 per 100,000 for SCC. The APC for the entire period was 1.8 % for BCC and 4.3 % for SCC. In the last two years, the APC was 14 % for SCC (Figure 1).

Surgery was performed in 90,541 BCC cases and 35,496 SCC cases. The incidence rate increased from 35 to 134 per 100,000 for BCC and from 14 to 64 per 100,000 for SCC. Among the surgical courses, 25,571 (28 %) BCC cases and 13,688 (39 %) SCC cases underwent reconstructive surgery.

Figure 1



Conclusions
The number of NMSC cases in Denmark is considerable. SCC incidence has increased dramatically the last few years. The rising incidence of SCC, combined with a substantial demand for reconstructive surgery, emphasizes the importance of timely and effective medical intervention. We need to consider the consequences on the specialized management of NMSC now and in the future

A-408

Integrating a Clinicopathological Risk Prediction Model into the European Guideline for Cutaneous Squamous Cell Carcinoma

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Background

Reliably assessing metastatic risk in cutaneous squamous cell carcinoma (CSCC) patients poses a significant clinical challenge despite established staging systems and guidelines. Integrating a recently developed clinicopathological (CP) model into existing staging systems and guidelines may help to achieve better risk stratification. This study focuses on refining risk stratification in the current European CSCC Guideline.

Methods

We applied the CP model to a Dutch nested case-control (NCC) cohort (n=390) derived from a population-based cohort (n=12,325). Per Guideline based low-risk and high-risk group, we binarized 5-year metastatic risk into CP High-Risk and CP Low-Risk, setting clinically meaningful thresholds to identify CP High-Risk based patients with increased risk of metastasis. Thresholds were evaluated using weighted metrics to adjust for the case-control design of the study.

Results

In the NCC cohort, individuals in the Guideline low-risk and high-risk group had a metastatic risk of 0.44% group, and 3.13% respectively (Figure 1). Among the Guideline low-risk patients, we identified a CP High-Risk group with increased risk (1.87%) and a CP Low-Risk group with reduced risk (0.33%). Similarly, in the guideline high-risk group, we further stratified patients into CP High-Risk and CP Low-Risk, respectively having a risk of 12.30% and 1.85%.

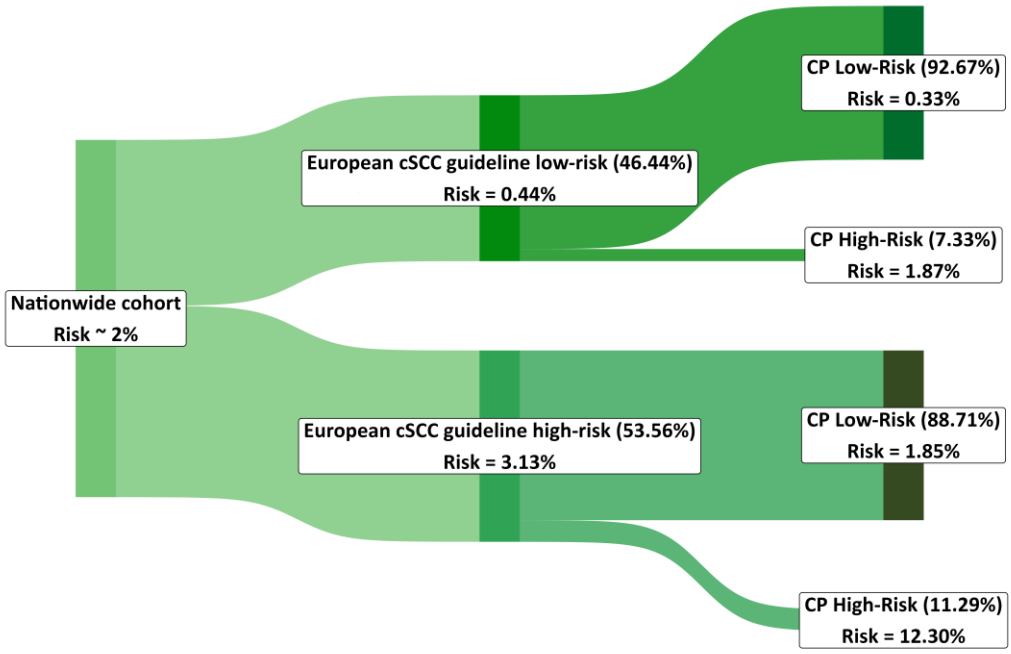

Figure 1. Sankey plot of stratification by CP model in combination with European guideline

The performances of the CP model stratifying the guideline are shown in Table 1. The CP model showed clear added value; however, these results need to be further validated in an independent cohort.

European cSCC guideline risk group (risk %)	NPV (%)	Risk in CP Low-Risk (=100-NPV) (%)	Risk in CP High-Risk (= PPV) (%)	Specificity (%)	Sensitivity (%)	LR+	LR-
Low-risk (0.44%)	99.67	0.33	1.87	92.77	30.90	4.33	0.74
High-risk (3.13%)	98.15	1.85	12.30	89.75	43.52	4.36	0.63

Table 1. Table with performances of CP model in stratifying the European cSCC guideline (NPV: Negative Predictive Value, PPV: Positive Predictive Value, LR: Likelihood Ratio).

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Conclusions

This study, using a nationwide cohort, suggests that our risk model can refine the Guideline-based risk stratification in low and high-risk groups. The current European CSCC Guideline categorizes patients into two coarse-grained risk groups. The CP model subsequently facilitates the identification of a CP Low-Risk group within the low-risk category, who could be considered for minimal surveillance. Similarly, those identified as CP High-Risk within the high-risk group of the Guideline could be candidates for intensified surveillance and potential adjuvant therapies. Ultimately, the integration of the CP model into guidelines may lead to more tailored approaches to follow-up and treatment decisions, alongside optimizing healthcare resource allocation.

A-122

Malignant transformation during anti-TNF treatment of Hidradenitis suppurativa

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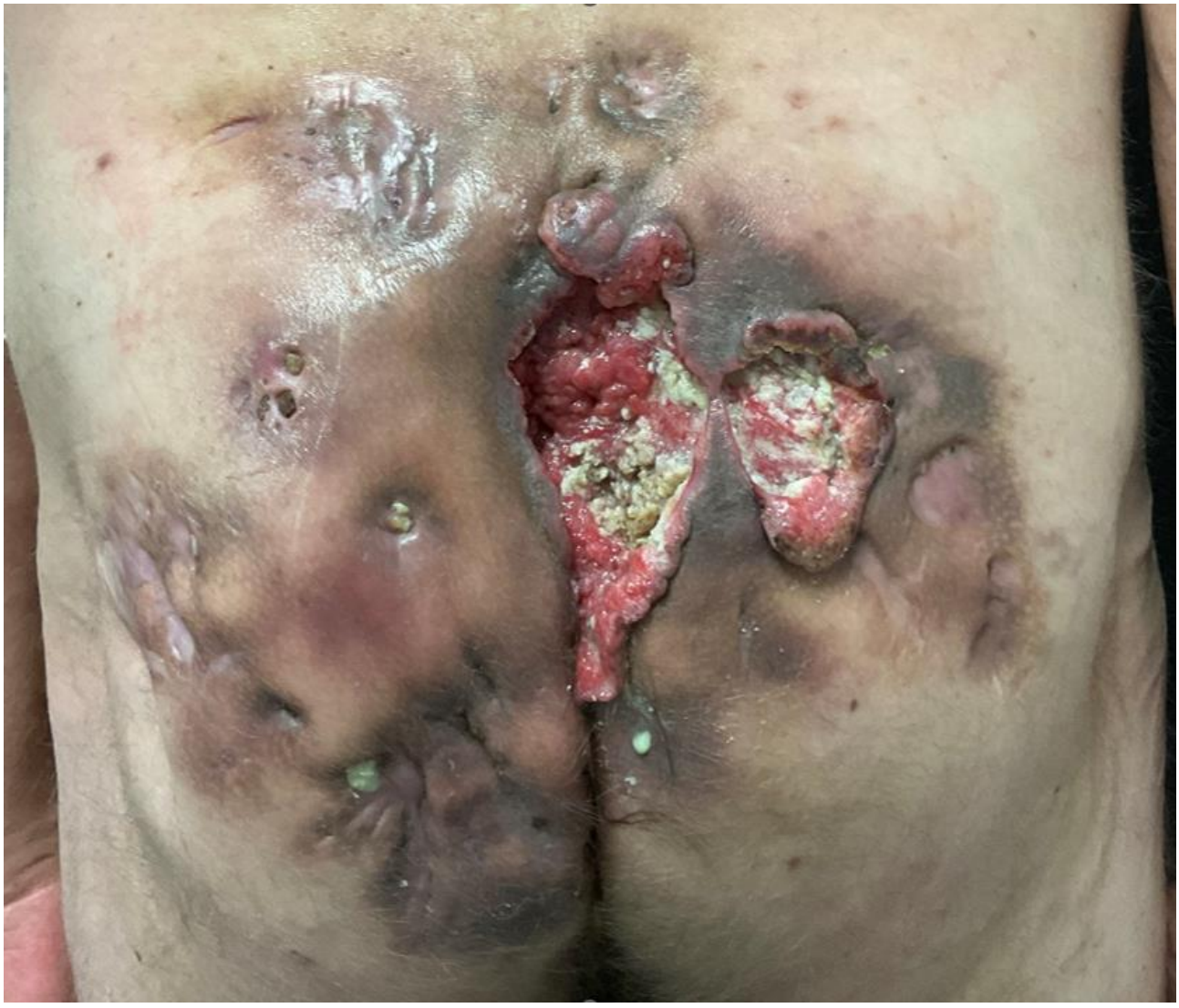
Background

Squamous cell carcinoma occurs in 4.1% of Hidradenitis suppurativa (HS) patients, with a mortality rate of 40%. Key risk factors include male gender, prolonged disease duration, perianal lesion localization, and Hurley stage III. Aggressive tumor treatment, including wide excision, is recommended, with radiotherapy in specific cases. This presentation aims to report a rare and complex case of extensive malignancy in the context of Hidradenitis suppurativa.

Methods

A 53-year-old male with a 16-year history of severe hidradenitis suppurativa was treated with adalimumab 40 mg weekly for 5 years. The disease was stable, but in 2023, a relapse occurred with new purulent eruptions, diffuse infiltration, and rapid ulceration in the sacral and perineal area.

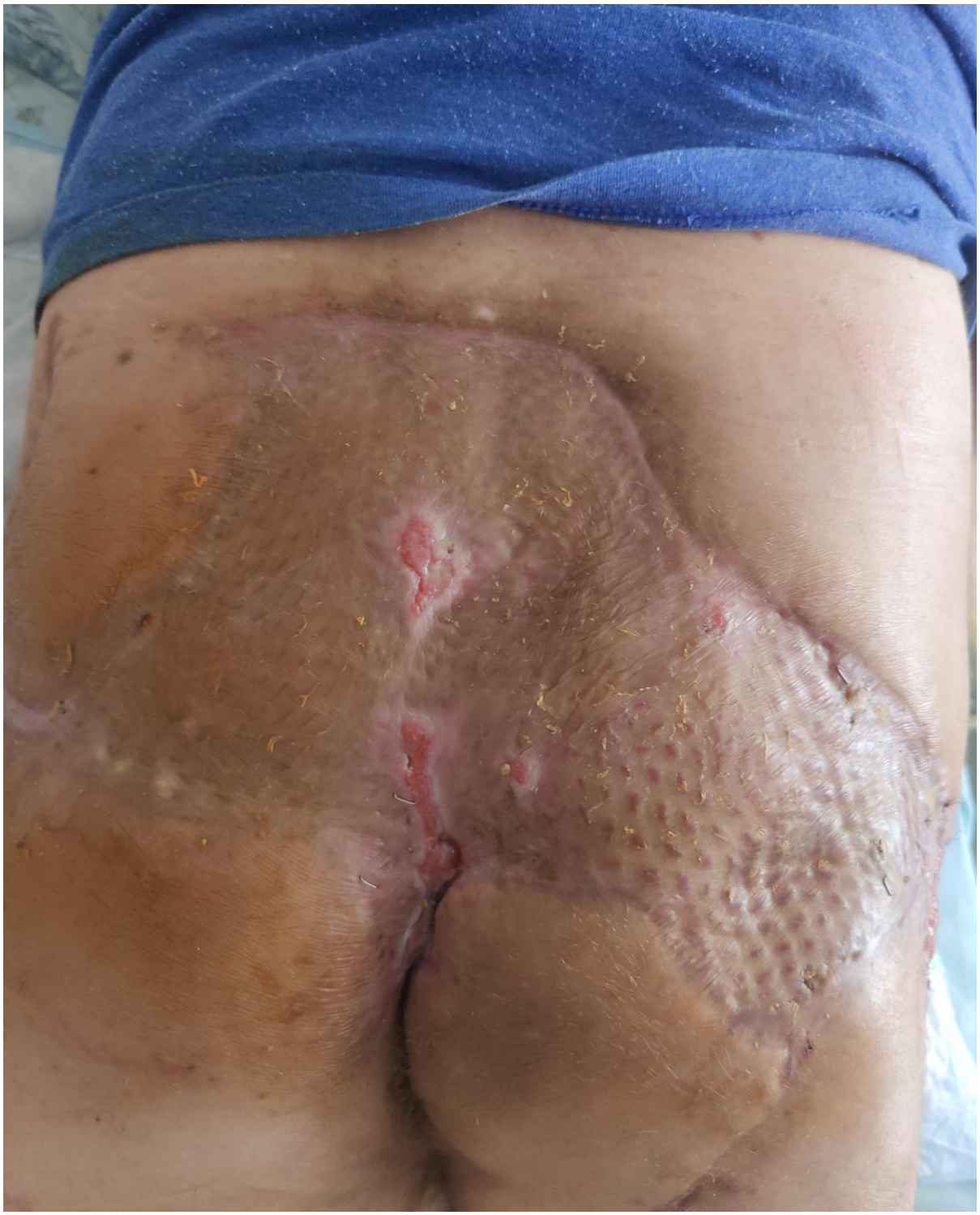


Rapid ulceration in the area affected by Hidradenitis abscesses and prurulent sinus tracts.
Methods employed included physical examination, laboratory tests, microbiological cultures, imaging studies, histopathological evaluation and surgical measures.

Results

Adalimumab was discontinued. Biopsy from the ulcer confirmed well-differentiated squamous cell carcinoma. HPV high-risk subtypes were negative. CT scan revealed sacral lesions with infiltration, liquefaction zones, skin involvement and inguinal lymphadenopathy. Suspicious lesion in the right lung's S6 segment suggests possible metastasis. A course of radiation therapy was administered to reduce the tumour size. A wide excision with a 20x20 centimeter tissue defect, followed by a reconstructive surgery was later

performed. Combined intravenous antibiotic therapy was administered due to multidrug-resistant *Acinetobacter baumanii* strain and highly elevated inflammatory markers. Additionally, Vacuum-Assisted Closure (VAC) system was applied, along with staged debridements, wound irrigations, and dressings, alongside with the skin grafting procedure performed for four times. Follow-up CT scan after 6 months did not show any disease progression. Patient is under close follow-up schedule.



Treatment outcome

Conclusions

The case presented emphasizes the complexity of the the combination of purulent and cancerous processes, complicated by a large tissue defect, pockets formed under the skin, high resistance to hospital flora and high possible mortality rate. The timely and routine screening of individuals with hidradenitis suppurativa for this complication is of utmost importance.

A-165

Management and outcomes following the first cutaneous squamous cell carcinoma in kidney transplant recipients: the United Kingdom COAST (Contemporary Outcomes After cutaneous SCC in Transplant recipients) study

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Background

After their first cutaneous squamous cell carcinoma (cSCC), up to 75% of kidney transplant recipients (KTR) will develop a further cSCC and their risk of metastasis is increased. Evidence is limited about which secondary prevention strategies are currently being undertaken in transplant centres across the United Kingdom. To address this, the UK COAST multicentre retrospective cohort study is evaluating management after first cSCC in KTRs.

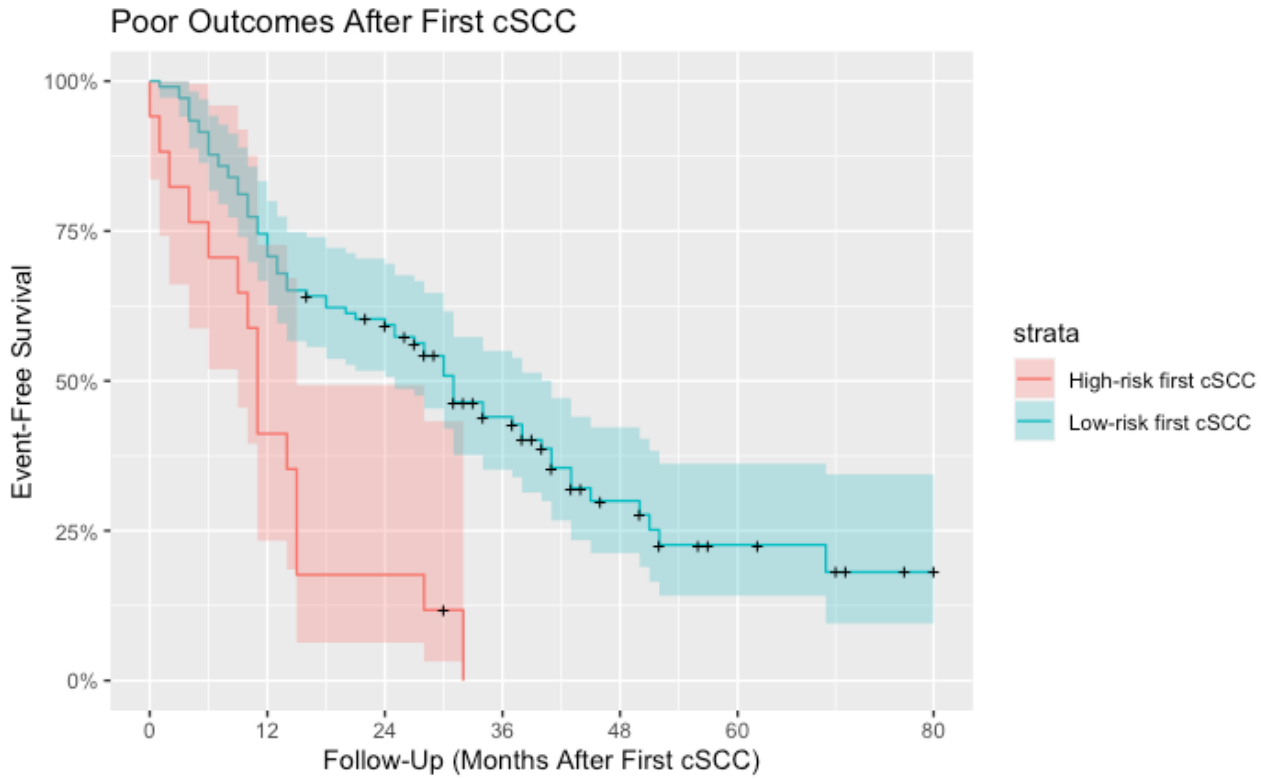
Methods

Adult KTRs with a first-ever cSCC were recruited from 8 centres over 5 years (1/2016-12/2020) with follow-up to 12/2022. Data were collected on outcomes of interest (further malignancies, graft loss and death).

Results

In 139 KTRs, cumulative duration of immunosuppression was 136mo(IQR 72-200); median age 63y(IQR 57-72); 49% had actinic keratoses(AK), 28% cSCC-in-situ, 32% other skin cancer, and 8% non-cutaneous malignancies. The first cSCC was high-risk (HR) in 25% by AJCC8, 14% by Brigham and Women's Hospital criteria, 75% by British Association of Dermatologists' 2020 guidelines criteria, and 4% had >10% 5-year risk of metastasis using a newly-published clinicopathologic risk calculator.[1]

Within 6-months of the first cSCC, 5% started systemic chemoprevention (acitretin/nicotinamide), 19% had topical chemoprevention (mainly 5-fluorouracil cream), 5% destructive therapies, and immunosuppression reduction(IR) was undertaken in 31%. cSCC was the stated reason for IR in 63%. IR was significantly more frequently undertaken for HR-cSCC, incomplete histological margins and perineural invasion ($p<0.05$). Overall, 49% developed further cSCCs (at median 14mo after first cSCC), 12.2% had metastatic cSCC (11mo), 14% suffered graft loss (32mo), and 30% died (23mo), with cSCC-specific deaths in 9.4%. On multivariate adjustment, sex, previous AK, cSCC-in-situ, previous basal cell carcinoma and HR-cSCC were associated with risk of further cSCCs. Male sex and HR-cSCC were significant risk factors for a composite of other poor outcomes. IR was also a risk factor, but this may be partly explained by their higher risk features and analysis for residual confounders is ongoing.



Poor outcome-free survival after first cSCC, stratified by tumour grade (based on Brigham and Women's Hospital staging). Poor outcomes include further malignancies, metastases, graft loss and death.

Conclusions

Although there is evidence that the incidence of first post-transplant cSCC is reducing in KTRs transplanted over the past 20 years, our data suggest that once KTRs have had a first cSCC, their outcomes have not improved compared to historical cohorts. This highlights the urgent need for further research on the most effective prevention strategies for KTRs following a first cSCC.

References:

[1] Rentroia-Pacheco B, Tokez S, Bramer EM, Venables ZC, van de Werken HJG, Bellomo D, van Klaveren D, Mooyaart AL, Hollestein LM, Wakkee M, (2023), Personalised decision making to predict absolute metastatic risk in cutaneous squamous cell carcinoma: development and validation of a clinico-pathological model, EClinicalMedicine, 102150, 63

A-386

Neutrophil-lymphocyte ratio as a predictive marker for progression free survival in patients with advanced cutaneous squamous cell carcinoma prior to Cemiplimab treatment – a real-life setting

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Background
Patients with locally advanced (La)/metastatic (M) cSCC for which curative surgery or radiation is not available benefit from treatment with anti-programmed cell death 1 (PD-1) monoclonal antibody Cemiplimab. The predictive role of hematological inflammatory markers in such patients remains unclear.[1]
A real-life cohort study was conducted to evaluate the predictive role of hematological inflammatory markers as prognostic factors in patients with LA/cSCC or M/cSCC who underwent first-line treatment with Cemiplimab.

Methods
Lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), albumin, creatinine, systemic immune-inflammation index (SII) and LDH were assessed prior to Cemiplimab therapy. Optimal cut-off points associated with progression free survival (PFS) was calculated based on the receiver operating characteristic curve (ROC). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated by a multivariate Cox proportional-hazards model to identify independent prognostic factors.

Results
A total of 43 advanced cSCC patients, 6 (14.0%) diagnosed with M/cSCC and 37 (86.1%) with La/cSCC, were retrospectively analyzed. After a median 33.1 weeks of exposure to Cemiplimab, ORR (partial or complete) was 72% (31/43), including 41.9% (13/31) complete responses. The median PFS was 6.4 months. 7% of patients discontinued due to adverse events (renal insufficiency and liver toxicity), and none of the observed deaths are related to Cemiplimab. Based on the ROC curve, the optimal cut off point of NLR that predicted prognosis was 4.05, [area under the curve: 0.64; 95% confidence interval (CI): 0.46–0.83], with a sensitivity of 54.6% and specificity of 75.0%. A multivariate Cox proportional-hazards model revealed that NLR≥4.05 was significantly associated with worse PFS (HR=4.6; 95%CI: 1.2-18.2; p=0.027), irrespective of the ECOG status, age, sex and the presence of metastasis.

Conclusions
NLR prior to Cemiplimab treatment might be a hematological predictive marker of progression free survival in patients with advanced cSCC.
References:

[1] Matsuki T, Okamoto I, Fushimi C, et al. , Hematological predictive markers for recurrent or metastatic squamous cell carcinomas of the head and neck treated with nivolumab: A multicenter study of 88 patients., Cancer Med. 2020;9(14):5015-5024, https://onlinelibrary.wiley.com/doi/10.1002/cam4.3124

A-218

Patient reported outcomes in the multidisciplinary treatment of patients with high-risk cutaneous squamous cell carcinoma in the head-neck area.

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Background
Multidisciplinary care pathways may improve quality and efficiency of care. To date, the patients' perspective on the multidisciplinary care pathway in patients with high-risk cutaneous squamous cell carcinoma in the head-neck area (HR-HNcSCC) is unknown. Furthermore, the patient-reported outcomes that are of interest for improving the care pathway have not been identified.
This study aimed to evaluate health-related quality of life (HR-QoL), the degree of decisional conflict, and satisfaction with care in patients with HR-HNcSCC, and to identify patient-reported topics in need of optimization in the current multidisciplinary care pathway.

Methods
Included were patients with a HR-HNcSCC visiting the multidisciplinary head-neck dermatology outpatient clinic at one of the participating tertiary centers. At the start of the care pathway, patients completed a baseline questionnaire, the decisional conflict scale, and the EuroQoL-5D-5L. One month after completing the care pathway, patients completed the EuroQol-5D-5L, the Basal and Squamous Cell Carcinoma Quality of Life and the European Organization for Research and Treatment of Cancer Patient Satisfaction questionnaires. Corresponding user manuals and the existing literature were used to interpret scores.

Results
Seventy-eight patients were included. At baseline, HR-QoL was high and increased slightly but insignificantly after completing the care pathway. The degree of decisional conflict was only slightly elevated, and did not impact decision-making. The subscales on the decisional conflict scale with the highest impact on decisional conflict were information provision and value clarification. Patients reported a high satisfaction with care.

Conclusions
In a multidisciplinary tertiary care pathway for patients with HR-HNcSCC, HR-QoL is high, decisional conflict is only slightly elevated, and there is a high level of satisfaction with care. Optimizing care should focus on information provision and value clarification.

A-237

Performance of a new classification system based on the eight most relevant prognostic factors for cutaneous squamous cell carcinoma: a retrospective cohort study showing limits to risk stratification with clinical and histopathological risk factors.

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Background
Risk stratification of cutaneous squamous is relevant for guiding patients' management. A recent comprehensive meta-analysis by Zakhem GA et al., collected all the risk factors (RF) identified to date in CSCC and demonstrated that of those which have been evaluated in more than one study, there were eight RF with the greatest prognostic impact (tumor size, invasion beyond the subcutaneous fat, immunosuppression, lymphovascular invasion, perineural invasion, desmoplasia, tumor budding and poor degree of differentiation). We aimed to explore the impact of a classification system derived from all those relevant RF found in that meta-analysis with the most popular staging systems (BWH and AJCC8) in a retrospective cohort study of 794 patients.

Methods
We explore the outcome depending on the accumulation of RF and derived a 4-stage classification system (0RF, 1-2RF, 3-4RF and >4RF). We explored the cumulative incidence function(CIF) for local recurrence, nodal metastasis (NM), distant metastases and disease-specific death(DSD) using Fine–Gray proportional hazard regression, for this classification system, the BWH and the AJCC8. Death from other causes was considered a competing risk. Also, we explored sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and C-index.

Results
The 5-year cumulative incidence (5y-CIF) were quite similar between BWH and the 8RF classification system. Concerning DSD, the 5yCIF for BWH was 1.7(0.6-3.7) for T1-BWH, 4.7(2.4-8.2) for T2a-BWH, 16.0(10.8-22.2) for T2b-BWH and 43.0(22.1-62.4) for T3-BWH. For DSD, the 5yCIF for the 8RF classification system were 1.0(0.2-3.4) for 0RF, 4.3(2.5-6.9) for 1-2RF, 15.9(10.3-22.6) for 3-4RF and 43.2(24.7-60.5) for >4FR. The C-index and accuracy calculations remained better for BWH and the 8RF than for for AJCC8.

Conclusions
Adding many risk factors to the models does not seem to improve much the distinctiveness of the classification systems compared to the BWH. However, considering many risk factors combined in a same patient may pinpoint towards certain very high-risk patients who may need more careful surveillance and aggressive management. Indeed, 80% of those cases with 7 risk factors at the same time died from CSCC in this cohort. Incorporating molecular biomarkers to clinical practice may be the next step to improve the classification of patients.

A-274

Perineural invasion for risk stratification in cutaneous squamous cell carcinoma: a scoping review.

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Background
Microscopic perineural invasion (mPNI) is a histopathological feature that can be found in cutaneous squamous cell carcinoma (cSCC). In the eight edition of the American Joint Committee on Cancer (AJCC), mPNI defined as involvement of nerves ≥0.1mm and nerves deeper than the dermis, is included in risk stratification of cSCC. The question remains whether other histopathologic mPNI features are important for optimal cSCC staging.
The objective of this scoping review is to summarize the evidence from published studies on the independent association between various histopathological mPNI features and the risk of recurrence, metastasis and disease-specific death in patients with cSCC.

Methods
Embase, PubMed, and Web of Science were searched from January 2023 to February 2024 to identify studies which reported on the prognostic impact of histopathological mPNI features in patients ≥18 years with histopathological verified cSCC. Data on study and tumor characteristics were extracted.

Results
Nineteen studies met the inclusion criteria and evaluated one or more histopathological mPNI features in cSCC including nerve diameter, the extent of mPNI, the number of affected nerves, and depth of mPNI. Two studies provided evidence that ‘mPNI ≥0.1mm’ and ‘mPNI deeper than the dermis’ are significantly and independently associated with poor prognosis after correction for other mPNI features and high-risk factors. One of these studies additionally identified ‘involvement of ≥3 nerves’ as an independent and significant predictor of higher risk of local recurrence (HR, 2.17; 95% CI, 1.03-4.56; p=0.04).

Conclusions
Besides ‘nerve diameter of ≥0.1mm’ and ‘depth of mPNI involvement’, ‘involvement of ≥3 nerves’ was found to be an independent risk factor for poor prognosis and should also be considered for appropriate risk stratification.

A-331

Phase 2 study of intratumoral vidutolimod in combination with intravenous cemiplimab in patients with selected advanced cancer or metastatic cancer: trial in progress

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Background

There is an unmet need in patients with advanced non-melanoma skin cancers to overcome resistance to PD-1 blockade and enhance effectiveness of first-line immune checkpoint blockade (ICB). Vidutolimod (CMP-001) is a toll-like receptor 9 (TLR9) agonist that activates tumor-associated plasmacytoid dendritic cells (pDCs). Preclinical data show that intratumoral (IT) administration of vidutolimod promotes pDC activation, eliciting antitumor responses in local and distant tumor sites. Addition of a TLR9 agonist may improve clinical response to PD-1 inhibitors. The NCT04916002 trial evaluates the combination of vidutolimod and intravenous (IV) cemiplimab in patients with advanced cancer.

Methods

NCT04916002 is an ongoing multicenter, open-label, phase 2 study in patients with advanced non-melanoma skin cancers and other selected tumors (defined as metastatic or unresectable locally and/or regionally advanced). Planned enrollment for this study is 25 patients per cohort. Key eligibility criteria include histopathologically confirmed diagnosis and measurable disease by RECIST v1.1 (with ≥1 accessible lesion amenable to repeated IT injection). Cohorts A1 and A2 include patients with metastatic or locally and/or regionally advanced unresectable cutaneous squamous cell carcinoma. Cohorts B1 and B2 include patients with metastatic or locally and/or regionally advanced unresectable Merkel cell carcinoma. Cohorts C1 and C2 are placeholder cohorts and are not planned to open. Cohorts A1 and B1 include patients who have not received prior systemic therapy (ICB naïve). Cohorts A2 and B2 include patients with disease progression during/after PD-1 inhibitor treatment (ICB exposed). Cohort D includes patients with basal cell carcinoma who have not received prior treatment with a hedgehog pathway or immune checkpoint inhibitor. All cohorts receive vidutolimod 10 mg IT weekly for 7 doses, after which vidutolimod is administered every 3 weeks (Q3W). Cemiplimab 350 mg IV will be given Q3W for the duration of the study. Treatment may continue for up to 2 years. Radiologic assessments are performed every 9 weeks. The primary objective is to determine confirmed ORR by investigator assessment per RECIST v1.1 criteria. Secondary endpoints include safety, tolerability, and efficacy (duration of response, progression-free survival, overall survival). Adverse events are evaluated using the CTCAE v5.0 criteria.

Results

Not applicable; trial is in progress.

Conclusions

Not applicable; trial is in progress.

A-243

Porokeratosis Ptychotropica: The risk of cancerization and treatment options

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Background
Porokeratosis ptychotropica(PP) is a rare and unusual variant of porokeratosis which involves the genitalia and associated-flexural areas. There is a dearth of information on the risks of cancerisation and optimal treatment options.

Methods
We performed a literature search of all reported cases of PP in major databases, and conducted analyses primarily on the epidemiology, clinical features, risk of malignant transformation and treatments reported for PP.

Results
A total of 59 cases of PP had been reported. Most of the cases originated from the United States, followed by China, Germany, and South Korea. The worldwide crude incidence rate is estimated at 2.7 - 5.4 x 10^{-10} per year. The median age of patients affected with PP was 49 years. Of all the reported cases, 86.4% were male, and 11.9% were female. The most involved body locations are the buttocks and gluteal cleft. Characteristic clinical features include well demarcated red-brown scaly or verrucous plaques with raised keratotic borders, and peripheral lesions. The mean duration of lesions at the time of presentation was 9.8 years. The risk of malignant transformation in PP is approximately 1.7%. The most commonly utilised treatment options are topical retinoids, oral retinoids and topical corticosteroids. Treatment with topical cholesterol/simvastatin cream is a novel treatment option that had been reported to be useful for PP.

Conclusions
PP is a rare and under-recognised variant of porokeratosis. A multitude of treatments had been attempted but the optimal treatment modality remains uncertain. Long term surveillance appears to be prudent for PP due to a risk of malignant transformation to SCC.

A-137

Predictors of recurrence and progression in poorly differentiated cutaneous squamous cell carcinomas: insights from a real-life experience.

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Background

Surgery represents the primary treatment option for cutaneous squamous cell carcinoma (cSCC) aiming for complete tumor resection (R0). Recurrence and metastasis significantly affect survival and outcomes, and poorly differentiated (G3) cSCC is associated with a higher risk of recurrence. However, the specific clinical and histopathological features that predict recurrence and progression in G3-cSCC remain unclear.

Methods

A retrospective analysis was conducted on a series of patients with primary G3-cSCC diagnosed at a referral University Hospital between January 2016 and January 2021. After independent histological revision, logistic regression models were used to identify clinico-pathological predictors of cutaneous recurrence, lymphnode/metastatic progression, and both types of progression.

Results

Among the 161 G3-cSCC patients, 80.1% (129/161) showed no signs of local recurrence or metastatic progression, while 19.9% (32 patients) had progressed.

	Not recurred/progressed (n=129)	Recurred/progressed (n=32)	p-value
Sex			0.401
Female	31 (24.1%)	10 (31.3%)	
Male	98 (75.1%)	22 (68.7%)	
Age			0.950
Mean (range)	80.1 (47-96)	79.0 (45-98)	
pT, (%), according to AJCC 8th edition [14]			**0.017**
pT1	77 (59.7%)	11 (34.3%)	
pT2	33 (25.6%)	9 (28.1%)	
pT3	18 (13.9%)	12 (37.5%)	
pT4	1 (0.8%)	0 (0%)	
Tumor diameter (cm)			**0.009**
Mean (range)	1.90 (0.4-6)	2.7 (1.0-13.0)	
Anatomical level			**0.004**
3	5 (3.9%)	0 (0%)	
4	59 (45.7%)	5 (15.6%)	
5	65 (50.4%)	27 (84.4%)	
Vertical tumor thickness (mm)	6.0 (1.4-24)	7.9 (2-40)	0.205
Mean (range)			
<2mm [27]	8 (6.2%)	3 (9.4%)	0.4582
>2mm [27]	121 (93.8%)	29 (90.6%)	
Depth of infiltration (mm)	3.9 (1-18)	5.4 (1-15)	**0.005**
Mean (range)			
Tumor horizontal size (mm)	15.3 (3-50)	19.0 (9-45)	**0.014**
Mean (range)			
Perineural invasion (PNI)			**0.001**
Present	16 (12.4%)	12 (37.5%)	
Absent	113 (87.6%)	20 (62.5%)	
Lymphovascular invasion (LVI)			**<0.001**
Present	7 (5.4%)	10 (31.3%)	
Absent	122 (94.6%)	22 (68.7%)	
Desmoplasia			**0.007**
Present	18 (14.0%)	11 (34.4%)	
Absent	111 (86.0%)	21 (65.6%)	
Histological distance to lateral margin	3.8 (0.0-22)	3.1 (0.0-8)	0.752
Mean (mm)			
Histological distance to deep margin (mm)	2.3 (0.0-12)	1.8 (0.0-9)	0.064
Mean (range)			
Ulceration			0.205
Present	95 (73.6%)	27 (84.3%)	
Absent	34 (26.4%)	5 (15.6%)	
Immunosuppression*			0.483
Yes	14 (10.9%)	5 (15.6%)	
No	115 (89.1%)	27 (84.3%)	
TILs infiltrate grade			**0.007**
0-1	82 (63.6%)	12 (37.5%)	
2-3	47 (36.4%)	20 (62.5%)	
Follow up time, months			0.082
Mean (range)	33.0 (4-8)	27.5 (6-74)	
Tumor site	**H&N**: 104 (80.6%) **Trunk**: 11 (8.5%) **Extremities**: 14 (10.9%)	**H&N**: 27 (84.3%) **Trunk**: 2 (6.3%) **Extremities**: 3 (9.4%)	0.877
Temple-ear-lip localization [3]	27 (20.9%)	7 (21.9%)	0.907

Legend to table 1. Clinical and histopathological features in our cohort of patients. Statistically significant P-values are highlighted in bold font. TILs (Tumor-Infiltrating lymphocytes) infiltrate is defined according to the Melanoma Institute of Australia (MIA) scoring system: grade 0 (TIL absent), grade 1 (mild multifocal or mild/moderate focal infiltrate), grade 2 (moderate or marked multifocal, marked focal or mild diffuse TIL pattern), grade 3 (moderate or marked diffuse infiltrate). H&N (head or neck localization). *Immunosuppressed patients were presenting the following conditions: kidney transplant (12), heart transplant (1), liver transplant (1), chronic lymphocytic leukemia (1), diffuse-large B-cell leukemia (1), myelodysplastic syndrome (1), multiple myeloma (1), chronic autoimmune hepatitis (1).

In the univariate logistic regression, tumor clinical diameter, depth of infiltration (DOI), and lymphovascular invasion (LVI) were identified as significant predictors across the various types of progression ($p<0.05$). In the context of multivariate logistic regression, distinct models proved to be significant. For skin recurrence, a 3-variable model incorporating DOI (OR 1.16, 95% CI 1.01-1.35, p=0.050), LVI (OR 3.61, 95% CI 1.11-11.8, p=0.034), and desmoplasia (OR 3.45, 95% CI 1.25-9.5, p=0.017) was selected. Regarding lymphnode/metastatic progression, a 3-variable model combining pT2 (OR 6.10, 95% CI 1.15-32.35, p=0.034), pT3 (OR 14.33, 95% CI 2.79-73.63, p=0.001), and LVI (OR 3.86, 95% CI 1.10-13.62, p=0.036) was identified. Lastly, a 2- variable model for both types of progression consisted of vertical tumor thickness (OR 5.45, 95% CI 1.11-27.32, p=0.039) and LVI (OR 1.15, 95% CI 1.04-1.26, p=0.006).

Progression and analysis type	Parameter	Odds Ratio (95% CI)	*p*-value
Skin recurrence: univariate LOGIT			
	pT3	3.30 (1.20-9.30)	0.021
	Tumor clinical diameter	1.35 (1.01-1.81)	0.043
	Depth of infiltration	1.21 (1.05-1.39)	0.008
	Perineural invasion	5.13 (1.96-13.42)	0.001
	Lymphovascular invasion	5.60 (1.87-16.77)	0.002
	Desmoplasia	4.82 (1.85-12.53)	0.001
	TILs > 1	0.32 (0.13-0.81)	0.016
Skin recurrence: multivariate LOGIT			
	Depth of infiltration	1.16 (1.01-1.35)	0.050
	Lymphovascular invasion	3.61 (1.11-11.8)	0.034
	Desmoplasia	3.45 (1.25-9.5)	0.017
Lymph node/visceral progression: univariate LOGIT			
	pT2	7.17 (1.38-37.29)	0.019
	pT3	18.43 (3.70-91.71)	<0.001
	Tumor clinical diameter	1.50 (1.06-2.11)	0.022
	Vertical tumor thickness	1.13 (1.03-1.23)	0.007
	Depth of infiltration	1.20 (1.03-1.39)	0.016
	Tumor horizontal size	1.07 (1.01-1.13)	0.023
	Lymphovascular invasion	6.60 (2.05-21.24)	0.002
Lymph node/visceral progression: multivariate LOGIT			
	pT2	6.10 (1.15-32.35)	0.034
	pT3	14.33 (2.79-73.63)	0.001
	Lymphovascular invasion	3.86 (1.10-13.62)	0.036
Skin recurrence and lymph-node/metastatic progression: univariate LOGIT			
	pT3	21.75 (2.50-189.49)	0.005
	Tumor clinical diameter	1.44 (1.03-2.03)	0.003
	Vertical tumor thickness	1.15 (1.04-1.27)	0.006
	Depth of infiltration	1.32 (1.10-1.59)	0.003
	Lymphovascular invasion	5.96 (1.29-27.60)	0.023
Skin recurrence and lymph-node/metastatic progression: multivariate LOGIT			
	Vertical tumor thickness	5.45 (1.11-27.32)	0.039
	Lymphovascular invasion	1.15 (1.04-1.26)	0.006

Conclusions

Tumor size, depth of infiltration, and LVI were significant predictors of recurrence and metastatic progression. Notably, the size of histologically defined tumor-free margins did not affect the risk of recurrence, whilst LVI emerged as a key predictor of all forms of progression. Interestingly, the recent EADO-EORTC 2023 guidelines do not mention LVI as a defining feature of high-risk cSCCs.[1] These findings provide insights into risk stratification and suggest that close monitoring and potential adjuvant therapies, such as radiation therapy, may be necessary especially for patients with lymphovascular involvement.

References:

[1] Stratigos AJ, Garbe C, Dessinioti C, et al. European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma. Part 1: Diagnostics and prevention-Update 2023. Eur J Cancer. 2023;193:113251. doi:10.1016/j.ejca.2023.113251

A-438

Prognostic factors for treatment failure of photodynamic therapy and5-fluorouracil in Bowen's disease

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Background
Little is known about prognostic factors that may influence the response to non-invasive treatments of patients with Bowen's disease. The aim of this study was to identify patient and lesion characteristics that are associated with higher risk of treatment failure after 5-fluorouracil and PDT in Bowen's disease. The hypothesis that thickness of the Bowen's lesion and extension along the hair follicle are associated with risk of treatment failure after noninvasive treatment was also explored.

Methods
Data were derived from a non-inferiority trial in which the patients had been randomly assigned to 5% 5-fluorouracil cream twice daily for 4 weeks or 2 sessions of MAL-PDT with 1 week interval. All patients had histologically confirmed Bowen's disease of 4-40mm. The initial 3 mm biopsy specimens were re-examined to measure the maximum histological lesion thickness and extension along the hair follicle. To evaluate the association between potential risk factors for treatment failure at one year follow-up, univariate and multivariate logistic regression analyses were used to calculate odds ratios (ORs) with 95% confidence intervals and p-values.

Results
Histological lesion thickness was not significantly associated with treatment failure (OR 0.84, p=0.806), nor was involvement of the hair follicle (OR 1.12 , p=0.813). Lesion diameter was the only risk factor that was significantly associated with one-year risk of treatment failure (OR=1.08 per mm increase, p=0.021).When using the median value of 10 mm as cut-off point, the risk of treatment failure was 23.4% for lesions > 10 mm compared to 10.3% for lesions ≤10 mm (OR 2.66, p=0.028).

Conclusions
Only clinical lesion diameter was identified as prognostic factor for response to non-invasive therapy in Bowen's disease

A-239

Proteomic Profiling of Cutaneous Squamous Cell Carcinoma Samples from Solid Organ Transplant Recipients and Immunocompetent Patients

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Background
Solid organ transplant recipients (SOTRs) are known to have a higher risk of developing cutaneous squamous cell carcinoma (cSCC) compared to immunocompetent (IC) patients. Despite this, genomics studies have found little difference in the molecular mechanisms underlying cSCC pathogenesis between these two patient groups, resulting in a lack of new therapeutic targets.

Methods
To address this gap, this study used a novel approach of data-independent acquisition mass spectrometry (DIA-MS)-based proteomics to analyze clinical samples of cSCC from SOTRs (n=20) and IC (n=18) patients. The study performed differential abundance analysis and bioinformatics analysis using Ingenuity Pathway Analysis (IPA) to identify protein biomarkers and dysregulated pathways in SOTR cSCC samples compared to the IC cohort.

Results
The analysis revealed 103 differentially abundant proteins between SOTR and IC groups. Among the most significantly downregulated proteins in SOTRs were IGHG4 and OSBP, which play a role in immunosuppressive changes that could contribute to the development of cSCC in SOTRs. Pathway analysis revealed the activation of proteins associated with cell proliferation, metastasis, and necroptosis signaling in SOTRs, providing new insights into the molecular mechanisms behind the aggressiveness of this cancer and identifying potential therapeutic targets for future clinical applications.

Conclusions
Overall, this study sheds light on the proteome differences between cSCC samples from SOTR and IC patients, providing a better understanding of the lesions and uncovering potential protein targets for the development of therapeutics in the future.

A-341

Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator (SUNTRAC): Perspectives from the EUSCAP database in a cohort of kidney transplant recipients

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Background

The incidence of skin cancer is significantly higher in kidney transplant recipients (KTRs) compared to the general population. To identify those patients who are at particularly high risk of developing post-transplant skin cancer, the Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) was developed in the US, which includes 4 risk categories: low, medium, high, and very high risk[1]. This study aims to assess the applicability of the SUNTRAC tool to a cohort of KTRs at Erasme Hospital in Brussels, Belgium.

Methods

This monocentric retrospective study analysed data from two registries: the European Skin Cancer Risk Factor Platform (EUSCAP) dermatological registry[2] and the kidney transplant registry. A total of 90 KTRs who underwent transplantation before 2019 or 2014 were selected in order to assure follow-up periods of 5 and 10 years. Patients were assigned to their corresponding risk group based on their total SUNTRAC score. Due to their limited number, patients in the very high-risk group were excluded.

Results

The relative risk of post-transplant skin cancer, calculated using subdistribution hazard ratios (SHRs) with the low-risk group as the reference, was significantly increased for patients in the high-risk group (risk at 5 years: SHR 12.6 [95% CI, 1.5-108.1]; P = 0.02; risk at 10 years: SHR 23.4 [95% CI, 2.9-185.3]; P = 0.003). The observed 10-year skin cancer incidence was 4.5% for the low-risk group, 14.7% for the medium-risk group, and 69.2% for the high-risk group.

Conclusions

Our analysis supports the efficacy of SUNTRAC as a screening tool to stratify kidney transplant recipients into various risk groups for post-transplant skin cancer. Implementing this approach would enhance the effectiveness of screening and surveillance efforts, particularly targeting the high-risk group.

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[1] Jambusaria-Pahlajani A, Crow LD, Lowenstein S, Garrett GL, Melcher ML, Chan AW, Boscardin J, Arron ST, Predicting skin cancer in organ transplant recipients: development of the SUNTRAC screening tool using data from a multicenter cohort study, Transpl Int, doi: 10.1111/tri.13493

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A-406

Slow Mohs Micrographic Surgery: A Service Evaluation

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Background

Slow Mohs Micrographic surgery is a method for margin controlled removal of cancerous lesions. We present the patient outcomes from 5 years' experience of one surgeon operating from Addenbrooke's Hospital, Cambridge.

Methods

Patients were identified using the EPIC® record of patients who received Mohs surgery between 02-October-2017 and 06-July-2022. 11 patients received slow Mohs surgery. 6 patients were male; 5 patients were female. 26 slow Mohs surgeries were performed on these 11 lesions. 3 lesions were dermatofibrosarcoma protuberans, 3 were squamous cell carcinomas, 2 were basal cell carcinomas, 1 was extramammary paget's disease and 2 were other forms of skin cancer. 5 were located on the face and scalp, 5 on the torso, and 1 on the groin.

Results

The average diameter of excised lesion was 30mm (range: 10-60mm). 4 lesions were scars from prior incomplete excisions, a common reason for slow Mohs. For complete excision, the average margin removed was 12mm (range: 5-22mm). 6 patients required >1 excision to completely remove the lesion; the average number required was 2. Patients waited on average 20 days between subsequent excisions. Procedures were either under general (n=8) or local (n=3) anaesthesia. Patients attended hospital on average 20 times (range: 5-41). Regarding reconstruction, 5 patients had primary closure, 3 received a split skin graft and 3 received a flap. After a minimum follow up period of 18 months, 0 patients experienced recurrence following complete excision.

Conclusions

The purpose of slow Mohs surgery is confidence that the entire cancerous lesion is removed, whilst excising the least amount of tissue. This is especially important given that many (n=5) lesions occur on the face and scalp, areas of high aesthetic importance. The results suggest that the chosen margins are usually appropriate, as the average number of surgeries is 2. Slow Mohs has proved to be an excellent method of preventing recurrence; in a 6 year period, 0 patients had recurrence. This data will be helpful for comparing against other methods of treating skin cancer.

A-125

Sun Protection Patterns Among Organ Transplant Recipients and Non-Organ Transplant Patients with Skin Cancers

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Background
Organ transplant recipients are at much higher risk of developing cutaneous malignancies especially squamous cell carcinoma (SCC). As sun exposure is a risk factor for SCC, sun-protection is of utmost importance in organ transplant recipients. Sun protection has not been reported in transplant patients in Singapore, nor about their dermatological quality of life after repeated skin cancers events. We sought to document the sun protection patterns and dermatology quality of life among organ transplant recipients and non-organ transplant patients who had cutaneous SCC.

Methods
66 adults (organ transplant and non-organ transplant recipients) with cutaneous SCC who were seen at the dermatology clinic at a tertiary hospital from January 2019 to March 2022 were surveyed regarding sun protection and history of a full-body skin check. They also completed the dermatology life quality index (DLQI) questionnaire

Results
Univariate analysis revealed significant association between self- skin check and history of organ transplant (p=0.0221). There was otherwise no other statistically significant difference between sun protection patterns (hours spent in midday sun, use of sunscreen, umbrellas, sunglasses, or shirt covering shoulders) in SCC patients who were organ transplant recipients versus those who were not transplant recipients. DLQI scores were low in both groups with means scores of 2.23 and 2.42 for the control and transplant group respectively.

Conclusions
Our findings demonstrate that transplant patients performed more self-skin check possibly due to increased awareness of cutaneous malignancies. Sun protection patterns were otherwise similar in both transplant and control groups, which needs further improvement. Skin cancers did not affect DLQI in both groups, possibly due to the localized nature of the skin tumours.

A-359

Survival Outcomes in T3N0 versus N1 in Head and Neck Cutaneous Squamous Cell Carcinoma – Implications for Neoadjuvant Immune Checkpoint Inhibitor Immunotherapy

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Background

Based on encouraging clinical outcomes in unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC), the role of immune checkpoint inhibitor (ICI) immunotherapy in the (neo)adjuvant setting for earlier-stage [AJCC stage II-IV (M0)] disease is being investigated. Although pN1 disease is not included in current adjuvant trials, including C-POST (NCT03969004) and Keynote 630 (NCT03833167) where postoperative adjuvant radiotherapy remains a prerequisite, pathological staging is unavailable for neoadjuvant clinical trials and therefore, patients with isolated cN1 disease will still be included. Our anecdotal experience suggests significant differences in prognosis between the T3N0 and isolated N1 subgroups of stage III disease, with the latter having a significantly favourable outcome. Better risk-stratification of T3N0 versus isolated N1 disease is warranted to enable improved communication of the longer-term risks and benefits of neoadjuvant ICI, and critical appraisal of clinical trial data.

The objective of this study is to undertake a systematic review and meta-analysis of survival outcomes in pT3N0 versus pN1 head and neck cSCC (HNcSCC).

Methods

Five databases were searched for studies reporting survival outcomes (disease free survival; DFS or disease specific survival; DSS) in either pT3N0 or isolated pN1 HNcSCC between 2010 and January 2024. Two reviewers independently extracted data. Risk of bias was estimated with the Newcastle-Ottawa Scale. Kaplan-Meier curves were extracted, digitised and aggregated as per established procedure. The Kaplan-Meier method, log-rank test and univariate Cox analysis were used to describe and compare survival outcomes for aggregated pT3N0 and pN1 cohorts.

Results

The aggregated groups contained 405 pT3N0 and 161 isolated pN1 patients. DFS could not be assessed due to lack of data. DSS was significantly worse for pT3N0 disease compared to pN1 disease (HR 1.800, 95% CI 1.168-2.774, log rank p-value = 0.007) with 5-year DSS of 69.3% [standard error (SE) 3.5%] for pT3N0 disease versus 81.6% (SE 3.0%) for pN1 disease (Figure 1).

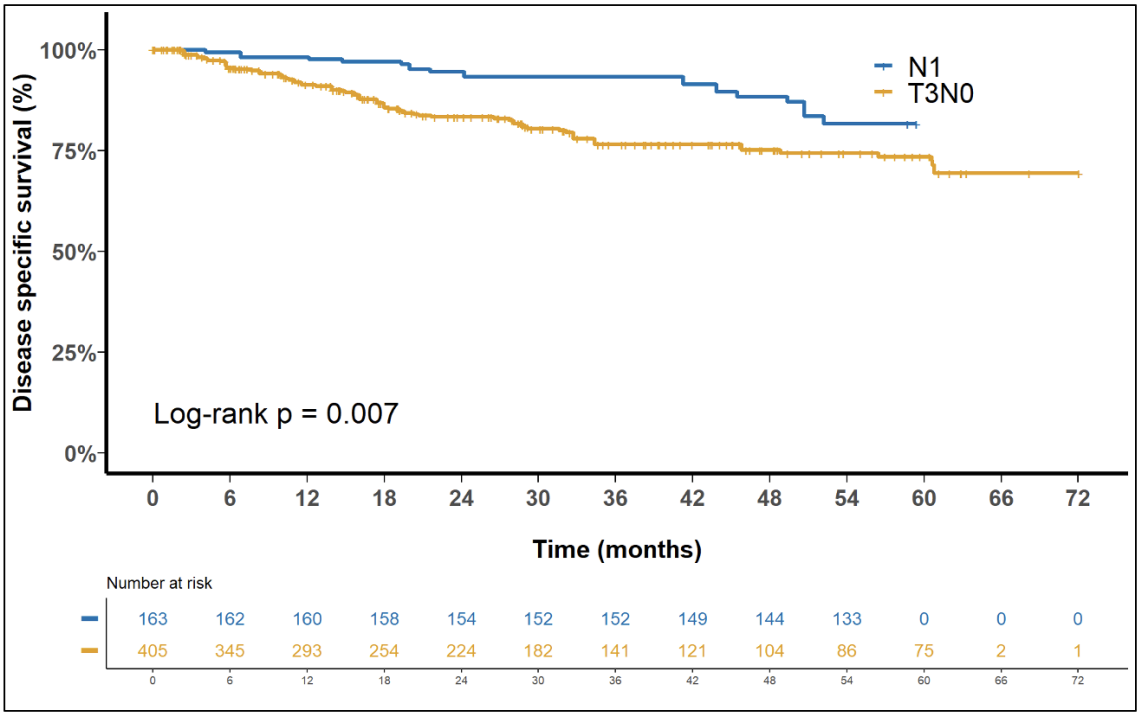

Figure 1 - Kaplan-Meier curve for disease specific survival in aggregated groups of patients with N1 versus T3N0 cutaneous squamous cell carcinoma of the head and neck

Conclusions

The risk-benefit implications from ICI immunotherapy differ for T3N0 versus isolated N1 patients. Appreciation of the significant survival outcome difference between these two stage III subgroups is critical when designing neoadjuvant ICI clinical trials and interpreting trial data.

A-389

The Correlation Between Clinical and Pathological Tumor Size in Cutaneous Squamous Cell Carcinoma and the Risk of Erroneous Downstaging

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Background
The clinical tumor size is one of the most important factors for AJCC-staging of cutaneous squamous cell carcinoma (cSCC). This poses a problem in registry-based studies where only data from pathological reports are available, or in cases of missing pre-operative clinical tumor sizes. An alternate approach is to perform AJCC-staging based on pathological tumor sizes (pT stage). However, as a result of tissue shrinkage due to tissue fixation, the correlation between clinical and pathological tumor sizes remains uncertain. Therefore, the aim of this study is to determine the correlation between clinical and pathological tumor sizes, and to assess whether pathological tumor sizes can be used for AJCC-staging without the risk of erroneous downstaging.

Methods
We included eligible patients from Copenhagen, Denmark with excised cSCC and a registered clinical and pathological tumor size in the period 2012-2018. The data was extracted from medical charts. The correlation between clinical and pathological tumor size was estimated as the mean difference and the correlation was assessed with a simple linear regression and reported as R^2. The risk of erroneous downstaging was investigated by comparing clinical T-stage (cT) and (pT) in two separate classifications of stage: tumor size alone or using the full AJCC classification.

Results
We included 100 patients with cSCC with a mean pathological tumor size of 18.0 mm (95% CI 15.4-20.5) and a mean clinical tumor size of 19.5 mm (95% CI 15.7-23.3). The mean shrinkage of the pathological tumor size compared with the clinical tumor size was -1.53 mm (95% CI -3,43 – 0,37), p = 0.06, with a high correlation, R^2 = 0.88. When allocating patients to T-stages we found an overall risk of downstaging of 17%, p = 0.03, when applying only tumor size and 13% when using the full AJCC, p = 0.02.

Conclusions
Our study suggests that pathological tumor sizes cannot be used to safely perform AJCC-staging of cSCC, due to a significant risk of erroneous downstaging. Further studies are needed to estimate a correction factor, to ensure that pathological tumor sizes can be validly utilized in future registry-based studies.

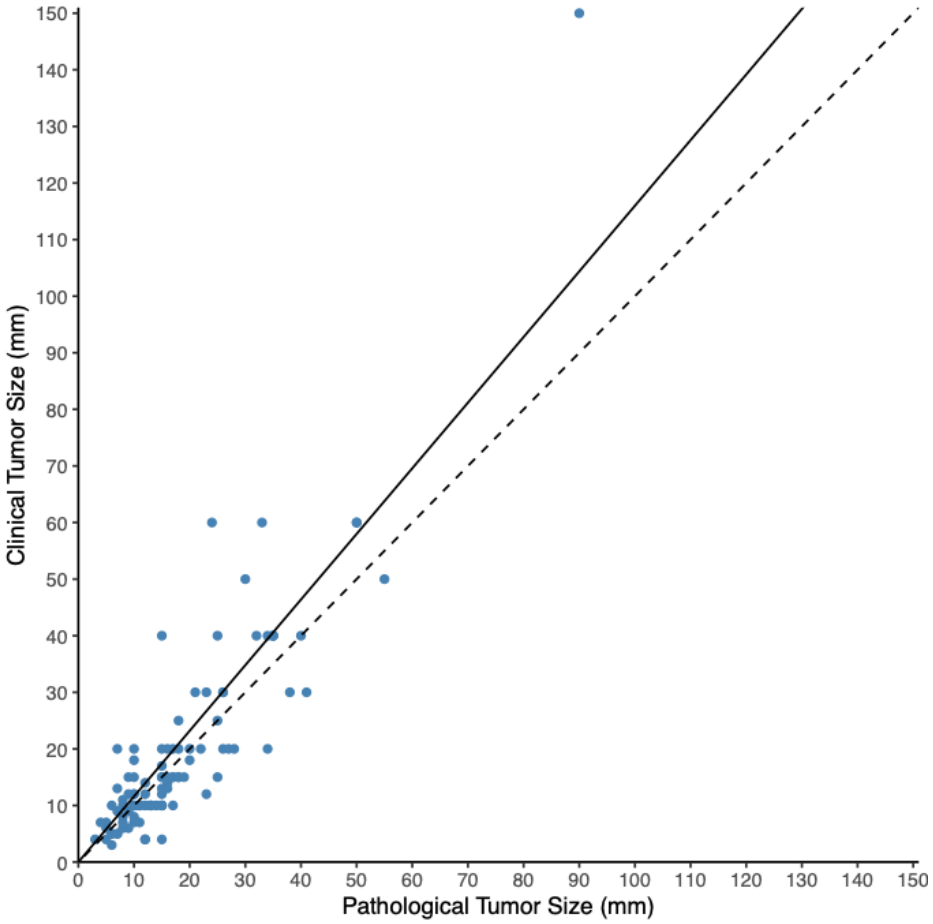

Figure 1: Scatter plot of the pathological and clinical tumor sizes. A simple linear regression shows a high correlation, R2 = 0.88. The mean difference was -1.53 mm (95% CI -3,43 – 0,37). The dashed line indicates perfect agreement.

Only tumor size

		Clinical		
		T1	**T2**	**T3**
Pathological	**T1**	62	7	1
	T2	3	12	9
	T3	0	1	5

Full AJCC

		Clinical		
		T1	**T2**	**T3**
Pathological	**T1**	52	5	0
	T2	2	10	8
	T3	1	0	2

Table 1: The correlations between cT-stages and pT-stages when using only tumor sizes (upper) and when using the full AJCC-classification (lower).

A-403

The Dutch Keratinocyte Cancer Collaborative: real-world linked health care data to identify and follow-up patients with advanced cutaneous squamous carcinoma on a nationwide level

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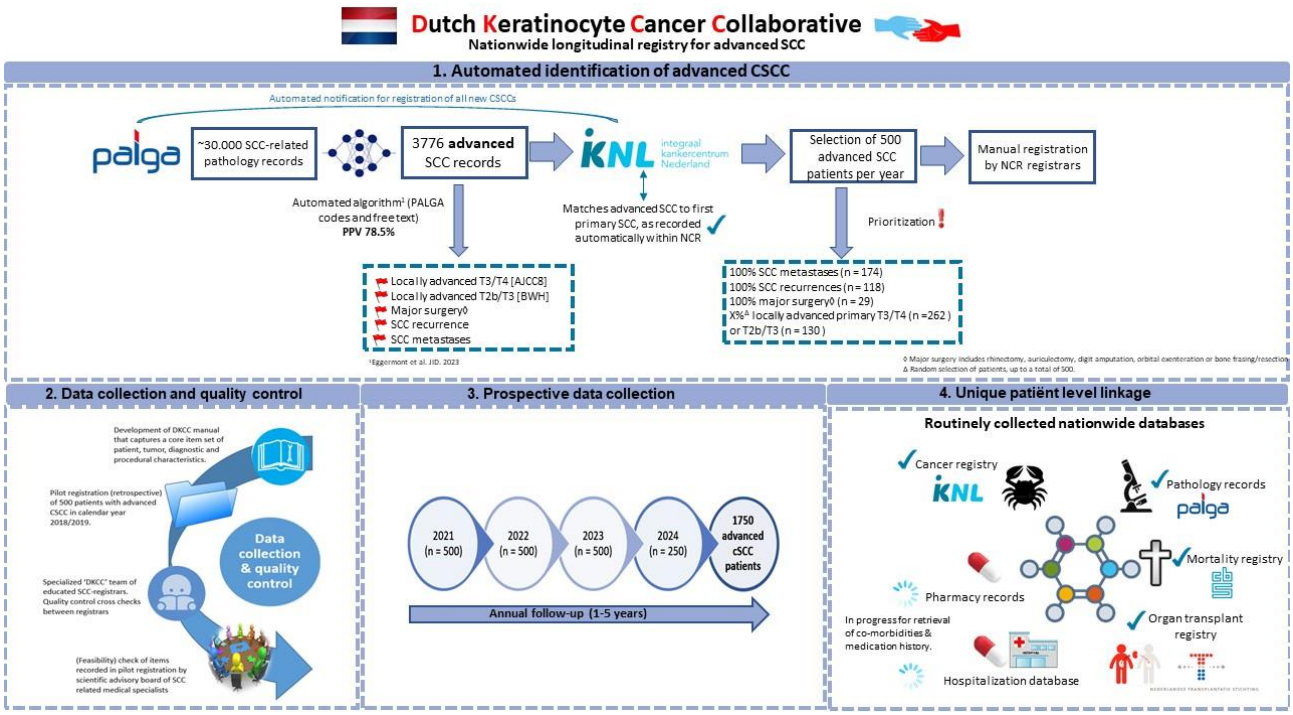
Background

The exceedingly high incidence rate of cutaneous squamous cell carcinoma (CSCC) results in a large numbers of patients with advanced CSCC who are at risk of death. Nationwide data on advanced CSCC is scarce since few registries include CSCC and those that do only include the primary tumor without collecting follow-up data.

Methods

To facilitate nationwide epidemiological research on advanced CSCC, a validated algorithm that identifies advanced CSCC (i.e., locally advanced, recurrent, and metastatic CSCC) from free-text pathology reports was used. On a nationwide level, cancer registry data was linked to pathology data, hospitalization data, organ transplant recipients registry and cause of death registry to obtain data about the patient journey. Manual registration from hospital records was performed for all selected cases to obtain data on: primary tumor characteristics, diagnostics, time to progression, treatment of the primary tumor, recurrences and metastasis, adverse events and treatment response.
A nationwide estimation of the incidence of advanced CSCC was made using the sensitivity of the pathology reports algorithm.



Design of the Dutch Keratinocyte Cancer Collaborative

Results

In 2021, 503 patients with advanced CSCC were included in the real-world data collection. This included all patients on a nationwide level with metastasis (n=171), recurrences (n=118) and a selection of patient with primary locally advanced CSCC(n=262 according to AJCC T3/T4 and n= 130 according to BWH T2b/T3). We calculated that the registered patients correspond to a nationwide incidence of 257 (95% CI: 214-321) patients per year with metastatic CSCC in a population of 16 million people with an incidence of 14,700 newly diagnosed patients per year. 47 of 171 (27%) patients with metastasis had recurrent CSCC before the metastasis occurred. Most patients (137/171) developed metastasis during follow-up. The median time to progression was 6 months for patients with skin metastasis (n=14), 13 months for patients with lymph node metastasis (n=131) and 9 months for patients with distant metastasis (n=26).

Conclusions

This real-world collection of data will provide a comprehensive characterization of patient, primary tumor and treatments of patients with advanced CSCC. These data will inform health care providers and policy makers to improve guidelines for diagnostics, treatment and follow-up.

A-400

The treatment of elderly patients with locally advanced or metastatic cutaneous squamous cell carcinoma using Cemiplimab monotherapy or Cemiplimab associated with palliative radiotherapy: A single centre experience from the United Kingdom.

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Background
Cutaneous squamous cell carcinoma (cSCC) is a common disease in the elderly population and accounts for around 20% of cases of skin cancer in the UK. Locally advanced and metastatic cSCC is particularly challenging to manage with traditional treatment such as surgery and radiotherapy. The advent of immunotherapeutic agents such as Cemiplimab has produced results in clinical trials. We present real-world experience in managing cSCC in an elderly population.

Methods
12 (80%) patients with locally advanced cSCC and 3 (20%) patients with metastatic cSCC were included. These patients were elderly (median age 83, IQR 75.5 – 87.5) and ECOG performance status 0 (13.3%) or 1 (86.7%) upon commencing Cemiplimab. These patients were generally frail (median Rockwood Clinical Frailty Score 5, IQR 3.5 – 6) and co-morbid (median Charlson Co-morbidity Index 7, IQR 6-8). 33.3% of patients were immunosuppressed. 26.7% of patients had previously undergone radical radiotherapy but had a recurrence of the disease.

Results
12 (80%) patients with locally advanced cSCC and 3 (20%) patients with metastatic cSCC were included. These patients were elderly (median age 83, IQR 75.5 – 87.5) and ECOG performance status 0 (13.3%) or 1 (86.7%) upon commencing Cemiplimab. These patients were generally frail (median Rockwood Clinical Frailty Score 5, IQR 3.5 – 6) and co-morbid (median Charlson Co-morbidity Index 7, IQR 6-8). 33.3% of patients were immunosuppressed. 26.7% of patients had previously undergone radical radiotherapy but had a recurrence of the disease.
The ORR to Cemiplimab in this cohort was 93.3%. A clinical response was observed after a median of 2.5 treatment cycles (IQR 1 – 3), and a radiological response was observed after a median of 5 treatment cycles (IQR 4 – 7.5 cycles). 53.3% of patients had undergone palliative radiotherapy whilst on Cemiplimab or within 6 weeks prior to starting Cemiplimab. 86.7% of patients experienced an adverse event in response to Cemiplimab, and these were mostly CTCAE grade 1/2 fatigue or skin reactions. 20% of patients experienced a CTCAE grade ≥3 reactions, and only 1 of these led to the cessation of Cemiplimab therapy.

Conclusions
In our experience, Cemiplimab is an effective and well-tolerated therapy for cSCC in an elderly, frail and multimorbid population in which other options may be limited. Compared to phase II clinical trials, the high response rate of this cohort suggests that concomitant radiotherapy may increase the antitumor activity of Cemiplimab.

A-186

Using the free flap to repair the postoperative defect of the head and neck squamous cell carcinomaUsing the free flap to repair the postoperative defect of the head and neck squamous cell carcinoma

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Background

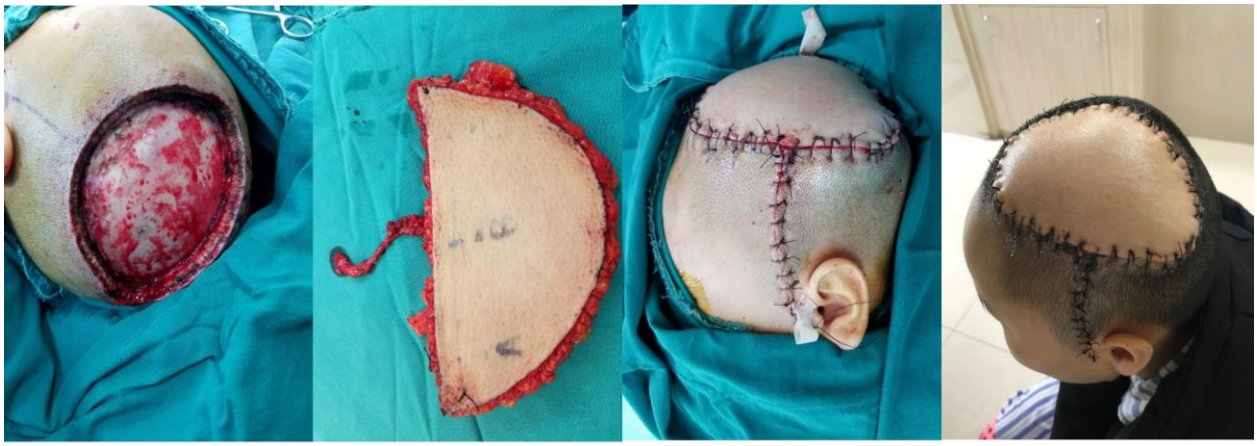
Cutaneous squamous cell carcinoma（cSCC）is a kind of malignant tumor that stems from the formation of cutin forming cells, which has increased the incidence of the disease in recent years. The current treatment of cSCC, still with surgical resection, the main reason for the failure of patients with head and neck cSCC is local recurrence or local transfer. For the local terminal head and neck cSCC, the operation is still the main treatment, the simple removal of the lesion can cause the patient's local defect to affect the appearance, the skin or the cuff flap cannot meet the needs of the repair.

Methods

In January 2018 to 2023, there were 37 cases of the head and neck cSCC treated in our center, and the defect of the posterior surgery area was repaired by free flap included radial forearm free flap and anterolateral femoral free flap.

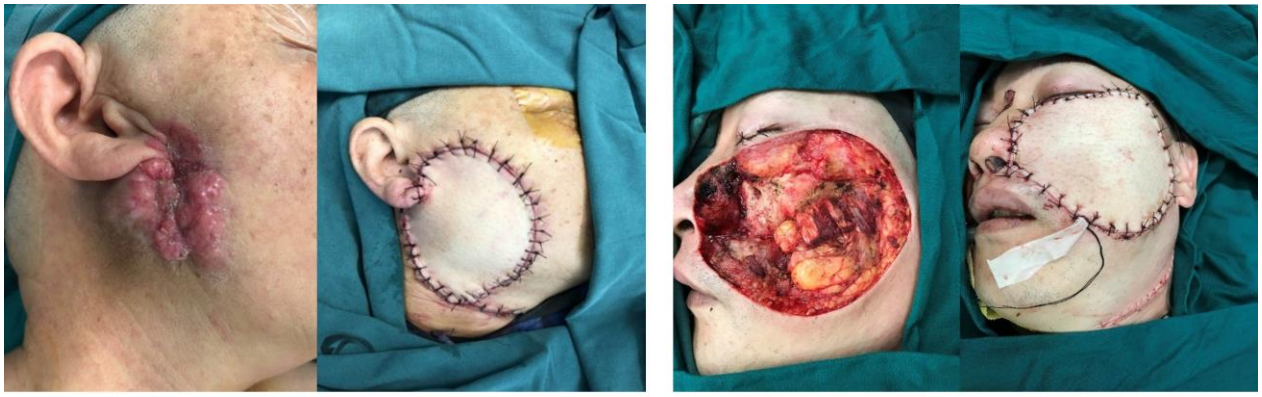
Results

After the operation, there was a patient's incision infection, and after the treatment of anti-infection, the flap was not dead. The skin flap of the scalp is not hairy, and the patient needs to wear a wig. While the skin flap repair of the neck and surface is good.



A. Preoperative and postoperative scalp scale cancer

Preoperative and postoperative scalp scale cancer



B. Preoperative and postoperative facial scale cancer

Preoperative and postoperative facial scale cancer

Conclusions

For the local recurrence of advanced head, face, neck skin malignant tumors, free flap can be a good repair of the surgical area defect, to a great extent to alleviate the patient's condition and cosmetic effect.