



19th EADO CONGRESS

April 20th–22nd, 2023

ROME, ITALY

AUDITORIUM DELLA TECNICA

BOOK OF ABSTRACTS

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ABSTRACTS



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A new standard imaging method to measure treatment area and follow-up of treatment of Actinic Keratosis and field of cancerization

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Introduction and objectives: The application of a treatment for Actinic Keratosis (AK) in clinical studies sometimes is limited to a specific area. There is a need for a follow-up of AK lesions within treated area to evaluate the efficacy and safety of the treatment. The classical acetate film method is not accurate due to the complex anatomic references and presents several difficulties. The objective was to develop new method with digital photography to monitor the area of treatment and the lesions in that area. A digital photography method to monitor the area of treatment and the lesions in that area has been developed and implemented in a phase 1 trial of maximal use of tirbanibulin in 100 cm² (Study code: M-14867-01).

Materials and Methods: 4weeks open label study with tirbanibulin in AK patients with at least 8 lesions in 100cm² of the face or scalp was conducted in 5 US sites. Multiple photos in treatment area were taken at baseline and x4 follow-up visits using the new method. The methodology consisted of using a device attached to mobile photographic system and dedicated software. 3D images to measure in real time the treatment area and 2D images with integrated Match-Pose tool to support image positioning.

Results: 28 AK patients with a mean age of 68.8 years and an average number of 10.8 AK lesions at baseline were included into the study. The digital documentation (557 photos) allowed to set up a predefined treatment area at baseline used as reference digital document or more precise follow-up of changes during the study. In all patients, the area corresponding to 100cm² was documented. In a user's survey, 5/8 investigators responded that the digital method was more precise to identify the lesions than the acetate, and 7/8 would like to use it in future clinical studies. Conclusion: The new system was successfully implemented in a phase I study and preferred by most of the investigators. Compared to acetate film the new method provides robust documentation, more accurate localization of the treatment area and reliable follow up of the identified lesions.

Actinic Keratosis in Optical Super-High Magnification Dermoscopy

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Introduction and objectives: Actinic keratosis (AK) occurs on sun-damaged skin and is regarded as a preliminary stage of squamous cell carcinoma (SCC). AK may take various forms from a flat, slightly erythematous macule to a pigmented lesion (pigmented actinic keratosis-PAK) and in this variant, it may mimic clinically or even dermoscopically lentigo maligna (LM).

Owing to its higher magnification, optical Super-High Magnification Dermoscopy (OSHMD) can allow for more efficacious differentiation of lesions, and thus increase the accuracy of dermoscopic diagnosis.

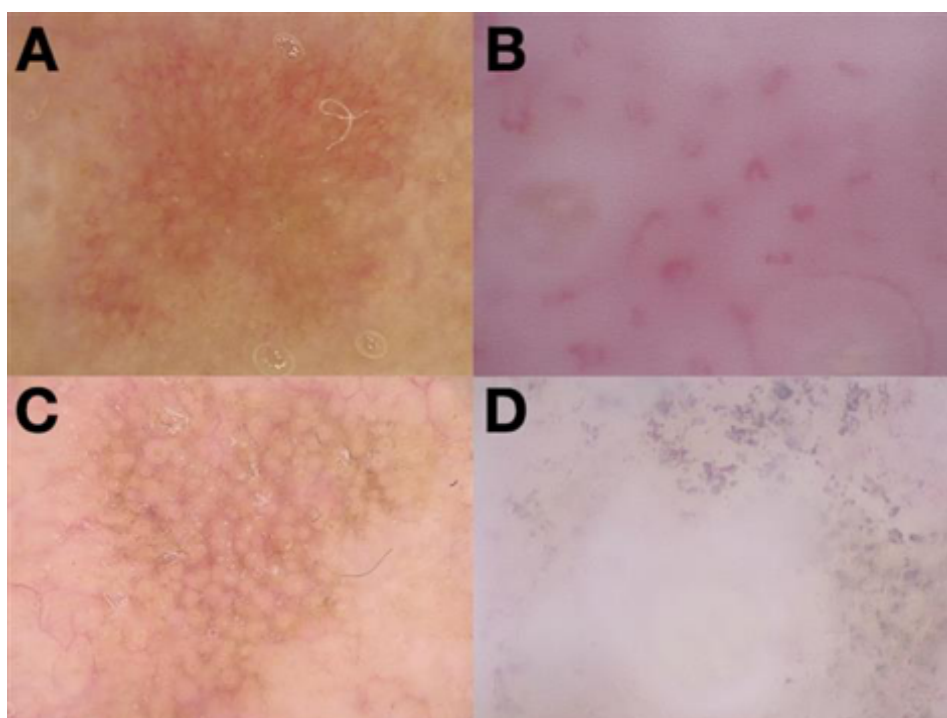
Material and Methods: A 62-year-old patient with an erythematous scaly plaque of the cheek and a 77-year-old patient with a brown macule of the temple presented for dermoscopy. Standard dermoscopy (20X) and OSHMD (400x) was performed in both patients.

Results: Dermoscopy of the lesion of the first patient showed a "strawberry pattern" in the form of background erythema with multiple keratin-filled follicular ostia, an image typical for AK (A). OSHMD unveiled that the erythema in the standard dermoscopy was caused by numerous curved vessels (B). Moreover, straight linear vessels on the edge of the ostia were visible.

Dermoscopy of the lesion of the second patient revealed features typical for PAK, namely scale, brown angulated lines and bright follicular openings (C). OSHMD revealed white follicular openings without "circle within a circle" – structures typical for LM. Melanin aggregates, single melanophages and sparse cells, probably corresponding to pigmented keratinocytes around the hair follicle were present (D).

Conclusions: In standard dermoscopy, PAK may present a pattern similar to LM. In addition to standard dermoscopy, OSHMD might be useful in differentiating the two lesions.

Supporting Document 1



Basal proliferation and acantholysis are histological high-risk factors for progression into invasive squamous cell carcinoma: a comparison study in solid organ transplant recipients and matched immunocompetent patients.

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Introduction and Objectives: Histological risk factors of AKs cannot be determined directly. Recent studies indicate that AKs restricted to the lower third of the epidermis (AK I), with marked basal proliferation (PRO III) and acantholysis are associated with an increased risk of progression to invasive squamous cell carcinoma (iSCC) (1). To confirm the aforementioned histological risk factors, this study compared AKs from solid organ transplant recipients (sOTRs), known to carry up to 250-fold higher risk for progression into iSCC, to a matched immunocompetent control group (ICG).

Material and Methods: Cases were selected retrospectively from the Skin Cancer Center of Heinrich-Heine-University Düsseldorf (Düsseldorf, Germany) database, in the period January 2008 – June 2021. Two independent investigators classified the samples as per their upward projected growth pattern (AK I, II, or III) (2) and downward projected growth pattern (PRO I, II or III) (3).

Results: 111 AKs from 43 sOTRs showed significantly more AKs graded AK I compared to the ICG (48.7% vs. 31.5%, $p=0.009$). In line with these findings, AKs from sOTRs showed more pronounced basal proliferation (PRO III) compared to the ICG (80.2% vs. 33.3%, $p<0.0001$). Acantholysis was significantly more frequent in sOTRs than the ICG (59.5% vs. 32.4%, $p<0.0001$) and significantly more frequently associated with advanced basal proliferation ($p<0.0001$).

Conclusions: In conclusion, this study showed that acantholytic AKs graded as AK I and PRO III are predominantly found in a population at high risk of iSCC. Thus, AKs with marked basal proliferation and acantholysis must be assumed as histological high-risk factors for progression into iSCC.

Clinician- and patient-reported satisfaction with tirbanibulin 1% in comparison with previous topical actinic keratosis medications in routine clinical practice across the U.S. (PROAK study)

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Introduction and Objectives: Actinic Keratosis (AK) has been shown to negatively affect emotional functioning and skin-related quality of life of patients. The objective of this analysis was to evaluate clinician- and patient-reported satisfaction with tirbanibulin in comparison with previous topical medications, using the expert panel questionnaire (EPQ)¹, among patients with AK receiving tirbanibulin in routine clinical practice across the U.S.

Material and Methods: A single-arm, prospective cohort study (PROAK: NCT05260073) was conducted among adult patients with AKs on the face or scalp who were newly initiated with once-daily tirbanibulin 1% ointment treatment (5-day course). Patients and clinicians completed surveys and clinical assessments at baseline, Week-8, and Week-24. Clinicians and patients rated the duration and severity of local skin reactions (LSRs), the impact on daily activities, the convenience and ease of use and the overall satisfaction (EPQ questions 4 to 8) with tirbanibulin treatment at Week 8 on a 5-point adjectival response scale from 0 (much shorter/better) to 5 (much longer/worse) compared to previous treatment. Clinician version refers to clinician experience/observation of tirbanibulin effects among their patients.

Results: A total of 290 patients with AK completed the study assessments at Week 8 (mean age: 66.3 years, female: 31.4%; history of skin cancer; 61.7%; Fitzpatrick skin type I: 7.6%, II: 71.4%, III: 18.6%, IV: 1.4%, V: 1.0%). All patients completed the 5-days treatment with tirbanibulin. A total of 111 patients (out of 290 patients) at Week-8 had used a topical medication in the past, with 5-fluorouracil (5-FU) being the most frequent (66.7%). At Week-8, clinicians and patients rated the duration and severity of LSRs, the impact on daily activities, the convenience and ease of use and the overall satisfaction with tirbanibulin treatment to be "much/somewhat shorter/better" in comparison with previous treatments (Table 1).

Conclusion: Clinicians and patients' overall satisfaction with once-daily tirbanibulin treatment for 5-days at Week-8 was confirmed. Compared to patient's previous treatment, tirbanibulin was more convenient/easy to use, much/somewhat better tolerated in terms of duration and severity of LSRs and with a better impact on patient's daily activity.

Supporting Document 1

	Much/somewhat shorter/better (%)		No change (%)		Much/somewhat longer/worse (%)	
	Clinician-reported	Patient-reported	Clinician-reported	Patient-reported	Clinician-reported	Patient-reported
Duration of skin reactions	89.2	73.9	9.0	18.9	0.9	7.2
Severity of skin reactions	91.0	76.6	8.1	18.0	0.0	5.4
Impact on daily activities	87.4	63.9	9.9	32.4	0.0	3.6
Convenience and ease of use	88.3	71.2	8.1	27.0	2.7	1.8
Overall satisfaction	82.9	72.1	9.9	22.5	5.4	5.4

Effect of tirbanibulin 1% ointment on Local Skin Reactions according to Fitzpatrick skin type in Actinic Keratosis patients: a post-hoc analysis of pooled data from two Phase III studies

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Introduction and Objectives: Tirbanibulin 1% ointment is indicated for the topical treatment of actinic keratosis (AK) on face or scalp based on the results of two Phase III studies (NCT03285477/NCT03285490). The aim of this post-hoc analysis is to assess the local skin reactions (LSRs) following exposure to tirbanibulin according to Fitzpatrick skin type (FST).

Material and Methods: This post-hoc analysis is based on pooled data from two identical Phase III, randomized, double-blinded, vehicle-controlled studies. Eligible patients (4-8 AKs in a 25cm² area) were randomized 1:1 to tirbanibulin:vehicle (5-day once-daily self-application). At each patient visit, LSRs (crusting, erosion, erythema, flaking/scaling, swelling, vesiculation/pustulation) were scored 0-3 (absent-severe) by the investigators, and summed to a composite score (0-18). Each individual LSR and the LSR composite score at their mean maximum value (days 5 and 8) were assessed by FST.

Results: Overall, 353 patients were randomized to tirbanibulin and 349 to vehicle. Among tirbanibulin-treated patients, 49 (13.9%) patients were under FST I, 200 (56.7%) FST II, 88 (24.9%) FST III, 15 (4.2%) FST IV, 1 (0.3%) FST VI. At day 5, mean (95% confidence interval [CI]) LSR composite score was 3.3 (2.7-3.8) for FST I, 3.0 (2.8-3.3) FST II, 2.6 (2.3-3.0) FST III, and 2.6 (1.9-3.3) FST IV (not enough FST VI sample). At day 8, mean (95% CI) LSR composite score was 4.4 (3.8-5.0) for FST I, 4.2 (3.9-4.6) FST II, 3.9 (3.4-4.4) FST III, and 3.4 (2.4-4.4) FST IV (not enough FST VI sample). Mean data for each individual LSR are mild to moderate and shown in Table 1. The LSR composite score and each individual LSR seem to be similar among the different FST at both day 5 and day 8, as suggested by the overlapping 95%CI.

Conclusion: This analysis suggests that FST has no impact on the severity of LSR in patients treated with tirbanibulin, being equally tolerated between the different FSTs, even with the more sensitive light skin types I-II susceptible to worse tolerability issues with other AK topical treatments. These results consolidate tirbanibulin as a good alternative to current AK treatments with good efficacy and tolerability profiles.

Effectiveness and skin photodamage among patients with Actinic Keratosis receiving tirbanibulin 1% in routine clinical practices (PROAK Study)

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Introduction and Objectives: Actinic Keratosis (AK) are epidermal lesions with potential to progress to squamous cell carcinomas if left untreated. The objective of this analysis was to evaluate the Investigator Global Assessment (IGA) success and changes from baseline in clinician-reported skin photodamage at Week-8, among patients with AKs administered 5-days tirbanibulin 1% once daily in routine clinical practices across U.S.

Material and Methods: Single-arm, prospective cohort study (PROAK) among adults with AKs on face/scalp who were newly initiated on tirbanibulin. Patients and clinicians completed surveys and clinical assessments at baseline, Week-8, and Week-24. Clinicians assessed AK responses using IGA on a 5-point response scale: 0 (completely cleared), 1 (partially cleared), 2 (moderately cleared), 3 (minimally cleared), and 4 (not cleared). IGA success defined as achieving IGA score of 0-1 ($\geq 75\%$ AK lesions clearance) at Week-8. Clinicians assessed the current severity of patient's skin photodamage on a 4-point response scale: 0 (absent), 1 (mild), 2 (moderate), 3 (severe). Change from baseline in proportion of patients with absent/mild and moderate/severe skin photodamage were assessed, as observed.

Results: A total of 290 AK patients completed the study assessments at Week-8 (mean age: 66.3 years; female: 31.4%; skin cancer history: 61.7%; Fitzpatrick skin type: I: 7.6%, II: 71.4%, III: 18.6%, IV: 1.4%, V: 1.0%). More than three-fourth of the patients were treated during summer 2022. At Week-8, the proportion of patients with completely/partially cleared AK (IGA1/0) was 73.8%; moderately cleared (IGA2) was 17.2%; and minimally cleared/not cleared (IGA3/4) was 9.0%. IGA success was 73.8%. Among 288 patients with available data at both baseline and Week-8, 77.4% had moderate/severe skin photodamage and 22.6% had absent/mild skin photodamage at baseline; at Week-8, 39.6% had moderate/severe skin photodamage and 60.4% had absent/mild skin photodamage. The reduction of skin photodamage severity at Week-8 measured by the changes from baseline was statistically significant ($p < 0.0001$).

Conclusion: Most of the AK patients using once-daily tirbanibulin for 5 consecutive days experienced IGA success in 73,79% of patients, consistent with Phase III trials reported efficacy¹ and a significant reduction in severity of skin photodamage at Week-8, as reported by their clinicians.

Efficacy of classic Er:YAG laser-assisted versus fractional Er:YAG laser-assisted photodynamic therapy in the treatment of actinic keratoses: a retrospective study

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Introduction and Objectives: Actinic keratoses (AK) is a precancerous lesion that can progress to squamous cell carcinoma if left untreated. Although studies have been published comparing various treatments for AK, no standard treatment has been established. Ablative lasers are an established pretreatment modality combined with photodynamic therapy (PDT) in clinical practice. We conducted a retrospective study to compare the efficacy of PDT with classic Erbium-doped yttrium-aluminum-garnet laser (Er:YAG laser) and fractional Er:YAG laser in the treatment of actinic keratosis.

Materials and Methods: We retrospectively analyzed the medical records of patients who underwent PDT with classic Er:YAG laser or fractional Er:YAG laser for actinic keratosis with histologic confirmation from 2016 to March 2022 at Seoul St. Mary's Hospital. To analyze the efficacy of both treatments, the presence of residual lesions and recurrence were evaluated after PDT.

Results: A total of 16 PDT+classic Er:YAG laser patients and 9 PDT+fractional Er:YAG laser patients were included. Patients with residual lesions after 2 or more PDT sessions were observed in 3 patients (18%) in the PDT+classic Er:YAG laser group and 1 patient (11%) in the PDT+fractional Er:YAG laser group. Post-treatment recurrence was observed in one patient in the PDT+ Er:YAG laser group and none in the PDT+fractional laser group.

Conclusions: Fractional Er:YAG laser assisted PDT was a relatively useful and effective treatment in terms of pain and comfort during treatment, with higher treatment efficacy of AK compared to classic Er:YAG laser assisted PDT. Further prospective studies with larger patient populations might be needed to clarify the treatment efficacy.

Impact of tirbanibulin 1% treatment on symptoms, emotions, and functioning of patients with Actinic Keratosis in routine clinical practices across the U.S. (PROAK Study)

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Introduction and Objectives: Actinic Keratosis (AK) has been shown to negatively affect emotional functioning and skin-related quality of life. Objective of this analysis is to evaluate changes in patient-reported AK symptoms, emotions, and functioning, among AK patients treated with tirbanibulin 1% in routine clinical practices across U.S.

Material and Methods: A single-arm, prospective cohort study (PROAK) was conducted among adult patients with AKs on the face or scalp who were newly initiated with tirbanibulin treatment as part of usual care. Patients and clinicians completed surveys and clinical assessments at baseline, Week-8, and Week-24. Skindex-16 (completed at baseline and Week-8) is a 16-items survey with 3 domains: symptoms (4 items), emotions (7 items) and functioning (5 items); each item potential score of 0 (never bothered) to 6 (always bothered); each domain score range: 0-100 (higher score indicates severe impairment). Changes from baseline in Skindex-16 scores and in proportion of patients reporting a score of 0 or 1 (never or least bothered) were analyzed.

Results: A total of 290 AK patients completed the study assessments at Week-8 (mean age: 66.3 years; female: 31.4%; history of skin cancer: 61.7%; Fitzpatrick skin type: I: 7.6%, II: 71.4%, III: 18.6%, IV: 1.4%, V: 1.0%). Patient self-reported skin-texture at baseline was 39.7% dry, 47.6% smooth, 19.7% rough, 18.6% bumpy, 35.2% scaly, 6.6% blistering/peeling. At Week-8, a statistically significant ($p < 0.0001$) decrease in scores from baseline was observed for all Skindex-16 domains (symptoms: 22.3 at baseline vs 8.2 at Week-8; emotions: 38.2 vs 13.5; functioning: 14.4 vs 4.6). Proportion of patients reporting “never or least bothered” increased significantly ($p < 0.0001$) at the items related to itching, burning/stinging, hurting, and irritation within symptoms domain; persistence of condition, worries about skin, appearance, frustration, embarrassment, being annoyed, and feeling depressed within emotions domain; and interactions with others, desire to be with others, show affection, effect on daily activities, and effect on work or enjoyable activities within functioning domain.

Conclusion: Patients with AKs who used once-daily tirbanibulin 1% treatment for 5-days reported a significant reduction in AK burden, as indicated by the improvement in AK symptoms and emotional/functional impact from baseline until Week-8.

Nicotinamide in chemoprevention of non-melanoma skin cancer and serum levels of its metabolites as predictive value for clinical response

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Introduction: Nicotinamide (NAM) is a water-soluble form of Vitamin B3 (niacin) and a precursor of nicotinamide-adenine dinucleotide (NAD⁺), which regulates cellular energy metabolism. Except for its role in the production of adenosine triphosphate (ATP), NAD⁺ acts as a substrate for several enzymes, including sirtuin 1 (SIRT1) and poly ADP-ribose polymerase 1 (PARP1). SIRT1 and PARP1 coordinate numerous physiological activities such as cell cycle, response to DNA damage and keratinocyte differentiation. For these reasons, NAM exerts a potent chemoprevention action and can inhibit the early damaging effects of UV radiation and become a strategy to prevent the recurrence of actinic keratosis (AK) and squamous cell carcinoma (SCC). We aimed to define if nicotinamide affects non-melanoma skin cancer (NMSC) chemoprevention and to establish whether specific metabolic profiles can be used as predictive value for clinical response.

Material and method: We enrolled 61 patients to evaluate the chemoprevention effect of NAM in terms of new NMSC and serum level of NAM and its metabolites, 1- methylnicotinamide (MNA), 1-methyl-2- pyridone-5- carboxamide (M2PY), 1-methyl-2- pyridone-5- carboxamide (M2PY) and vitamin D dosage as predictive value for clinical response.

Results: 61 patients followed for two years have been enrolled in this study. Systemic administration of NAM 1 gram daily results in decreasing and preventing AK and NMSC. We stratified the study population as responder and not-responder if new AKs or NMSCs arose after one year of NAM therapy. The net reduction of AK without treatment in the responder group was statistically significant. Patients who do not develop new NMSCs have higher MNA levels than patients who develop new lesions. Moreover, Vitamin D serum levels less than 30 ng/mL predispose to the onset of SCC compared to BCCs.

Conclusions: The use of NAM in the systemic chemoprevention of AK and NMSC showed a high safety profile and a clinical response regarding AK clearance. No adverse drug effects are noted in politreated patients. Moreover, MNA level seems to be a predictive marker for the development of AKs and NMSC, being able to be included in diagnostic and follow-up parameters.

Patient and clinician satisfaction with the use of tirbanibulin in the treatment of Actinic Keratosis in routine clinical practices, and likelihood to consider tirbanibulin again (PROAK study)

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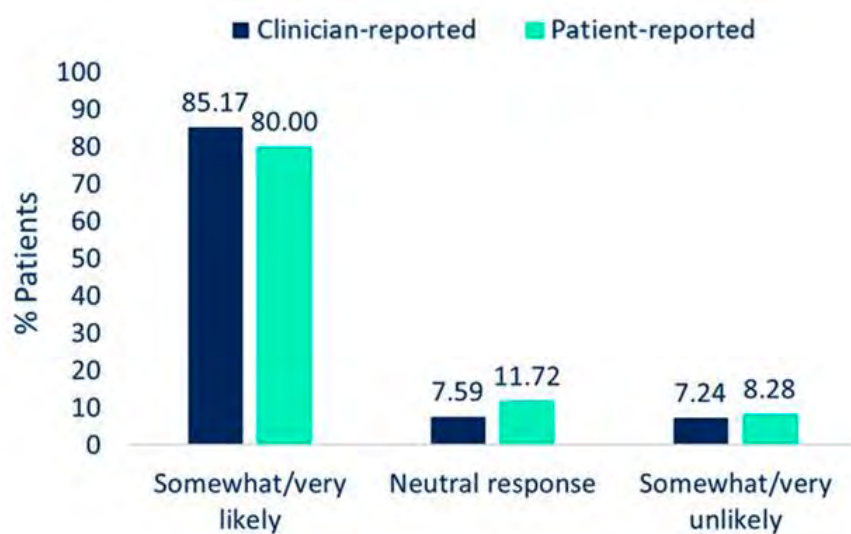
Introduction and Objectives: Actinic keratoses (AKs) are known to negatively affect emotional functioning and skin-related quality of life. The objective of this analysis was to evaluate clinician and patient satisfaction and likelihood to consider tirbanibulin in future AK treatment, among patients administered tirbanibulin in routine clinical practice across the U.S.

Material and Methods: A single-arm, prospective cohort study (PROAK: NCT05260073) was conducted in adults with AKs on the face or scalp who were newly initiated with once-daily tirbanibulin 1% ointment treatment (5-day course) as part of usual care. Patients and clinicians completed surveys and clinical assessments at baseline, Week-8 (timeframe for main endpoints), and Week-24. Patients and clinicians completed Treatment Satisfaction Questionnaire for Medication (TSQM-9) surveys at Week-8 comprising 3 domains: treatment effectiveness, convenience of use, and global satisfaction with treatment. Items within respective domains were combined and transformed into domain scores, ranging from 0 (least satisfaction) to 100 (most satisfaction). At Week-8, both patients and clinicians reported their likelihood to consider tirbanibulin as a future AK treatment. Data from Week-8 surveys are shown.

Results: A total of 290 patients with AK completed the study assessments at Week-8 (mean age: 66.3 years; female: 31.4%; history of skin cancer; 61.7%; Fitzpatrick skin type I: 7.6%, II: 71.4%, III: 18.6%, IV: 1.4%, V: 1.0%). At baseline, patient self-reported skin-texture was 39.7% dry, 47.6% smooth, 19.7% rough, 18.6% bumpy, 35.2% scaly, 6.6% blistering/peeling. All patients completed the 5-day treatment course. At W8, clinicians and patients reported similar, high levels of tirbanibulin treatment satisfaction for the 3 domains of TSQM-9 (Table 1), and a high likelihood for considering tirbanibulin treatment in the future, if need arises. (Figure 1).

Conclusion: Clinician and patient satisfaction with once-daily tirbanibulin treatment for 5-days was high at Week-8, and both clinicians and patients reported a great desire to consider tirbanibulin treatment in the future, highlighting tirbanibulin as a valuable option in treating AK lesions.

Supporting Document 1



Supporting Document 2

	Clinician-reported, mean (SD)	Patient-reported, mean (SD)
Effectiveness	76.4 (21.5)	73.0 (21.7)
Convenience of use	85.3 (14.9)	85.8 (14.3)
Global satisfaction	78.8 (20.1)	74.5 (23.5)

SD: standard deviation

Patient- and clinician-reported satisfaction with tirbanibulin to improve cosmetic outcomes in patients with actinic keratosis: an observational design (PROAK study)

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Introduction and Objectives: Actinic keratoses (AKs) are known to negatively affect emotional functioning and skin-related quality of life. The objective of this analysis was to evaluate clinician- and patient-reported satisfaction with tirbanibulin to improve the overall appearance, 'how skin looks', and 'skin texture' of skin in the treated area, among patients with AK receiving tirbanibulin in routine clinical practice across the U.S.

Material and Methods: A single-arm, prospective cohort study (PROAK) was conducted in adults with AKs on the face or scalp who were newly initiated on once-daily, 5-day course of tirbanibulin. Patients and clinicians completed surveys and clinical assessments at baseline, Week (W) 8, and W24. Clinicians and patients rated the overall appearance of the patient's skin in the tirbanibulin-treated area at W8 on a 5-point adjectival response scale of 0 (much worse), 1 (somewhat worse), 2 (no change), 3 (somewhat improved), and 4 (much improved). Clinician- and patient-reported satisfaction with tirbanibulin to improve 'how skin looks' and 'skin texture' in the treated area were assessed at W8 on a 7-point adjectival response scale of 1 (extremely dissatisfied) to 7 (extremely satisfied).

Results: A total of 290 patients with AK completed the study assessments at W8 (mean age: 66.3 years; female: 31.4%; history of skin cancer; 61.7%; Fitzpatrick skin type I: 7.6%, II: 71.4%, III: 18.6%, IV: 1.4%, V: 1.0%). Patient self-reported skin-texture at baseline was 39.7% dry, 47.6% smooth, 19.7% rough, 18.6% bumpy, 35.2% scaly, 6.6% blistering/peeling. All patients completed the 5-day treatment course. Clinicians and patients both rated the overall skin appearance after 8 weeks of tirbanibulin treatment to be mostly somewhat/much improved (Table 1). At W8, clinicians and patients reported high levels of satisfaction with tirbanibulin treatment to improve 'how skin looks' and 'skin texture' (Figure 1).

Conclusion: Both patients and their clinicians reported high improvement in the overall appearance of skin in the treated area after 8 weeks and high satisfaction with the ability of a 5-day treatment course of tirbanibulin to improve 'how skin looks' and 'skin texture'. These results highlight tirbanibulin as a valuable option for treating AK lesions.

Supporting Document 1



Supporting Document 2

	Clinician-reported %	Patient-reported %
Somewhat/much improved	91.0	84.1
No change	6.9	14.5
Somewhat/much worse	2.1	1.4

Prevalence and determinants of actinic keratosis in Europe based on the Euromelanoma campaign

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Introduction and objectives: Actinic keratosis (AK) represents the first severe sign of solar damage in the skin. AK can be defined as the precursor of cutaneous squamous cell carcinoma (SCC).¹ Despite being widespread, information on the epidemiology of AK is scarce and only derived from national surveys. Our objective was to assess the prevalence and the determinants of AK in Europe analyzing data coming from the Euromelanoma skin cancer prevention campaign.²

Materials and Methods: Participants in the Euromelanoma campaigns from 2009 to 2018 were evaluated by means of a standardized questionnaire, divided in two sections: the first to be completed by the screenees and enquiring about demographics and risk factors; the second filled in by the screening dermatologists and focused on clinical findings emerged during the visit. Prevalence of ≥ 1 AK was calculated overall and by country. Multivariate analyses were employed to find significant and independent determinants of AK.

Results: Overall, 355,255 individuals participated. Of these, 234,792 (66.9%) were females and 120,463 (33.1%) were males; median age was 45 (interquartile range 33-60) years; 47,452 (13.3%) presented ≥ 1 AK. The following emerged as significant and independent determinants of AK: male sex, age, fair skin type, sunburn during childhood/adolescence, lack of sunscreen application, having spent >1 year in a sunnier country, sunny holidays, family history for melanoma, personal history of non-melanoma skin cancer, presence of sun damage and skin lesions suspicious for skin cancer ($p < 0.001$ for all). A positive trend was detected between increasing latitude and prevalence of AKs (Fig. 1). A significant interaction between age, latitude and prevalence of AKs was also detected (Fig. 2).

Conclusions: To our knowledge, this is the first study evaluating the prevalence of AKs in Europe and exploiting data coming from the vast majority of European countries and in which a standardized tool (questionnaire) was used to gather information. The European overall crude AK prevalence was 13.3%. Several independent factors significantly influenced the AK prevalence, with interesting insights for latitude and age. This study provides valuable information to guide future prevention policies.

Supporting Document 1

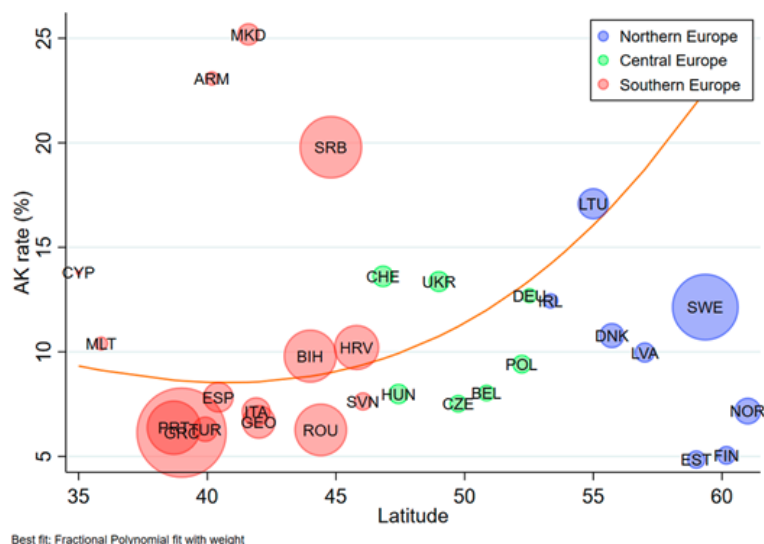


Figure 1. Positive trend between latitude and prevalence of AK.

Supporting Document 2

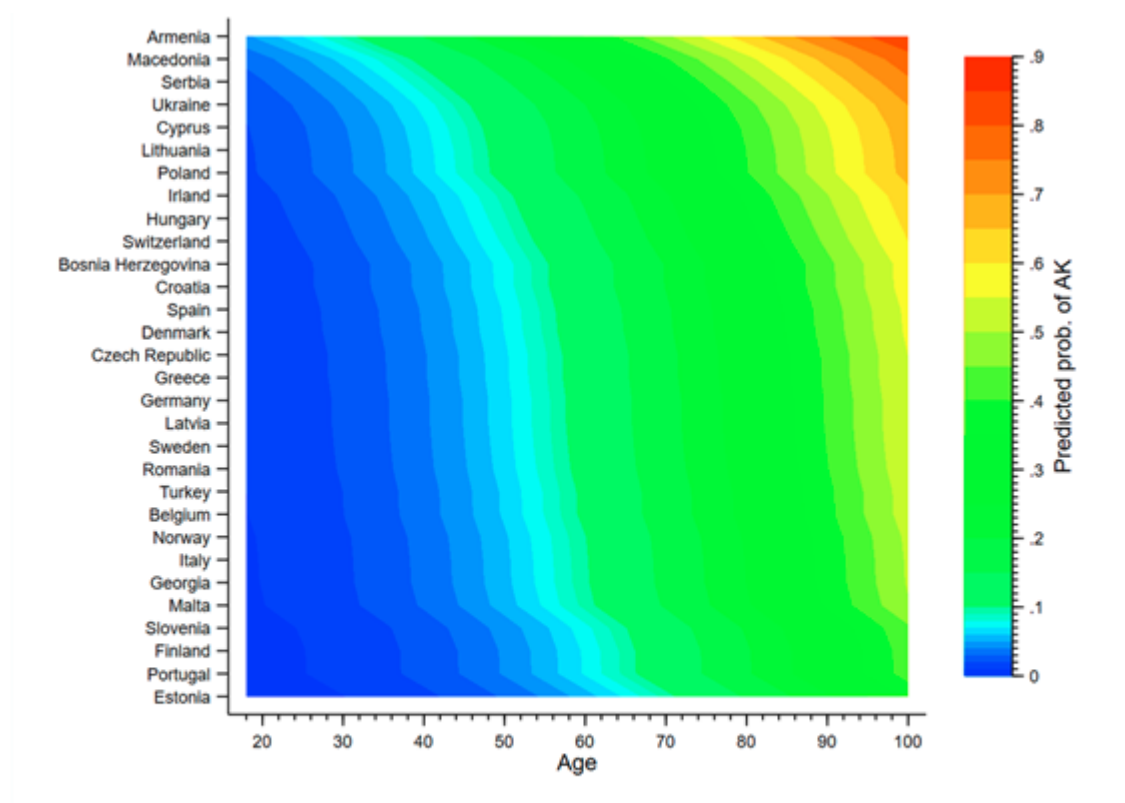


Figure 2. Predicted probability by age of AK in all countries participating in the Euromelanoma campaign ($p < 0.001$ for all).

Pulsed-dye laser followed by topical diclofenac: a promising new therapeutic approach for erosive pustular dermatosis of the scalp.

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Erosive pustular dermatosis of the scalp (EPDS) is an uncommon pustular, idiopathic disorder, typically affecting the scalp of elderly patients. High-potency topical corticosteroids are the mainstay of treatment. However, they can induce long-term side-effects like atrophy and telangiectasias. We report a case of EPDS treated with pulsed dye laser (PDL) and topical diclofenac, presenting with complete stabilization after six months of follow-up.

Case presentation: An 80-year-old man previously diagnosed with biopsy-proven EPDS consulted to the dermatology department due to cutaneous atrophy, erythema and multiple telangiectasias on the scalp. The patient had been applying topical clobetasol propionate 0.5mg/g cream daily for several months. Topical corticosteroids were stopped but EPDS recurred after three months, with persistence of cutaneous side effects.

We performed one session of PDL 7J/cm², 2ms, and spot 10mm with significant improvement of the erythema and telangiectasias. However, new hyperkeratotic lesions appeared soon after, hence, we started daily topical diclofenac 30mg/g. Six months after diclofenac initiation no signs of recurrence are present, and the patient reports the best control since disease initiation.

Discussion: EPDS is a chronic inflammatory dermatosis of unknown etiology, frequently misdiagnosed as actinic keratosis (AK). EPDS usually affects elderly men with moderate-to-severe androgenetic alopecia in heavily sun-damaged skin. Usually, it presents with eroded erythematous plaques with scattered pustules and scarring alopecia.

Multiple treatments have been reported, like high-potency corticosteroids, photodynamic therapy, dapsone, cyclosporine, among others. Of note, usual topical treatments for AKs aren't useful for EPDS and may worsen the disease. In our case, long-term use of corticosteroids induced atrophy and telangiectasias which were very bothersome to the patient. In this scenario, we performed PDL followed by daily topical diclofenac to minimize the inflammation associated with a potential EPDS flare. Diclofenac exerts its anti-inflammatory effect through COX-2 inhibition. This inhibition leads to a suppression of prostaglandin E₂ synthesis in neutrophils, and possibly an inhibitory effect on neutrophil chemotaxis. Therefore, the rationale for its use in EPDS seems reasonable since EPDS is actually a neutrophilic dermatosis associated with skin photodamage.

In conclusion, we present a novel EPDS treatment approach which needs to be tested further in larger cohorts.

Real world experience of topical tirbanibulin for the treatment of actinic keratoses Olsen grade 2 presenting as skin field cancerisation

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Introduction: Up to 80% and 30% of squamous and basal cell carcinoma (SCC and BCC) respectively, arise from a pre-existing actinic keratosis (AK). The presence of multiple AKs is often called skin field cancerisation, reflecting an increased risk for keratinocyte carcinoma. Treatment of AKs is effective at preventing keratinocyte carcinoma, particularly in patients with multiple AKs of the scalp and face, and a previous history of keratinocyte carcinoma.

Methods: This study describes the real-world experience of tirbanibulin 1% ointment use across two United Kingdom centres. Tirbanibulin was applied based on surface area as required, with one sachet (0.25g) used to treat an area of 5x5cm. Six patients were treated over a 6-month period between October 2021 and March 2022, 2 female and 4 males, with a mean age 59 year (range 43 to 83 years) and Fitzpatrick skin type I (n=1) and II (n=5).

Results: All patients had received prior treatment for AKs with; cryotherapy (n=5), topical diclofenac sodium 3% (n=2), topical 5-fluorouracil (n=4), topical imiquimod 5% (n=1), MAL-photodynamic therapy (n=0), and daylight photodynamic therapy (n=2). Five patients had a prior skin cancer history: 8 BCC (3 patients), 12 SCC (3 patients), 1 melanoma (1 patients) and in one case a pleomorphic dermal sarcoma. Two transplant recipients had been on immunosuppression for over 10 years. A total of 89 AKs, Olsen grade 2, were on the face (n=6, average number of AKs = 12) and scalp (n=2, average number AKs = 4). All completed the 5-day treatment regimen without interruption, with concomitant nicotinamide (n=1) and acitretin (n=1). Patients experienced erythema (mild=5, none=1) and scaling (mild=6), "similar to a mild sunburn", with mild soreness (n=2) and erythema (n=2) persisting for a few weeks. No swelling, erosions or crusting was observed. Complete (n=4, 39 AKs) and partial (AKs face=23 of 30, scalp=4 of 9) clearance was observed at follow-up appointments 1-5 months after treatment.

Conclusions: Tirbanibulin represents a new and novel synthetic class of therapy for the treatment of skin field cancerisation, which directly targets abnormal keratinocytes within AKs.

Safety and Tolerability of a single 5-day Treatment Cycle of Tirbanibulin Ointment 1% in Large Field (100cm²): A phase I Trial in patients with Actinic Keratosis

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Introduction and Objectives: Most topical treatments available for actinic keratosis (AK) are associated with severe skin reactions [1,2]. Tirbanibulin ointment 1% is approved in the US and Europe for the treatment of AK with demonstrated safety and tolerability when applied over a field up to 25 cm². However, patients with multiple AK lesions often require treatment of larger skin areas [3].

Material and Methods: This Phase-I maximal usage trial aimed to determine the safety, tolerability, and plasma pharmacokinetics (PK) of tirbanibulin ointment 1% (350 mg) following one 5-day treatment cycle of topical administration to a surface area of 100 cm² on the face or balding scalp in 28 adult patients with AK.

Results: Tirbanibulin applied to a field of 100 cm² showed good safety and tolerability. All treatment-emergent adverse events (TEAEs) and most tolerability signs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) were mild or moderate, similar to what was previously reported [3]. The most common treatment-related TEAEs were application site reactions. Only four severe transient erythema and flaking/scaling events occurred at day 7 or day 8 and resolved by day 29. On day 5, the overall mean (standard deviation) C_{max} was 1.06 (0.660) ng/mL and AUC was 16.2 (7.78) ng*h/mL. The systemic exposure was approximately 4-fold higher than a previous PK study when applied in a field of 25 cm² [4], consistent with the product amount increase in the treated area.

Conclusion: Tirbanibulin was safe and well tolerated, supporting a currently ongoing Phase-III study (NCT05279131) of tirbanibulin over a field of up to 100 cm².

Scientometric Analysis of Actinic Keratosis Literature Published between 1980 and 2022

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Scientometric Analysis of Actinic Keratosis Literature between 1980 and 2022

Introduction: Scientometrics also known as “Science of Science” is a popular scientific branch investigating academic literature in a certain field. Although scientometrics has been trending in recent years, to the best of our knowledge, dermatology literature lacks a comprehensive scientometric assessment of the publications on actinic keratosis. In this study, we aimed to evaluate the scientometric features of the actinic keratosis (AC) literature covering the 1980–2022 period.

Materials and Methods: In this study, all data were obtained from Web of Science (WoS, Clarivate Analytics) databases. The keyword “actinic keratosis” was used for the basic search line and the time interval between 1980 and 2022 was chosen.

Results: A total of 5459 documents were found to be indexed between 1980 and 2022 in WoS databases. Full-text articles covered 65.98% of all literature (3602 items) followed by reviews, meeting abstracts, letters, editorial materials, and proceeding papers (n=651, 558, 291, 223, and 155 documents, respectively). The most studied fields were Dermatology, Oncology, Surgery, General Medicine, and Pharmacology (64.664, 9.599, 7.034, 4.195, and 4.067%; respectively).

The USA was noted as the leading country with 1704 documents followed by Germany, Italy, Spain, and the UK (n=888, 508, 349, and 325 items; respectively, Figure). The most productive institutions in AC literature were the Free University of Berlin (Germany), the University of California System (USA), and the Humboldt University of Berlin (Germany) (n=171, 167, and 166 documents; respectively) (Table).

The H-index of AC literature was measured as 136 and the total number of citations on published AC documents was 60,291 (56,015 without self-citations). The average citations per item were calculated as 23.32 and the most cited manuscript was a review titled “The present and future role of photodynamic therapy in cancer treatment” written by Brown SB et al. published in 2004 (n=1402 citations in total).

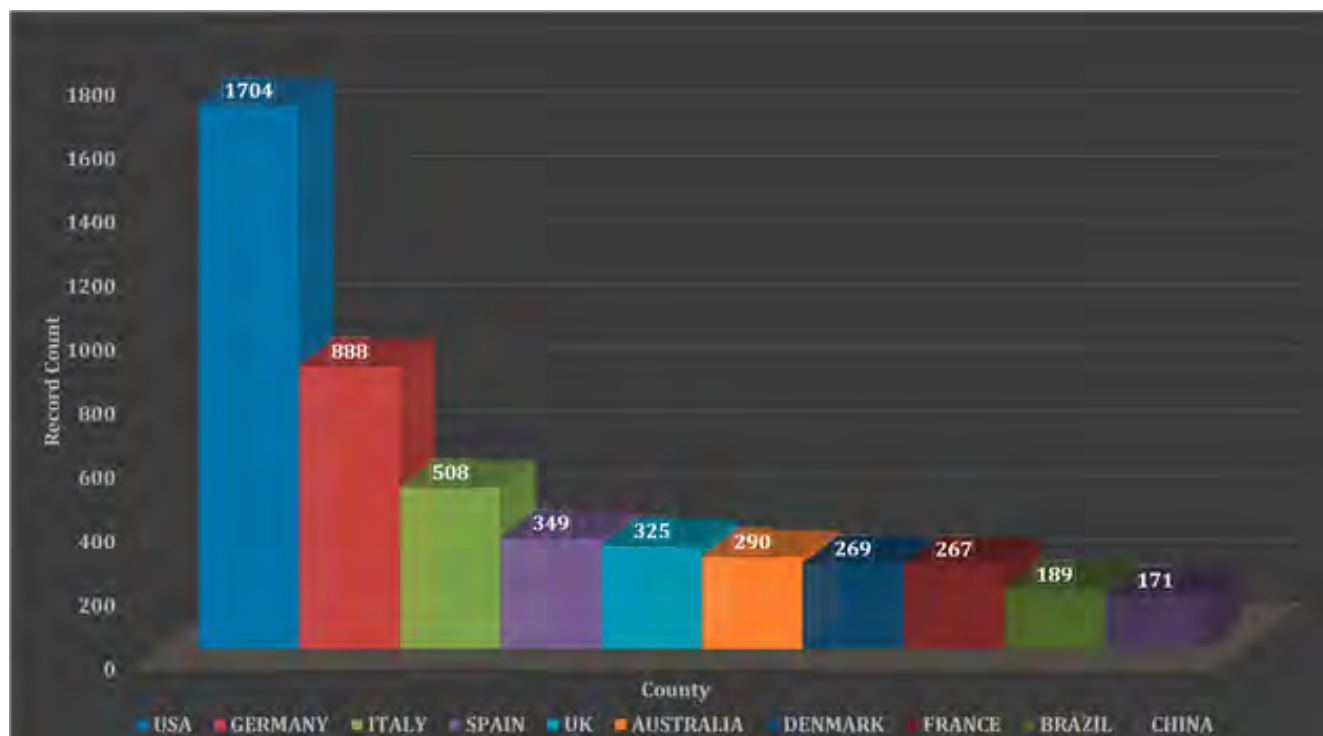
Supporting Document 1

Table 1. Top ten document types, research areas, source titles, authors, and organizations in actinic keratosis literature a

		Record count	% ^a
Document Type			
Original Article		3,602	65.983
Review		651	11.925
Meeting Abstract		558	10.222
Letter		291	5.331
Editorial Material		223	4.085
Proceeding Paper		155	2.839
Book Chapters		102	1.868
Correction		17	0.311
News Item		15	0.275
Note		12	0.220
Research Area			
Dermatology		3,530	64.664
Oncology		524	9.599
Surgery		384	7.034
General Medicine		229	4.195
Pharmacology		222	4.067
Pathology		202	3.700
Molecular Biology		167	3.059
Experimental Medicine		122	2.235
Biophysics		92	1.685
Optics		92	1.685
Journal Name			
British Journal of Dermatology		395	7.236
Journal of the American Academy of Dermatology		356	6.521
Journal of the European Academy of Dermatology and Venereology		220	4.030
Journal of Investigative Dermatology		214	3.920
Dermatologic Surgery		143	2.620
Photodiagnosis And Photodynamic Therapy		111	2.033
Journal Of Drugs in Dermatology		103	1.887
Journal Der Deutschen Dermatologischen Gesellschaft		99	1.814
International Journal of Dermatology		87	1.594
Lasers In Surgery and Medicine		85	1.557
Organizations	Country		
Free University of Berlin	Germany	171	3.132
University Of California System	USA	167	3.059
Humboldt University of Berlin	Germany	166	3.041
University Of Copenhagen	Denmark	165	3.023
Charite Universitätsmedizin Berlin	Germany	164	3.004
University Of Texas System	USA	129	2.363
Harvard University	USA	125	2.290
Bispebjerg Hospital	Denmark	103	1.887
Leo Pharma	Denmark	103	1.887
Icahn School Of Medicine at Mount Sinai	USA	100	1.832
Total		5,459	100

^a Total percentage may exceed 100% because certain items were included in more than one category.

Supporting Document 2



Src inhibition blocks HPV8 induced skin field cancerisation

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Introduction: Actinic keratoses (AKs) precede 80% of squamous cell carcinoma and 30% of basal cell carcinoma and therefore represent an essential therapeutic target to prevent the rising burden of keratinocyte carcinoma.

Objective: Determine the biological basis for AK.

Materials and Methods: Regulatory approval allowed the study of wild type and 9 transgenic models and recruitment of 443 immunocompetent individuals with AK.

Results: Conventional histology determined epidermal koilocytes in 44% of AK cases. Detailed genotyping of a subset of AK (n=79) identified HPV8 in only those AK with koilocytes (n=42), but not those without (n=37). Using the lineage tracing HPV8 complete early region mouse (HPV8tg) models we show that the coloured clones emanate from the Lrig1+ hair follicle junctional zone keratinocyte stem cell (HFJZKSC) population expansion, but not the classical bulge KSC, to give rise to both infundibulum and perifollicular epidermal keratinocytes (n=7). Warthin-Starry staining showed that the expanded population had no melanin “cap”. To determine the HPV8 associated signalling pathway leading to UV sensitive epidermal KSC expansion, we undertook paired RNA sequencing of HPV8tg flow sorted skin for Lrig1 and bulge KSC. Bioinformatic analysis using IPA, identified transcriptional regulators cMYC in wild type but STAT3 in HPV8tg mice (n=6, p<0.01). In addition to in vitro and in vivo validation experiments, unlike the HPV8tg the STAT3+/-:HPV8tg cross did not exhibit HFJZKSC proliferation, develop spontaneous papilloma nor SCC. To study the upstream pathway, we identified HFJZKSC proliferation and expansion in the HPV8 mouse model with the single early region gene E6, but not E2, E4 and E7 (n=30). We found that E6 bound p300, which in turn activated STAT3 leading to transcriptional activation of the KSC regulator of proliferation NP63. Having established the signalling pathway, which we believe represents the cellular basis for HPV8 associated AK, we found that HFJZKSC expansion could be blocked by Src, Jak and STAT3 inhibitors.

Conclusions: Collectively our findings define the mechanism for HPV8 associated skin field cancerisation, wherein HFJZKSC are displaced into the perifollicular epidermis without melanin protection and are amenable to Src inhibition.

A New Approach for In Vivo Skin Cancer Diagnostics – Laser Induced Plasma Spectroscopy Combined with Deep Learning-based Diagnostic Algorithm

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Introduction and Objectives: There have been many attempts to develop and apply in vivo skin cancer diagnostic methods based on different technologies, such as multi-spectral imaging, reflectance confocal microscopy, optical coherence tomography, Raman spectroscopy and electrical impedance spectroscopy. However, they have insufficient diagnostic accuracy for clinical use, resulting in none of the aforementioned technologies are widely used as reliable skin cancer diagnostic method in clinical settings.

We investigated the diagnostic accuracy and safety of a real-time noninvasive in vivo skin cancer diagnostics utilizing non-discrete molecular LIPS combined with a deep neural network (DNN)-based diagnostic algorithm.

Materials and Methods: Laser-induced plasma spectroscopy (LIPS) can noninvasively extract biochemical information of skin lesions using an ultrashort pulsed laser. A Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG) laser with a wavelength of 1064 nm and pulse duration of 4 ns was used to irradiate the skin tissue and generate microplasma plumes. The microplasma emission induced from the tissue was collected and delivered to the optical fiber (Fig 1). A total of 353 patients were recruited for this study. In vivo LIPS spectra were acquired from 296 skin cancers (186 BCCs, 96 SCCs and 14 melanomas) and 316 benign lesions in a multisite clinical study. The diagnostic performance was validated using 10-fold cross-validations. For each round, an average of 7,731 and 859 spectral data points were used for training and testing respectively.

Results: The sensitivity and specificity for differentiating skin cancers from benign lesions using LIPS and the DNN-based algorithm were 94.3% (95% CI: 91.6 – 96.9%) and 88.6% (95% CI: 85.1 – 92.1%), respectively. The area under the curve (AUC) of the receiver operating characteristic (ROC) was recorded to be 0.955. No adverse events, including macroscopic or microscopic visible marks or pigmentation due to laser irradiation, were observed.

Conclusions: The LIPS and deep learning-based skin cancer diagnostic device can be an objective tool to assist medical professionals for the evaluation of suspicious lesions and the decision for biopsy. This study shows promising opportunities for an accurate, real-time, in vivo skin cancer diagnostics in real clinical settings.

Advanced periocular basal cell carcinoma treated with sonidegib: our experience in a tertiary referral hospital

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Introduction and Objectives: Basal cell carcinoma (BCC) is the most common cancer in the world. Regarding location, 80% of BCCs develop over the head and neck and 20% involve the eyelids.

Primary treatment of BCC is surgery, but there is no effective therapy for locally advanced or infiltrative BCC. Inhibition of the Hedgehog (Hh) signaling pathway is among the few treatment options available for patients with advanced BCCs.

In this poster we describe our experience with sonidegib for advanced BCC involving a complex location such as the periocular region.

Materials and Methods: We present a series of 6 patients diagnosed with locally advanced periocular BCC who, following a decision by a multidisciplinary committee, were started on sonidegib. We analysed the variables age, sex, location, previous treatments, drug dose, adverse effects and clinical response. Patients underwent periodic follow-up with analytical control.

Results: We included 5 women and 1 man with a mean age of 88 years diagnosed with advanced periocular BCC who started sonidegib 200mg daily between November 2022 and February 2023. The most frequent locations were the lower eyelid and inner canthus. In most cases patients had been previously treated with surgery. One patient had self-limited CK elevation that did not lead to discontinuation. No other adverse effects were reported.

Conclusions: The periocular region is a delicate territory with a challenging surgical management including the risk of functional compromise. Sonidegib has already demonstrated its efficacy in other areas, although the evidence in the periocular region is still limited. We report our experience with sonidegib 200mg daily in this series of cases showing rapid responses after introduction of the drug, with acceptable tolerability and no associated adverse effects requiring discontinuation or change of regimen.

Anti-PD1 antibody cemiplimab combined with pulsed hedgehog inhibitor sonidegib in advanced basal cell carcinoma

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Introduction and Objectives: Basal cell carcinoma (BCC) is the most common skin cancer and is driven by genetic alterations in the hedgehog (HH) pathway. BCC has a high tumor mutational burden, despite this, BCC has little or no immune-cell infiltration. Local therapies are curative in most BCCs, however in advanced cases systemic therapy is needed. HH inhibitors (HHI) are effective, yet some tumors progress. Immunotherapy with the antiPD1 antibody demonstrated a 30% RR after HHI therapy in BCC. As HHI increases the immune-cell infiltration and, potentially, immune-susceptibility of the BCC, we initiated a clinical trial to investigate the combination of anti-PD1 antibody cemiplimab and HHI sonidegib in patients with advanced BCC (NCT04679480).

Materials and Methods: Patients with advanced BCC deemed unlikely to benefit from HHI monotherapy are eligible for this open label, single-arm, phase II clinical trial. A 2-week run-in with sonidegib is followed by cemiplimab (q3w) and pulsed dosing sonidegib (2w on, 2w off) for up to 26w. Primary endpoint is best response between treatment start and 26w by immune-related response criteria. Secondary endpoints are response at 26w, safety and immunologic changes in biopsy assessable tumors.

Results: Twelve patients (pts) have been included into the trial so far. Mean age is 74yrs (range, 57-88yrs). Six pts were enrolled with multiple BCCs, three with metastatic BCC and three with locally advanced BCC. Nine pts had prior skin cancer; three pts with locally advanced BCC had no prior skin cancer. Three pts had concurrent hematologic malignancy. Ten pts have completed the trial, one patient is still ongoing treatment and one patient has died during the run-in phase due to a treatment-unrelated cause. Best response was CR in one patient, PR in 6 pts and SD in 3. All pts have developed treatment related adverse events (trAE), most commonly muscle cramps (9/12pts), CPK increase (7/12pts), fatigue (4/12pts), lichenoid dermatitis (4/12pts), diarrhea (4/12pts), pruritus (3/12pts) and dysgeusia (3/12pts). 3.4% of trAEs were grade 3-4.

Conclusions: The combination of antiPD1 antibody and pulsed HHI is tolerable in patients with multiple comorbidities and shows efficacy signals. Longer follow-up is required.

CemiplimAb-rwlc Survivorship and Epidemiology (C.A.S.E.): A prospective study of the safety and efficacy of cemiplimab in patients with advanced basal cell carcinoma in a real-world setting (trial in progress)

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Introduction and objectives: Basal cell carcinoma (BCC) is the most common form of non-melanoma skin cancer in the United States. Surgical excision is the standard treatment, with <1% of cases progressing to locally advanced or metastatic disease. Hedgehog pathway inhibitors (HHIs) are the first-line therapy for advanced BCC (aBCC): the US Food and Drug Administration and European Medicines Agency have approved the use of cemiplimab (a programmed cell death-1 inhibitor) in advanced BCC patients previously treated with, or who are inappropriate for, HHI.

Limited real-world data exist on the clinical characteristics, disease management and progression, and survivorship of patients with aBCC. The ongoing C.A.S.E. study aims to evaluate the efficacy, safety, disease evolution, survivorship, and patient reported outcomes (PRO) in patients treated with cemiplimab in the real-world setting.

The aim of this trial in progress (NCT03836105) is to describe the effectiveness and safety of cemiplimab 350 mg administered every 3 weeks for treatment of patients with aBCC in real-world clinical settings.

Materials and methods: Up to 100 adult patients with aBCC who are prescribed commercially available cemiplimab from ~65 study sites in the United States will be included. The duration of follow-up will be 24 months. Endpoints for this study relate to real-world efficacy, including overall survival, progression-free survival, objective response rate (partial or complete response), and disease control rate, defined as the percentage who do not progress for ≥ 6 months. Time to response, duration of response, time to treatment failure, and disease-specific death will also be assessed.

Real-world safety outcomes will be captured, including immune-related adverse events, infusion-related reactions, and serious adverse events. Patient selection criteria and treatment patterns will be analyzed using descriptive statistics. This study also aims to describe the patient experience of real-world treatment with cemiplimab. Patient-reported outcomes (PROs) including global quality of life, functioning, and symptoms will be captured at baseline and follow-up visits using the EORTC QLQ-C30 and the Skin Care Index.

Results: Results are not yet available for this trial-in-progress; recruitment is ongoing.

Clinical characteristics of an Italian patient population with advanced Basal Cell Carcinoma and real-life evaluation of Hedgehog inhibitors safety and effectiveness

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Introduction and Objectives: Advanced basal cell carcinoma (aBCC) represents a complex and clinically heterogeneous group of lesions for which curative surgery and/or radiotherapy is unlikely¹. Systemic therapy with hedgehog pathway inhibitors (HHI) changed the treatment landscape for this complex patient population²⁻⁵.

We describe the clinical characteristics of a real-life Italian cohort diagnosed with aBCC, and we investigate effectiveness and safety of HHI.

Materials and Methods: a multicenter ambispective observational study was performed by twelve Italian centers in the period January 1, 2016 – August 1, 2023. Patients aged ≥ 18 years and diagnosed with aBCC (locally advanced and metastatic BCC) were eligible for the study. Methods for investigating tumor response to HHI included clinical and dermatoscopic evaluation, radiological imaging, and histopathology. For HHI safety assessment, therapy-related adverse events (AEs) were reported and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: 220 aBCC patients were included, of which 178 underwent treatment with HHI: 126 (70.8%) and 52 patients (29.2%) received sonidegib and vismodegib, respectively. Comprehensive data on HHI effectiveness and disease outcome was available for 132 (74.1%) of 178 patients: 129 patients had a diagnosis of locally advanced BCC (laBCC) (n=84, sonidegib; n=45, vismodegib), and 3 patients of metastatic BCC (mBCC) (n=2, vismodegib; n=1, sonidegib, off-label). Objective response rate (ORR) was 76.7% (95% CI: 82.3-68.7) and 33.3% (95% CI: 88.2-1.7) for laBCC (CR: 43/129; PR: 56/129) and mBCC (CR: 0/3; PR: 1/3), respectively (Table 1). High-risk aBCC histopathological subtypes and occurrence of >2 therapy-related AEs were significantly associated with non-response to HHI therapy [(OR: 2.61; 95% CI: 1.09-6.05; p:0.03) and (OR: 2.74; 95% CI: 1.03-7.9; p:0.04)], respectively.

We recorded 309 therapy-related AEs in 97 patients (54.5%), Table 2. Muscle spasms were the most common (n=86, 27.9%) AE, followed by ageusia and/or dysgeusia (n=82, 26.2%), alopecia (n=45, 14.6%) and weakness (n=37, 12%). Toxicities were mostly mild to moderate in severity [CTCAE grade 1, 50% (n=156); CTCAE grade 2, 30.2% (n=93)].

Conclusions: our results demonstrate the effectiveness and safety profile of HHI and confirm the reproducibility of pivotal trial results in real-life clinical setting.

Supporting Document 1

Best response N (%)	All patients (N=132)	LaBCC (N=129)	mBCC (N=3)	Vismodegib (N=47)	Sonidegib (N=85)
CR	43 (32.6)	43 (33.3)	0 (0)	7 (14.9)	36 (42.3)
PR	57 (43.2)	56 (43.4)	1 (33.3)	23 (48.9)	34 (40)
SD	25 (18.9)	24 (18.6)	1 (33.3)	12 (25.6)	13 (15.3)
PD	7 (5.3)	6 (4.7)	1 (33.3)	5 (10.6)	2 (2.4)
ORR (95% CI)	75.8 (82.3-67.8)	76.7 (83.2-68.7)	33.3 (88.2-1.7)	63.8 (76-49.5)	82.4 (89-72.9)
DCR (95% CI)	94.7 (97.4-89.5)	95.3 (97.9-90.2)	66.7 (98.3-11.8)	89.4 (95.4-77.4)	97.6 (99.6-91.8)

CI, confidence interval; CR, complete response; DCR, disease control rate; LaBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; N, number; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Supporting Document 2

	AEs (N=309), N (%)	Sonidegib (N=168), N (%)	Vismodegib (N=141), N (%)
CTCAE grade 1-2	249 (80.6)	139 (82.7)	110 (78)
CTCAE grade 3-5	60 (19.4)	29 (17.3)	31 (22)
Muscle spasms	86 (27.9)	51 (30.3)	35 (24.8)
Dysgeusia/ageusia	82 (26.2)	45 (26.7)	37 (26.3)
Alopecia	45 (14.6)	19 (11.3)	26 (18.4)
Weakness	37 (12)	21 (12.5)	16 (11.4)
Nausea/Vomit	12 (3.9)	6 (3.6)	6 (4.3)
Anorexia	12 (3.9)	0 (0)	12 (8.5)
Weight loss	11 (3.6)	8 (4.8)	3 (2.1)
Diarrhea	7 (2.3)	3 (1.8)	4 (2.8)
Increase in CPK enzyme	6 (1.9)	5 (3)	1 (0.7)
Other	11 (3.6)	10 (6)	1 (0.7)

AEs, adverse events; CPK, creatinine phosphokinase; CTCAE, common terminology criteria for adverse events; N, number

Table 2: Safety outcomes of HHI therapy

Clinical features and outcomes of advanced basal cell carcinoma.

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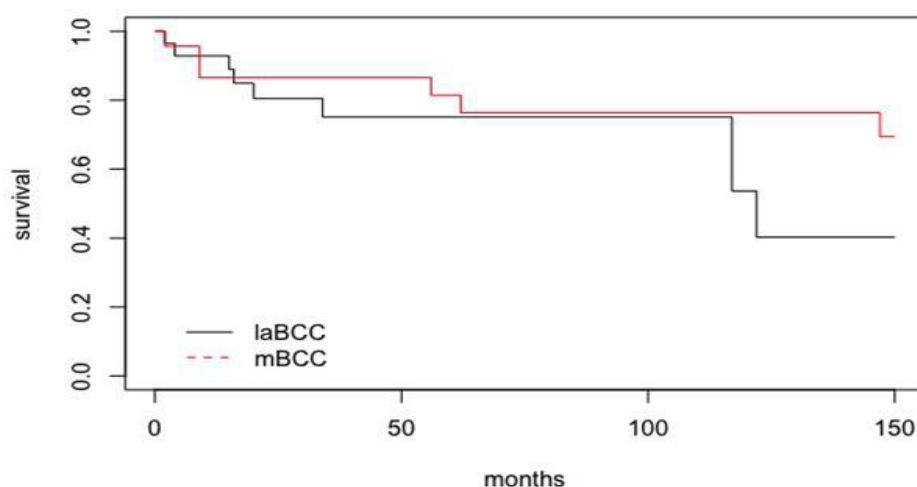
Introduction and Objective: Cutaneous basal cell carcinoma (BCC) is a mostly indolent tumour that is easily cured. However, locally advanced BCCs (laBCC) present a therapeutic challenge, and while metastatic behavior is rare, the prognosis is poor. The aim of this study is to report the characteristics and clinical course of laBCC and metastatic BCC (mBCC).

Materials and Methods: A retrospective cohort study was conducted at a tertiary oncological hospital over a 32 year period to identify all laBCCs and mBCCs. LaBCC was defined as a non-metastasized BCC, that was either locally irresectable, staged T3 following the AJCC 8th edition, or a giant BCC (gBCC) measuring 5cm or larger. Patient-, tumour-, and clinical outcome characteristics were recorded.

Results: Fifty-one patients were included, 23 mBCC and 28 laBCC, with a median follow-up of 34 months. Thirty-five patients were men (69%), with a mean age of 72 years. Most primary BCCs were located in the head-and-neck (30, 59%), and were primarily treated with surgery (78%). Eleven laBCC occurred in a recurrent tumour (39%). Giant BCC was seen in 18 laBCC (64%) and a large subset was larger than 9cm. Of laBCC, 50% experienced local recurrence after resection after median 16 months, which was seen in 35% of mBCCs after median 29 months. Median time to metastasis was 33 months. First metastasis presentation included locoregional nodal metastasis in 78% of mBCC. Most patients developed nodal metastases only (70%), but 26% developed oligometastasis, mostly to the lungs, bones, or both. Fifteen patients died during follow-up (29%), of which 7 of BCC (3 laBCC, 4 mBCC). Median overall survival (OS) was 49 months. Five year OS was 79% for laBCC and 83% for mBCC.

Conclusion: Advanced BCC was mostly seen in the head-and-neck area, in male patients. Treatment of laBCC and mBCC consists predominantly of surgery, but tumour recurrence was high in all advanced BCCs. When metastasized, locoregional lymphnodes were primarily involved, but oligometastasis was seen in 26%. Prognosis of advanced BCC is relatively poor, highlighting the need for better follow-up strategies and treatment options for these patients.

Supporting Document 1



Supporting Document 2

Table 1. Clinical outcomes of advanced BCC

	All patients n = 51	laBCC n = 28	mBCC n = 23
Local recurrence n (%)	22 (43%)	14 (50%)	8 (35%)
Metastasis n (%)	23 (45%)	-	23 (100%)
First metastasis type n (%)		-	
Nodal	16 (31%)		16 (70%)
Subcutaneous	3 (6%)		3 (13%)
Visceral	2 (4%)		2 (9%)
Nodal + visceral	1 (2%)		1 (4%)
Nodal + subcutaneous	1 (2%)		1 (4%)
Locoregional n (% of metastases)	21 (91%)	-	21 (91%)
All metastases n (%)		-	
Nodal only	13 (25%)		13 (56%)
Subcutaneous only	2 (4%)		2 (9%)
Visceral only	2 (4%)		2 (9%)
Nodal + visceral	3 (4%)		3 (13%)
Nodal + subcutaneous	2 (4%)		2 (9%)
Subcutaneous + visceral	1 (2%)		1 (4%)
Overall survival			
Died n (%)	15 (29%)	9 (32%)	6 (26%)
5 year OS (%)	80.4%	79%	83%
Disease specific survival			
Died of BCC n (%)	7 (14%)	3 (11%)	4 (17%)
5 year DSS (%)	92%	93%	91%

Complete response of metastatic cutaneous squamous cell carcinoma and multiple locally advanced basal cell carcinomas with concomitant pembrolizumab and sonidegib therapy

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Introduction: The treatment of patients with metastatic squamous cell carcinoma (SCC) who also have multiple locally advanced basal cell carcinomas (BCC) can be challenging and requires multidisciplinary management. A previous report described a patient treated with sequential cemiplimab and sonidegib with complete response of both tumors and good tolerance. In this case report, we present our clinical experience with concomitant treatment with pembrolizumab and sonidegib in a patient with metastatic SCC and multiple locally advanced BCCs.

Case report: A 73-year-old man with a history of occupational exposure to different substances from an electrical resistance factory and multiple BCCs since the age of 40, was referred to our center for evaluation of keratinocyte carcinomas. Following our assessment, 18 BCCs were clinically and histologically diagnosed located mainly on the head and trunk. Three of them were locally advanced with a diameter greater than 5 cm, ulcerated and invading deep structures. In addition, the patient was diagnosed with a left cervical poorly differentiated SCC with cervical and axillary lymph nodes and pulmonary metastases (T2N3M1, AJCC 8th edition).

The interdisciplinary tumor board (ITB) decided to initiate pembrolizumab at a dose of 200 mg every 21 days for the treatment of both, the metastatic SCC and the multiple BCCs. The patient presented a rapid response of the lung metastases after two months but with lymph node pseudoprogression. After 7 months the patient had an excellent tolerance (minimal arthralgia) and almost complete response of the SCC, however the response of BCC was very modest. The ITB decided then, to add sonidegib 200 mg daily for the treatment of the BCCs, presenting a clinical complete response after 4.5 months of treatment. It was then discontinued due to transient elevation of transaminases. As the complete response was confirmed by histological examination, sonidegib was not reinitiated and the patient is still maintained on treatment with pembrolizumab.

Conclusions: To our knowledge, we present the first patient treated concomitantly with pembrolizumab and sonidegib achieving a complete response in both SCC and BCC and with good overall tolerance.

Efficacy and safety of sonidegib to treat an advanced basal cell carcinoma in a liver transplant recipient

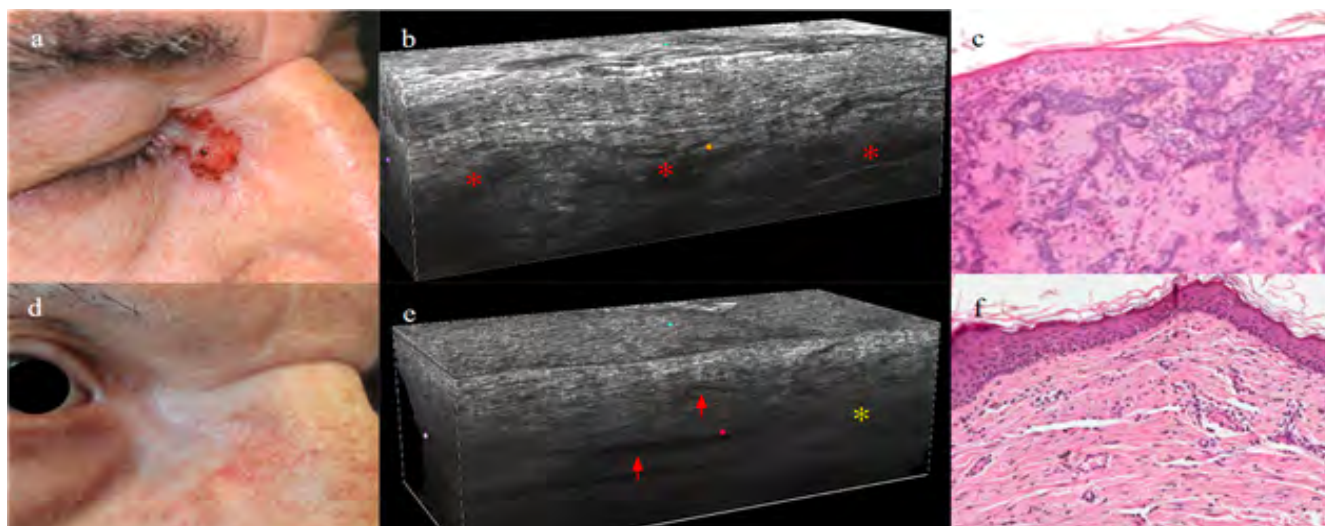
Dr Alfredo Piccerillo, MD SIMONE CAPPILLI, MD Alessio Constantini, Prof Ketty Peris, Dr Alessandro Di Stefani

A 69-year-old male who had received liver transplantation since 2017 was referred to the dermatology department for the rapid growth in about 8 months of a large ulcerated lesion on the right eye during treatment with everolimus 1.25 mg twice/daily. Physical examination showed an ulcer with a slightly central depressed fibrotic area and ill-defined margins, measuring 1 cm x 1.5 cm in size, located on the medial canthus, and upper and lower palpebral areas of the right eye. Dermatoscopic examination showed ulceration, arborizing vessels and scar-like areas. Skin lesion was then imaged by Line-field confocal optical coherence tomography (LC-OCT), revealing bright strands in the superficial dermis, highly suggestive for an infiltrative basal cell carcinoma (iBCC). Several incisional biopsies followed by histopathologic examination confirmed the diagnosis, showing cords of basaloid cells that extend downwards from the epidermis and create a fenestrating pattern. Magnetic resonance imaging (MRI) of head and neck, revealed superficial ulceration and subcutaneous surface irregularities; no pathological changes were detected in deep soft tissues and along the periosteum of the nasal bones.

The multidisciplinary tumor board chose treatment with sonidegib, a systemic hedgehog inhibitor (HHI) since curative surgery and/or radiotherapy were considered not feasible. The patient was treated with sonidegib, 200 mg every other day, due to the potential interaction with everolimus. The patient experienced mild adverse events including grade 1 muscle cramps and grade 1 alopecia within the first month and after 2 months, that did not lead to discontinuation of therapy. A complete clinical response, as assessed by dermatoscopy, LC-OCT, histopathology and MRI of head and neck, was obtained after 7 months when the treatment was stopped. After 2 months of follow up complete clinical response was maintained.

In conclusion, the treatment of advanced BCC in organ transplant recipients (OTRs) is still a challenge and data on the use of HHIs in this population are limited. The efficacy and safety of sonidegib shown in our patient suggest that this drug might be successfully used in this fragile population, even with alternating dose.

Supporting Document 1



Health-related quality of life in patients with metastatic basal cell carcinoma treated with cemiplimab: Analysis of a Phase 2 open-label clinical trial

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Introduction and Objectives: Cemiplimab is approved in the US and Europe for patients with locally advanced basal cell carcinoma (laBCC) and metastatic basal cell carcinoma (mBCC) following hedgehog inhibitor (HHI) treatment or, in the US, for whom HHIs are not appropriate. In a Phase 2 clinical trial (NCT03132636), cemiplimab demonstrated an objective response rate of 24.1% (95% confidence interval [CI] 13.5–37.6%) in patients with mBCC who progressed on or were intolerant to HHIs. Efficacy and health-related quality of life (HRQoL) data for patients with laBCC were previously reported. This analysis evaluated HRQoL in patients with mBCC.

Materials and Methods: Adults with mBCC received cemiplimab 350 mg intravenous every 3 weeks for up to 9 treatment cycles. At baseline and Day 1 of each cycle, patients completed the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 (QLQ-C30) and Skindex-16 questionnaires. Mixed-effects repeated-measures models were used to estimate overall least-squares (LS) mean (95% CI) change from baseline across Cycles 2–9. Changes ≥ 10 points were considered clinically meaningful. Responder analyses determined the proportion of patients with clinically meaningful improvement, maintenance, or deterioration on all scales.

Results: Baseline scores showed moderate to high levels of functioning and low symptom burden. Overall LS mean changes from baseline indicated maintenance for QLQ-C30 global health status/quality of life (GHS/QoL), functioning, and symptom scales. In the responder analysis, clinically meaningful improvement or maintenance on GHS/QoL, functioning, and symptoms scales were reported at Cycle 2 by 77%, 77–86%, and 70–93% of patients, respectively. Similar proportions were reported at Cycle 6 (~1 year of treatment), with consistent results at Cycle 9 except for fatigue. On the Skindex-16, overall changes from baseline showed maintenance on emotional, symptom, and functional subscales. Responder analysis showed clinically meaningful improvement or maintenance across all three subscales in 76–88% of patients at Cycle 2 that were generally maintained at Cycles 6 and 9.

Conclusions: Most patients with mBCC treated with cemiplimab reported maintenance in GHS/QoL and functioning while maintaining low symptom burden.

Clinical Trial Identification: NCT03132636

Hedgehog Inhibitors (HHI) in the management of multiple BCCs in patients with nevoid basal cell carcinoma syndrome: a single centre evaluation of Sonidegib efficacy after Vismodegib discontinuation.

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Background: Nevoid basal cell carcinoma syndrome (NBCCS) is a rare genetic condition characterized by the early development of numerous cutaneous basal cell carcinomas (BCCs). Although most BCCs are surgically treated with total resection, some of these lesions may proceed to a locally advanced or metastatic stage. Systemic treatment with a HHI, such as Vismodegib or Sonidegib, is indicated in this population.

Methods: We report the case of two patients with confirmed diagnosis of NBCCS. Both patients previously underwent multiple surgical excisions and have been treated with oral Vismodegib 150 mg/day for a locally advanced tumor. They both discontinued the therapy due to its specific adverse effects (AEs) and they are now being treated with oral Sonidegib with better tolerability and complete response. Case 1: 54-year-old male with NBCCS evaluated for a tumor located on the left nasal fold and multiple BCCs on the back, previously treated with Vismodegib 150mg/day for 13 months and discontinued for AEs such as G2 muscular cramp, G2 alopecia, and moderate dysgeusia now under treatment with Sonidegib 200mg/day with overall complete response (CR) and no drug-related AEs; Case 2: 74-year-old woman referred to our clinic for diffuse spreading BCCs located on the back treated with Vismodegib 150 mg/day for 36 months then halted due to its specific AEs, specifically G2 alopecia, G2 muscular spasm, G1 dysgeusia, and nausea now under treatment with Sonidegib 200mg/day with overall (CR) and no drug-related AEs.

Discussion: Antagonistic effect on Hedgehog signaling is a major treatment possibility for patients with locally advanced, metastatic BCCs as well as NBCCS patients who have a high risk of developing numerous BCCs throughout their lives. The half-life of Sonidegib is longer than that of Vismodegib, but both Vismodegib and Sonidegib have strong overlapping class-dependent AEs. However, In the case of Sonidegib, dose adjustments are viable options for reducing the need for treatment discontinuation without jeopardizing its specific efficacy.

Conclusions: Sonidegib should be considered in all respects a first line treatment for patients with NBCCS not amenable for surgery or radiotherapy, and for sure a second line option in patients previously treated with other HHI.

HHIs for laBCC: long term assessment by means of LC-OCT

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Prof Ketty Peris¹, Dr Alessandro Di Stefani¹**

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Introduction: The risk of locally advanced basal cell carcinoma(laBCC)-recurrence after discontinuation of treatment with Hedgehog inhibitors (HHIs) remains significant. Cicatricial areas may be difficult to evaluate by clinical and dermoscopy alone.

Line-field confocal optical coherence tomography (LC-OCT) is a novel, non-invasive in-vivo technique with an increasing literature reporting its potential diagnostic in epithelial skin cancer. The aim of this study was to evaluate whether LC-OCT may contribute to non-invasively assess laBCC response in patients treated with HHI.

Materials and Methods: LC-OCT was performed in 12 patients who obtained a complete clinical response after sonidegib 200 mg daily therapy. LC-OCT was performed on the whole primary tumor site to confirm the therapeutic success and was further performed after 6-month follow-up to confirm the absence of recurrency. Histological assessment confirmed diagnosis.

Results: Both LC-OCT and histological examination confirmed a complete response in all patients. At 6-months follow-up clinical/dermoscopic features indicative of BCC-recurrence were not recognized in all patients, although LC-OCT examination in patients discontinuing treatment detected early subclinical recurrence in 50% (n=2) of them. In 100% (n=8) of our sample staying on therapy, LC-OCT confirmed therapeutic success.

Conclusion: LC-OCT allowed the detection of subclinical BCC-recurrence after complete clinical response and was a useful tool in choosing the site for performing histological examination and confirm BCC recurrency. Patients with early recurrences in cosmetically sensitive areas, such as the periocular and nasal region, that might have significant functional compromised by demolitive surgery, are the most suitable patients to undergo follow-up with non-invasive imaging, like LC-OCT.

INCIDENCE OF KERATINOCYTE CARCINOMAS IN ITALY: AN EXERCISE IN INDIRECT ESTIMATION FROM MELANOMA DATA

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Background: There is evidence of a continuous increase in the occurrence of keratinocyte carcinomas (KC) worldwide. However, information on the actual incidence of these tumors is often incomplete.

Objective: The aim of this work was to provide information on the ratios KC/melanoma in order to indirectly estimate the occurrence of KC.

Materials and Methods: Data were collected according to a snowball sampling procedure between Italian dermatologists. Colleagues working in melanoma and non-melanoma units were excluded. These ratios have been applied to estimates derived from histopathological records, and namely to the melanoma incidence estimates available from the Italian National Cancer Registry Network. The final estimates for KC incidence were thus obtained by the formula: KC Incidence (per 100,000) = Melanoma Incidence (per 100,000) * (KC/melanoma ratio).

Results: Our results highlight that the BCC/melanoma ratio was 4.4, the SCC/melanoma ratio was 1.7, with values that are approximately 4 to 5 times smaller than those self-reported by the dermatologists. Interestingly, this large discrepancy is not observed for the BCC/SCC ratio. In our survey it was 2.5 in the North, 2.7 in the Center, and 3.2 in the South of Italy, with an overall value of 2.8, while from the histopathology data it resulted to be 2.6.

Conclusions: In Italy, the histopathological data, compared to those reported by dermatologists, seem to vastly underestimate the actual occurrence of BCC and SCC.

Intralesional administration of L19IL2/L19TNF in difficult-to-treat BCC patients shows favorable safety profile and leads to complete remission of tumor lesions

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Introduction/Objectives: Basal cell carcinoma (BCC) is the most common form of skin cancer in white populations. Incidence of BCC is rising in many countries due to insufficient sun protection and increasing life expectancy. Treatment options encompass surgery, radiotherapy, immune and targeted or chemotherapies. Surgical resection of tumor lesions typically offers high cure rates; however, surgery's suitability and/or effectiveness in certain patients may be limited by disease factors (anatomical location, functional, cosmetic impairment) and patient factors (such as age, comorbidities, personal preferences). There is a medical need for effective non-surgical interventions in this patient group. Intralesional application of immunostimulatory drugs may be a therapeutic approach potentially curing BCC or making surgery less invasive and/or disfiguring.

Here, we investigated a combination of two antibody-cytokine fusion proteins Bifikafusp alfa and Onfekafusp alfa further referred as L19IL2 and L19TNF targeting the extradomain B of fibronectin (EDB) for the selective delivery of immunostimulatory payloads to the tumor site. EDB is virtually absent in healthy adult tissues but highly expressed in tumors, including melanoma and Non-Melanoma Skin Cancers (NMSC).

Methods: In this ongoing non-randomized open-label phase II study (NCT 04362722) patients with locally advanced non-metastatic node-negative, solitary or multifocal BCC or Squamous Cell Carcinoma (cSCC) not eligible to surgery or radiation therapy are treated with intratumoral administration of L19IL2/L19TNF once a week for four weeks. Fifteen patients (eleven BCC and four cSCC) have been treated so far and are evaluable for safety and preliminary signs of efficacy.

Results: The L19IL2/L19TNF administration was well tolerated. No unacceptable toxicities or grade 4-5 adverse events (AE) were observed. The most common treatment related grade 1-2 AEs were flu-like symptoms (33.33%) pyrexia (26.67%), face edema, vertigo and nausea (13.33%). Preliminary signs of efficacy were reported. Six out of eleven difficult-to-treat BCC patients showed complete clinical and/or pathological response upon four weekly injections with L19IL2/L19TNF. Complete responses were observed within two months from the first administration of the drug.

Conclusion: Intralesional L19IL2/L19TNF administration demonstrates good safety profile and clinical efficacy in difficult to-treat BCC. Further investigation of intralesional L19IL2/L19TNF in BCC as well as in other NMSC indications is needed.

Is resistance a common event in the treatment of locally advanced basal cell carcinoma with the hedgehog inhibitor sonidegib? Additional analysis from the pivotal trial BOLT

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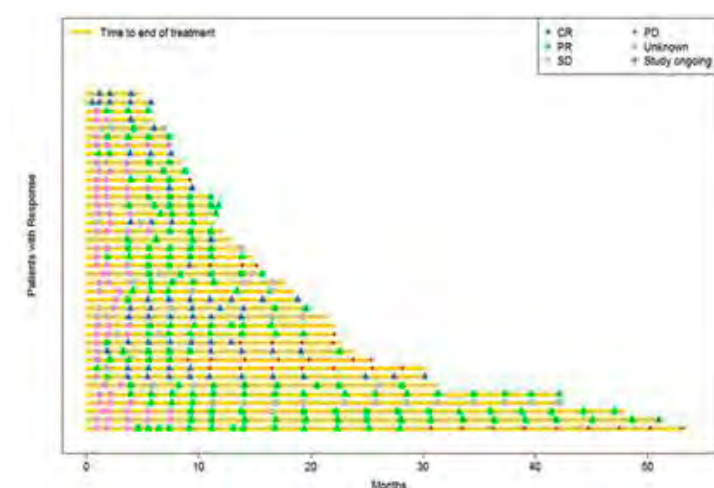
Introduction and Objectives: Sonidegib is a Hedgehog pathway inhibitor (HHI) approved for locally advanced basal cell carcinoma (laBCC) not amenable to curative surgery or radiotherapy. There is great interest in progressive disease during HHI treatment due to resistance. In the pivotal BOLT trial, primary resistance to sonidegib is rare. Secondary resistance rates have not been reported in HHI pivotal trials so far.

Materials and Methods: OLT was a randomised, multicentre, double-blind, phase 2 trial of patients with histologically confirmed laBCC or metastatic BCC randomised to sonidegib 200:800 mg once daily. The primary endpoint was objective response rate (ORR) per central review using modified Response Evaluation Criteria in Solid Tumors (mRECIST) for patients with laBCC. A pre-planned analysis assessed ORR based on RECIST-like criteria.

Results: Among the 230 patients enrolled, 66 with laBCC were randomised to sonidegib 200 mg. ORR was 60.6% (n=40) per RECIST-like central review. At 42 months, complete response (CR) was achieved in 14 (21.2%) patients and partial response (PR) in 26 (39.4%) patients. Clinical benefit (response and stable disease) reached 90.6% (n=66). Among the 40 responders at 42 months, 6 (15%) progressed during therapy (secondary resistance; Figure 1). Of these secondary resistant patients, 3 were PR and 3 were CR. Regarding duration of response, event-free probability estimates were 90.8%, 69.2% and 50.4% at 6, 12, and 24 months, respectively.

Conclusions: Since only 15% of responders progressed during treatment with sonidegib in the BOLT study, progression due to secondary resistance was not a frequent event. These new data, along with the previously published primary resistance rate of 1.5%¹, show that overall resistance to sonidegib is not an issue in 8.3 out of 10 patients. This is in contrast with the misconception of high resistance rates that arises from a lack of clear distinction between progression during treatment (resistance) and progression after discontinuation (recurrence). Additionally, sonidegib showed durable efficacy with half of the responders still responding to treatment after 2 years. In conclusion, we observed that a long-term first-line sonidegib treatment without resistance issues was common.

Supporting Document 1



Line-field confocal optical coherence tomography for basal cell carcinoma: preliminary results of a diagnostic algorithm study validation

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Introduction and Objectives: Line-field confocal optical coherence tomography (LC-OCT) is a new non-invasive skin imaging tool. Previous LC-OCT studies reported on morphologic criteria of basal cell carcinoma (BCC, Fig. 1), as well as diagnostic performance.¹⁻³ Based on these, a diagnostic algorithm was designed, which included the most useful LC-OCT criteria for BCC diagnosis (presence of lobules and millefeuille pattern) and subtype discrimination (lobule location and shape).⁴ The goal of the study was to validate the LC-OCT algorithm for BCC.

Materials and methods: To validate the previously proposed algorithm, 3 observers (blinded to any clinical and dermoscopic data) applied the algorithm on LC-OCT images/videos of lesions included in a parallel prospective study on diagnostic performance of LC-OCT for BCC including 213 lesions. Histopathology was obtained for all lesions. Herein, a preliminary analysis was performed on 60 lesions. Parameters of the algorithm's diagnostic performance (sensitivity, specificity) were calculated.

Results: A total of 213 lesions were included belonging to 119 patients [62 (52.1%) females; median age 66.4 (32.4-89.4) years; 97 (81.5%) with skin type I-II]. The 60 lesions assessed in the preliminary analysis included 46 (76.7%) BCCs and 14 (23.4%) BCC imitators; 19/46 (41.3%) BCC were purely superficial (sBCC) and 27/46 (58.7%) were non-superficial [6 purely nodular (nBCC), 11 superficial/nodular (snBCC), 5 superficial/infiltrative (siBCC), 4 nodular/infiltrative (niBCC), 1 superficial/nodular/infiltrative (sniBCC)]. The application of the algorithm produced the following diagnostic performance: (i) to differentiate BCC from BCC-imitators, 100% sensitivity (46/46 correctly classified BCCs) and 93% specificity (13/14 correctly classified imitators; 1/14 ruptured cyst erroneously classified as BCC); ii) to discriminate sBCC from other subtypes: 100% sensitivity (19/19 correctly classified sBCCs), 37.0% specificity [10/27 correctly classified non-sBCCs; 17/27 non-sBCCs (snBCC, siBCC, sniBCC – all including a superficial component) erroneously classified as purely sBCC].

Conclusion: Our preliminary analysis suggested that the current diagnostic algorithm can be validated for the differentiation of BCC from imitators. As for BCC subtype discrimination, the present algorithm is applicable to pure-subtype BCCs only. Modifications need to be implemented for mixed-subtype BCCs and will be provided at the end of the study to correctly classify all BCC subtypes, including the mixed ones.

Supporting Document 1

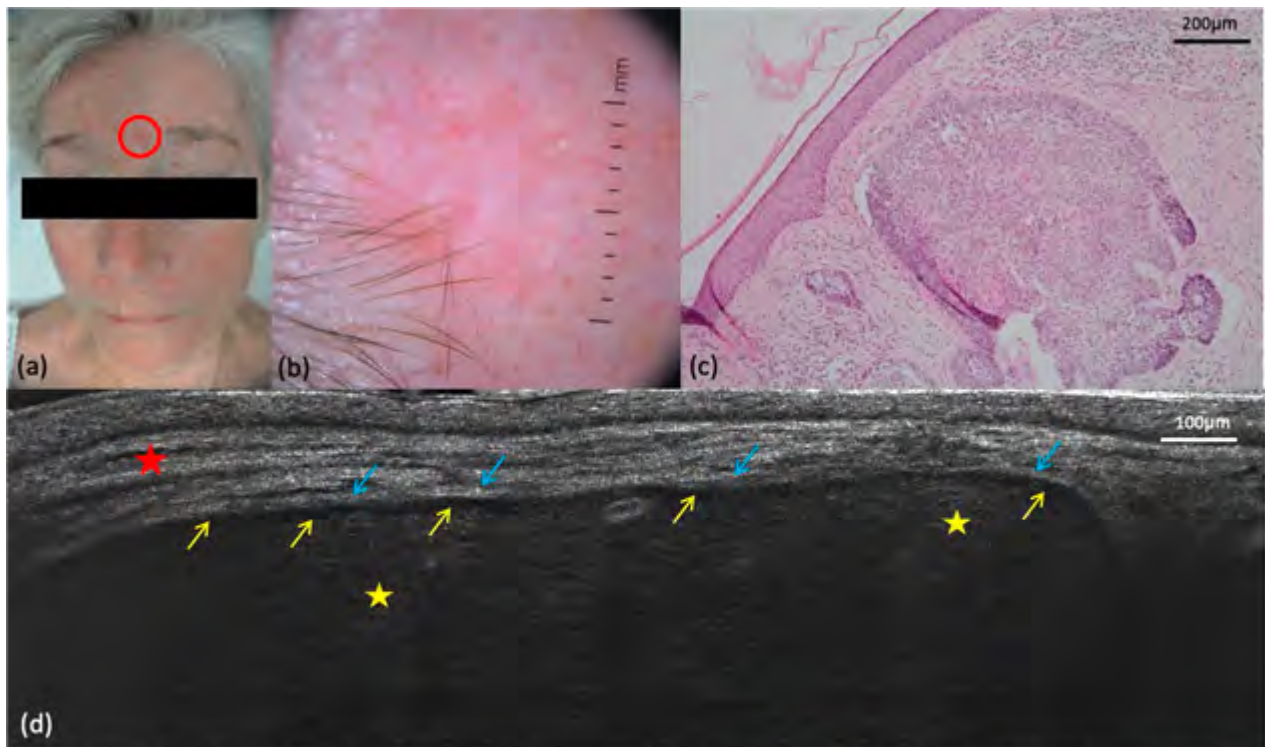


Figure 1. Nodular BCC on the left eyebrow of a 68-years-old woman : clinical (a), dermoscopic (b), and histopathological (c) presentation; line-field confocal optical coherence tomography (LC-OCT) images (d). Clinical (a) and dermoscopic (b) examination showed signs of infiltrative BCC (white shiny structures, short-fine telangiectasias), whereas LC-OCT (d) examination revealed the presence of a macrolobule clearly separated from the epidermis (red star) composed of an inner grey core featuring millefeuille pattern (yellow stars) surrounded by a middle dark rim (yellow arrows) and an outer bright rim (blue arrows).

Line-field confocal optical coherence tomography for basal cell carcinoma: preliminary results of a prospective study on diagnostic performance

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Introduction and Objectives: Line-field confocal optical coherence tomography (LC-OCT) is an innovative non-invasive imaging technique. Previous LC-OCT studies described morphologic criteria of basal cell carcinoma (BCC) and suggested that this technique facilitates BCC diagnosis and subtype discrimination¹⁻³. Available data about LC-OCT diagnostic performance in the field of BCC are derived from retrospective evaluations. The objective of the study was to report parameters of LC-OCT diagnostic performance for BCC (sensitivity, specificity, accuracy) derived from a prospective study performed at patients' bedside.

Materials and methods: Lesions clinically equivocal for BCC were prospectively included. Dermoscopic and LC-OCT diagnoses were obtained at patients' bedside by a single observer expert in LC-OCT imaging prior to surgical excision. Discordances between LC-OCT and histopathological diagnoses were reviewed by 2 different pathologists.

Results: A total of 213 lesions were included belonging to 119 patients [62 (52.1%) females; median age 66.4 (32.4-89.4) years; 97 (81.5%) with skin type I-II].

For the differentiation of BCC from BCC-imitators, the following diagnostic performance was found: sensitivity 97.0% (dermoscopy), 98.2% (LC-OCT); specificity 36.5% (dermoscopic), 88.5% (LC-OCT); accuracy 66.8% (dermoscopic), 93.35% (LC-OCT). Therefore, LC-OCT increased the diagnostic accuracy of dermoscopy by 26.6%.

For the discrimination of superficial BCC from other BCC subtypes, the following diagnostic performance was found: sensitivity 60.8% (dermoscopic), 60.8% (LC-OCT examination); specificity 85.2% (dermoscopic), 94.5% (LC-OCT examination); accuracy 73% (dermoscopic), 77.65% (LC-OCT examination). Therefore, LC-OCT increased the diagnostic accuracy of dermoscopy by 4.65%.

Conclusion: This prospective study confirmed that the diagnostic performance in the field of BCC can be increased by LC-OCT compared to clinical/dermoscopic examination alone, both in terms of BCC differentiation from clinical imitators and in terms of BCC subtype discrimination. LC-OCT should be included in the diagnostic process and management of BCC.

Locally advanced basosquamous carcinoma treated with sonidegib, radiotherapy and cemiplimab in a 'sandwich approach': real-life experience from the Dermato-Oncology Unit of Trieste

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Introduction and Objectives: Cutaneous basosquamous carcinoma (BSC) is a rare variant of basal cell carcinoma with areas of squamous differentiation, characterized by aggressive local growth and metastatic potential.

For locally advanced or metastatic BSC there is no definite therapy, although hedgehog signaling inhibitors such as sonidegib, anti-programmed death 1 (PD-1) receptor antibodies such as cemiplimab, and radiotherapy have been used.^{1,2} In this work we describe our real-life experience, presenting the case of a locally advanced BSC, treated with a combined approach at the Dermato-Oncology Unit of Trieste.

Material and Methods: We have followed up the patient (a 59-year-old woman) for 20 months, performing periodic clinical evaluation with photography (every 1-3 months). Response to treatment (according to RECIST criteria)³ and adverse events were collected.

Results: At the first visit, a 10x15cm mass was visible on the left upper limb and pectoral region, confirmed as a BSC by histology. A total-body CT scan showed infiltration of the subcutaneous tissue, deltoid and pectoralis major muscle, being the lesion in close contact with the cephalic vein and humerus bone. The patient was otherwise in good health condition, only showing a mild anemia due to thalassemic trait.

After thorough discussion with the patient, sonidegib 200 mg/day was initiated in July 2021. After 6 months (January 2022), more than 50% tumor reduction was achieved, without any adverse events. After 8 months (March 2022) a portion of the lesion grew, so a shift to cemiplimab 350 mg IV every 3 weeks was performed. After 4 months, in July 2022, the lesion showed progression, so the patient underwent radiotherapy for 2 months (55 Gy in 22 fractions) with partial response. In October 2022 cemiplimab was re-initiated, with further improvement; the patient just experienced a mild rash on the trunk as adverse event and is currently maintaining the response (Figure 1).

Conclusions: In our real-life experience, we observed partial response in a patient with a locally advanced BSC treated with sonidegib, radiotherapy and cemiplimab in a 'sandwich approach'. Our case demonstrates that a combination approach can be effectively and safely used in real-life patients, producing a good response.

Supporting Document 1



Mohs Micrographic Surgery for non melanoma skin cancer: Three years experience of a new unit

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Introduction and objectives : The objective of the presentation is to introduce the results of a new Mohs Surgery unit and illustrate the experience during the first three years of service activity. The lecture will expose the results and will focus on the four most representative cases, whose final defect constituted a reconstructive challenge due to its complexity and peculiarity.

Materials and Methods: From January 2020 to January 2023, a total number of 200 surgeries were performed for the treatment of non-melanoma skin cancer: 74.5% for basal cell carcinoma, 22.0% for squamous cell carcinoma, and 3.5% for other tumors.

Considering all the treated cases, (99%) were located on the face and scalp, (0.5%) in the cervical region, (0.5%) in other areas . Of these, 22 (11%) were reconstructed with direct closure, 157 with the application of a single reconstructive technique, that is, 9 by total skin graft (4.5%), 5 by secondary intention (2.5%), and 143 by flap (71.5%) and 21 cases (10.5%) through a combination of multiple surgical techniques.

Results: The purpose of the presentation is to expose the results obtained during the activity of the Mohs surgery service, analyzing histological types, recurrency rates, reconstructive techniques and complications during the three years follow up and, successively, to disclose the four most representative surgical cases whose final defect required, due to its complexity, an adequate reconstructive approach.

Discussion: Mohs surgery allows to excise the skin cancer with a minimal secure margin that is analyzed under the microscope.

Until surgery is performed it is impossible to predict the final defect. The resulting defect is often asymmetric, irregular and heterogeneous and often involves several aesthetic units. Mohs surgeon has to select the correct reconstructive technique or combine multiples techniques if needed. The target of the reconstruction is the restoration of the physiological function of the affected area without neglecting the aesthetic component. The desired result is being able to achieve functional reconstruction and preservation of the appearance and aesthetic balance of the tissues and organs involved by placing the sutures as much as possible on natural folds of the skin.

NEOADJUVANT PLUS MOHS SURGERY FOR LOCALLY ADVANCED PERIOcular BASAL CELL CARCINOMA. REAL WORLD SCENARIO.

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Introduction: 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. Patients and 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.

Neoadjuvant sonidegib for difficult-to-treat basal cell carcinoma: two case-reports

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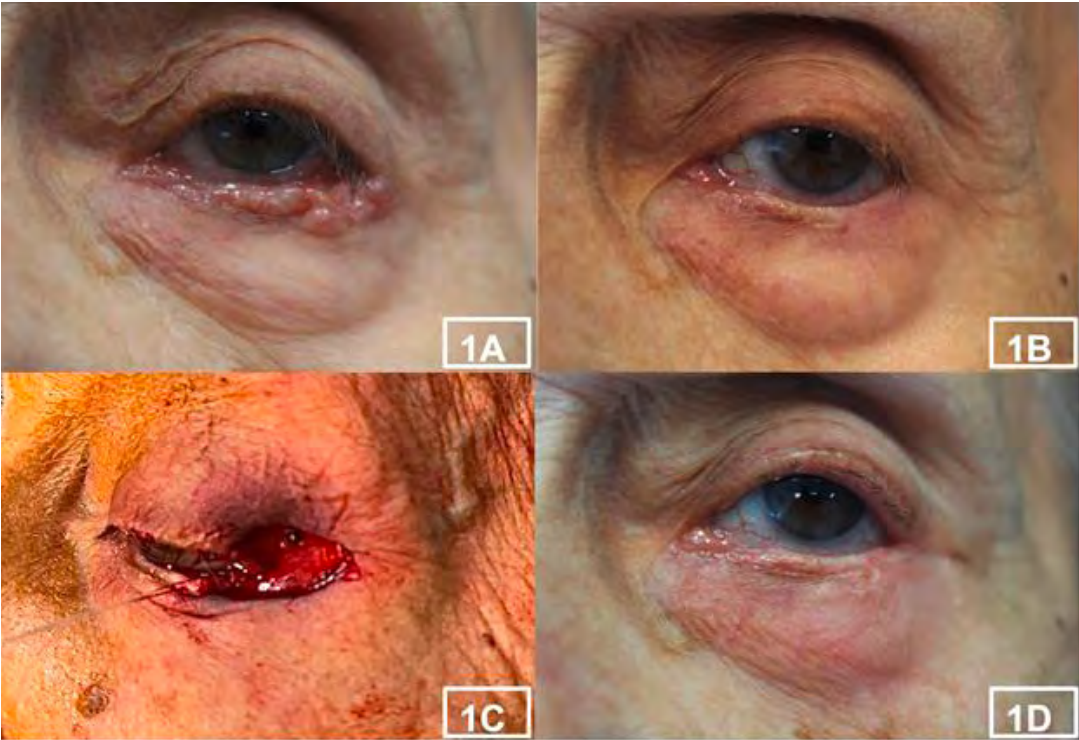
We report two cases of locally advanced basal cell carcinomas (laBCCs) successfully treated with sonidegib followed by surgical excision.

An 87-year-old female was referred from the ophthalmologists for an asymptomatic nodular BCC located on the lower eyelid, the tarsal conjunctiva and the lateral canthus of the left eye. The lesion, which had never been treated, measured 2.5x1.2 cm and was histopathologically diagnosed as a micronodular BCC. Because of patient's and lesion's characteristics, the multidisciplinary team chose to initiate systemic therapy with sonidegib (200 mg/daily), achieving a 70% reduction of tumor size after 9 months of treatment. Then, surgical excision of the residual lower eyelid lesions was performed allowing a downstaging from stage B to stage D, according to the classification used in the VISMONEO study. Indeed, final surgical defect measured 1.1 x 1.4 cm and it was repaired using a rotation flap avoiding surgical demolition of the inferior tarsus. Sonidegib was discontinued after surgery and no recurrence was observed after a follow-up of 6-months.

The second patient is an 83-year-old man with a 3-year history of two infiltrating, neglected BCCs involving the nasal tip (2.4x2.2 cm) and the left nasal ala (1.5x1.2cm) and no invasion of underlying tissues, as detected by MRI. The patient was treated with sonidegib 200 mg daily with a 60% decrease of the BCC nasal located on the tip size after 12 months of therapy. Then the patient underwent surgery achieving a downstaging from nasal stage C to stage D according VISMONEO classification. The surgical defect measured 1.6 x 1.2 cm and was repaired using a full-thickness skin graft. No recurrences were observed after 6 months follow-up. Both patients developed grade 1 adverse events (muscle cramps and dysgeusia) that resolved during treatment.

In conclusion, our two patients with laBCC located on the periocular and nasal region suggest that sonidegib followed by surgery might be an appropriate, effective approach with a favorable safety leading to downstaging of surgery and avoiding more complicated reconstructive procedures in cosmetically and functionally sensitive areas.

Supporting Document 1



Supporting Document 2



Optical coherence tomography for diagnosing recurrent basal cell carcinoma after non-invasive treatment

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Background: Superficial basal cell carcinoma (sBCC) can be treated non-invasively, but follow-up is necessary because lesions can reoccur. However, recurrences may not always be visible during clinical and dermoscopic examination (CDE). Optical coherence tomography (OCT), a non-invasive diagnostic modality, may detect these subclinical recurrences.

Objective: To compare the diagnostic accuracy of CDE and CDE with addition of OCT (CDE-OCT) for detection of recurrent BCC after non-invasive treatment of sBCC.

Methods: In this diagnostic cohort study the treating physician performed CDE after which an OCT scan was obtained and assessed. The treating physician and OCT assessor recorded their suspicion level for BCC recurrence on a 5-point Likert-scale. Patients with high suspicion of BCC recurrence (positive test result) based on CDE and/or CDE-OCT underwent punch biopsy. Patients with a low suspicion (negative test result) on CDE and CDE-OCT were asked to (voluntarily) undergo a control biopsy. Histopathological results of biopsy specimens were used for verification of the CDE and CDE-OCT diagnoses (gold standard).

Results: Included were 100 patients and a histopathologically verified recurrent BCC was found in 20 of these patients. Eight out of these 20 recurrences were detected solely on CDE-OCT. For recurrence detection, sensitivity was 100% (20/20) for CDE-OCT versus 60% (12/20) for CDE alone ($p=0.005$) and specificity was 95% and 96.3% respectively ($p=0.317$). The area under the curve for CDE-OCT (0.98) was significantly higher compared to CDE alone (0.77) ($p=0.001$).

Conclusion: Compared to CDE alone, CDE-OCT results in a significantly higher ability to detect recurrent BCCs after non-invasive treatment.

Optimizing treatment in BCC and CSCC: 3 years of oncology CME

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Introduction and Objectives: Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (CSCC) are the most common malignancies in the US. The FDA recently approved immunotherapy for the treatment of advanced disease, but provider knowledge of clinical trial data remains inadequate for optimal therapeutic selection. RMEI investigated commonalities across multiple proprietary BCC/CSCC CME programs to identify persistent learning gaps and relevant learner trends.

Materials and Methods: Systematic review of 18 RMEI oncology CME activities launched between 2019-2022 identified 10 CME activities focused on BCC and/or CSCC, which share at least one clinical area of focus. Consistent Pre/Post Test methodology to assess educational impact, incorporates Knowledge, Procedural Competence, Intent to Perform, and Confidence questions unique to each activity. Shared Clinical foci used for analysis included “safety and efficacy of immunotherapeutic agents” and “Select appropriate immunotherapy”.

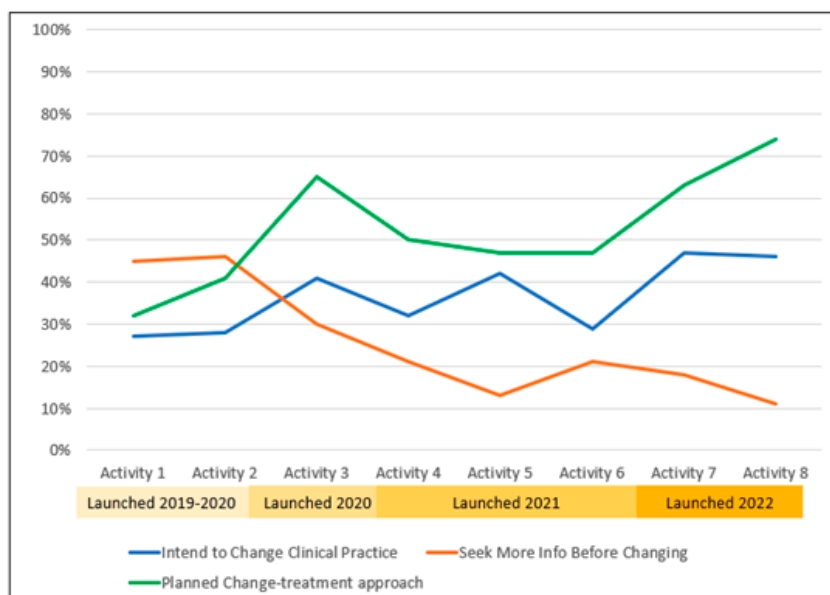
Learning gaps identified in the outcomes analysis for each activity were evaluated for commonalities and grouped thematically; of the 10 CME activities, 8 were defined as having a learning gap related to ‘therapeutic efficacy’ and ‘therapeutic selection’ which were cross-referenced with activity clinical foci to confirm validity. Individual activity data was combined into a collective CME data set for analysis.

Results: 68% of learners were oncology, dermatology, and surgery clinicians. Low pre-test scores were consistent across all activities (<50%), particularly in ‘therapeutic selection’. At post-test, improvements were observed in overall scores for Knowledge and Procedural Competence (+57%) and clinical foci (efficacy + 51%, selection +74%). This was accompanied by a reduction in learners seeking further information prior to implementing desired practice changes, (38-45% in 2020 to 11-18% in 2022) with more learners planning to change their practice, specifically treatment approach.

Conclusions: Learners have gained knowledge and procedural competence regarding the role and place of immunotherapy in BCC and CSCC, reflected in both educational improvements as well as intent to change their clinical practice. However, persistent clinical foci learning gaps indicate the need for educational reinforcement.

Supporting Document 1

Clinical Practice Changes over time



Patient with multiple basal cell carcinomas treated with vismodegib with an excellent response, with a new potential pathogenic variant in PTHC gene.

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Gorlin syndrome (GS) is inherited in an autosomal dominant pattern with high penetrance, various developmental anomalies, and genetic predisposition to several tumors, including basal cell carcinomas (BCCs). The etiology is due to germline mutations in the PTCH1 gene involved in the Sonic Hedgehog molecular pathway.

Vismodegib is a hedgehog pathway inhibitor approved for treating adults with locally advanced or metastatic BCC. In Gorlin patients, the response is variable.

We present the case of a patient with this pathology, with a mutation not described previously, and the excellent response to oral treatment with Vismodegib.

Development: A 44-year-old male patient with a history of harelip consulted in the Hospital de Clínicas, presenting multiple basal cell carcinomas. The larger lesions disfigured functionally sensitive areas such as the nose, eyelid, lower right, and upper lip.

Due to suspicion of Gorlin Syndrome, we performed a genetic study. As a result, we found a variation in PTCH1 gen, Exon 13, c.1846A>G (p.Ser616Gly), heterozygous, with uncertain significance (VUS). This variant has not been reported in the literature in individuals affected with PTCH1-related conditions or in population databases. Furthermore, algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site.

The patient received oral treatment with Vismodegib 150 mg/day, complementary to the surgical resolution of some of the lesions.

After 12 months, a significant decrease in the size of locally advanced lesions and complete resolution of the smaller ones was observed.

The patient did not present adverse effects, with paraclinical findings within ranges.

Conclusions: we present a patient with a new alteration in PTHC1 gene, probably associated with Gorlin's Syndrome (because of the protein's alteration genre) and not described previously. Algorithms suggest that this variant may disrupt the consensus splice site. In addition, the patients had an excellent response to vismodegib.

Supporting Document 1



PRE-OPERATIVE EVALUATION OF HIGH-RISK BASAL CELL CARCINOMA WITH LINE-FIELD CONFOCAL OPTICAL COHERENCE TOMOGRAPHY (LC-OCT) REDUCES MOHS MICROGRAPHIC SURGERY STAGES NUMBER: A PROSPECTIVE CROSS-SECTIONAL STUDY

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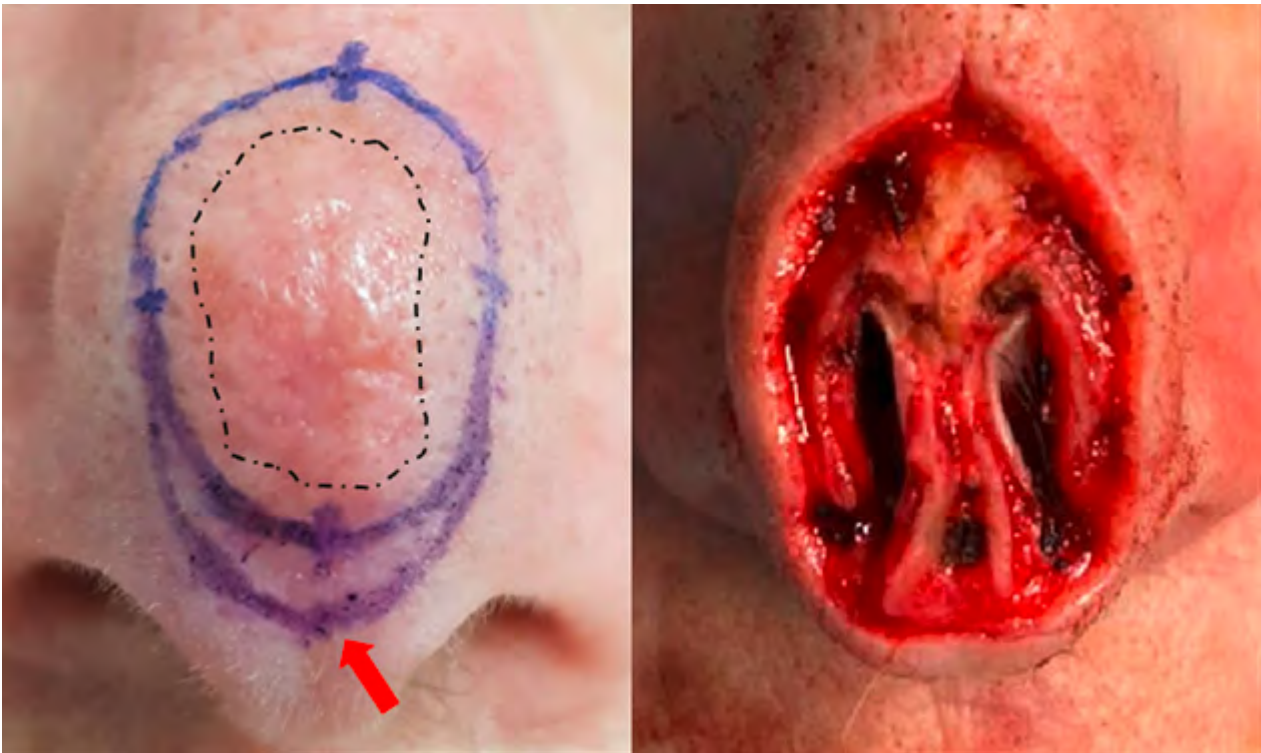
Introduction and Objectives: Mohs micrographic surgery (MMS) represents the preferred surgical approach for basal cell carcinoma (BCC) with high-risk features. Delineation of tumor margins prior to surgery influences the number of Mohs stages. BCC can be classified into high-risk and low-risk, based on the presence of factors associated with the risk of recurrence. Low-risk BCCs can be easily treated with surgery or non-surgical methods, while high-risk BCCs require a more aggressive approach. Line-field confocal optical coherence tomography (LC-OCT) is a new in-vivo skin tool imaging. The aim of the study is to estimate the feasibility of LC-OCT for the presurgical assessment of BCCs before MMS, and whether LC-OCT evaluation resulted in low MMS stages.

Materials and Methods: This was a prospective study evaluating patients with high risk BCCs who underwent MMS between January 2018 and December 2022. Adult patients with high-risk BCC who underwent MMS with the pre-operative demarcation by clinical, dermatoscopic and LC-OCT evaluation constituted the “LC-OCT group”, while patients who underwent pre-operative demarcation by clinical and dermatoscopic evaluation alone before MMS represented the “control group”. The overall agreement LC-OCT/histopathology for BCC subtype, was calculated estimating diagnostic accuracy. The averages of MMS stages per patient were compared using the Student’s t-test. The two study groups were compared for the main variables of interest, using the chi-square test, to see whether confounding factors may have influenced the primary outcome. We have also compared patients who completed MMS with a single stage to those who needed more than one stage, in order to associate LC-OCT to a more favourable outcome.

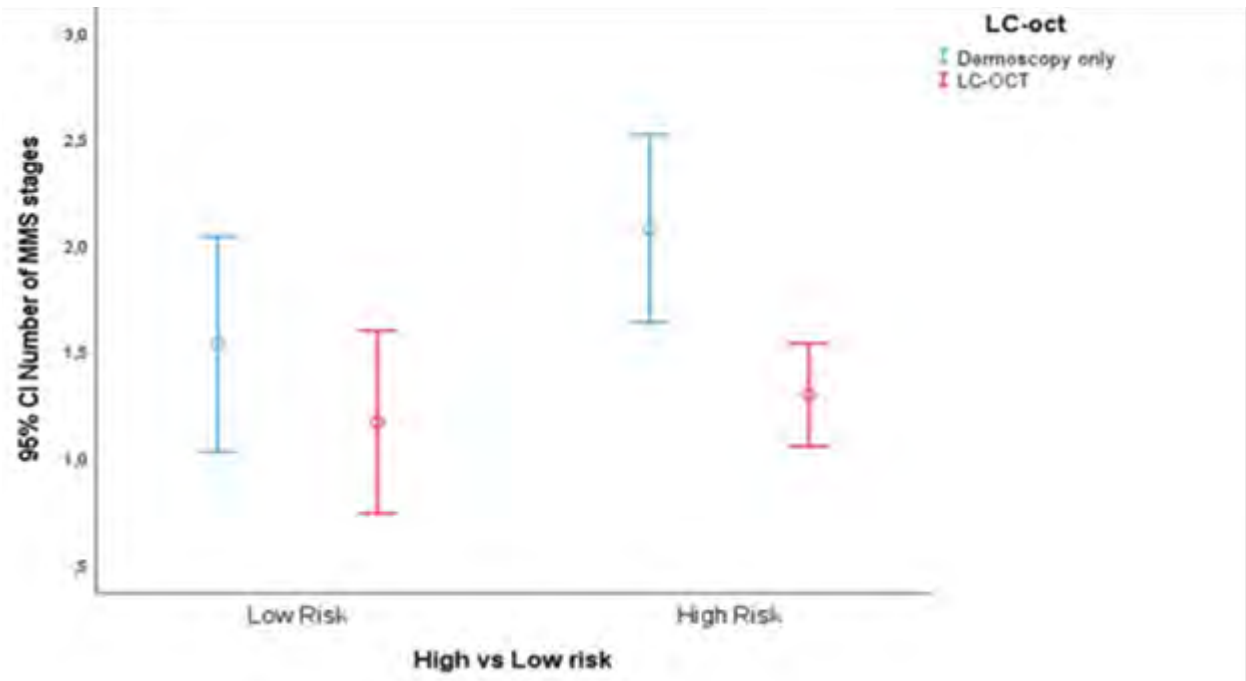
Results: We included 63 high-risk BCC lesions of 60 patients, mean age 68.3 years (SD 11.9 range 46-89). In the LC-OCT group we included 22 BCC; in the control group we included 41 BCC lesions. The agreement LC-OCT/histopathology for low-risk versus high-risk BCC subtypes was almost perfect (95.2%, kappa Cohen 0.88, $p < 0.0001$). The average of MMS stages was 1.65 (1.2 vs 1.9/ $p >$ for LC-OCT and control group respectively).

Conclusion: LC-OCT may represent a useful imaging tool for the pre-surgical evaluation of high-risk BCC to reduce MMS stages.

Supporting Document 1



Supporting Document 2



PROPOSAL OF A NEW DERMOSCOPIC CRITERION FOR PIGMENTED BASAL CELL CARCINOMA: A MULTICENTRE RETROSPECTIVE STUDY

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Introduction: Dermoscopy is widely used for the diagnosis of skin cancers and it increases the accuracy of basal cell carcinoma (BCC) detection. The dermoscopic criteria of BCC have recently been updated and they can be divided into three categories: vascular, pigment-related, and nonvascular/nonpigment-related.

Objective: The objective of our multicentre retrospective study was to report the validity of a new dermoscopic pigment-related feature utilized to detect pigmented BCC (pBCC) (i.e., brown homogeneous blotches (BHB)).

Methods: Cases of pBCC were collected from the databases of IDI-IRCCS of Rome and from three Italian private dermatology centres. BHB were defined as the presence of circumscribed areas of brown homogeneous pigmentation which are devoid of any dermoscopic specific arrangement (net, fat fingers, etc.) and of other internal dermoscopic structures, except for occasional vascular ones, such as arborizing vessels or globules/dots. Controls included melanocytic and non-melanocytic lesions.

Results: We examined images of 270 pigmented lesions (female 145; 51.8%) including 90 histopathological proven pBCC and 180 control cases (i.e., 90 melanocytic and 90 non-melanocytic lesions). BHB were present in 61 cases of 90 pBCC. These results showed a sensibility of 67.8 and a specificity of 93.3 with a positive predictive value of 83.6, negative predictive value of 85.3, posLR 10.2, negLR 0.3; OR 29.4, P value<0.001.

Conclusion Our multicentre retrospective study showed that the BHB may represent a new dermoscopic criterion for the diagnosis of pBCC.

Reconstructive Surgery of Defects of the Nose After Excision of Non-Melanoma Invasive Skin Cancers

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Introduction: The nose is anatomically the most exposed part of the face and the reconstruction of nasal skin defects is a challenge. The localization, size and depth of the defect are decisive factors for the type of reconstruction. [1] The principles of nose defects reconstruction are aimed at establishing excellent function and aesthetic appearance, so, reconstruction of the defect should be of similar tissue, all missing parts should be reconstructed. [2]

Objective: The aim of this study is to present our experience in surgical reconstruction of post excisional skin defects in the nose with satisfactory functional and aesthetic results.

Material and Methods: This study is retrospective randomized over a period of 4 years (2017 – 2020), with a follow-up period of 12 months. A total of 248 patients operated on due to malignant neoplasms of the nose were included. All patients underwent a complete preoperative dermatologic, surgical and anesthesiologic evaluation. Patients were grouped according to the : gender, localization, HP types, days of hospitalization, and operative techniques. Related to the skin defects of the nose, the following techniques were applied: primary closure , skin flaps and full-thickness skin grafts on well-vascularized beds.[3,4,5]

Results: Of the 248 patients examined, 169 (68%) were male, while 79 (32%) were female. Average age of 53.8 years from rank 28-83. Regarding the duration of hospitalization, a minimum of 3 days of stay after surgery, and a maximum of 16, where the mean value is 5.68. Basal cell carcinoma occurs in the majority, 143 patients,. We have primary closure of the defect in 43(17%), application of skin grafts in 30(12%), "V-Y" sliding flaps in 52(21%), rotation flaps in 42(17%), bilobular flaps in 28(11%), naso-labial transposition flaps in 21(8%) and glabelo-frontal flaps in 32(13%) patients.

Conclusions: It can be concluded a mean age of 54 years , mean value is 5.68 of duration of hospitalization , basal cell carcinoma occurs in the majority, the male population is predominant. and local skin flaps reconstruction dominated. In conclusion we can recommend the previously mentioned techniques for the reconstruction of these defects. [6,7,8]

Key words: reconstruction, nose, skin defects, cancer

Reflectance confocal microscopy characteristics of basal cell carcinoma

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Introduction: Basal cell carcinoma (BCC) is a common skin cancer, especially prevalent past the age of 55. Sun exposure, ionizing radiation, psoralens and arsenic are considered the most important risk factors in BCC. Clinically BCC has been classified into five subtypes: superficial, nodular, morpheaform, infundibulocystic and fibroepithelial tumor of Pinkus. Nodular BCC is diagnosed in the majority of cases and occurs as a firm, pinkish papule or nodule mainly located on the head. Superficial BCC is the second most common subtype.

Reflectance confocal microscopy (RCM) is a non-invasive tool useful in diagnosing BCC.

Methods: 36 patients (21 female, 15 male) were examined using videodermoscopy and reflectance confocal microscopy.

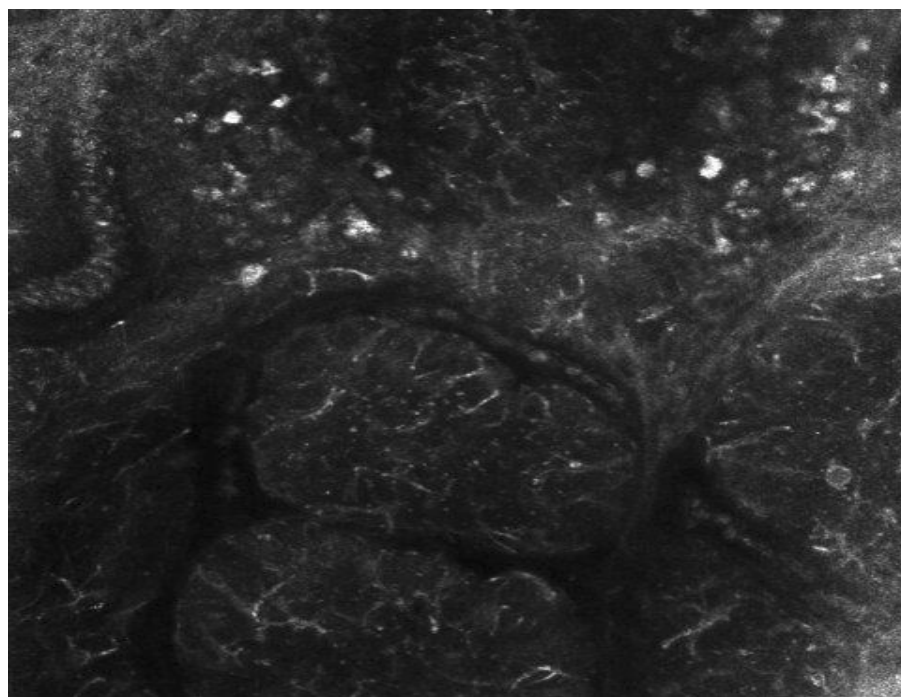
Dermoscopy was performed using Fotofinder. Three mosaics were made in RCM examination.

Results: All lesions were surgically excised and the final diagnosis of BCC was confirmed.

The mean age of patients was 65,72 (ranged 42-93). 29 lesions were nodular BCC, while 7 were superficial. 22 presented pigmented BCC; 14 were non-pigmented. Most of them (27) were located on the head. All BCC showed "streaming" of the epidermis. At dermo-epidermal junction 22 BCC revealed bright tumor islands, while in 14 cases dark "silhouettes" were observed. 31 lesions revealed numerous atypical cells surrounding tumor islands.

Conclusions: BCC was more prevalent among female than male patients. The head was the main location of the lesions. All BCC presented "streaming" of the epidermis. Bright tumor islands or dark "silhouettes" observed at DEJ allow to establish the final diagnosis of BCC.

Supporting Document 1



Retrospective analysis of Sonidegib in advanced basal cell carcinoma: A single center experience

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Hedgehog pathway inhibitors (vismodegib and sonidegib) are approved for the systemic treatment of locally advanced basal cell carcinoma (laBCC) not amenable to surgery/conservative procedures.

Objectives: To evaluate clinical determinants of complete response in laBCC patients receiving sonidegib in a retrospective, observational study.

Methods: 19 adult patients with laBCC treated with sonidegib at Dermat oncology Unit of IFO San Gallicano between June 2020 and September 2022 were included in the study. Patient, tumor and treatment characteristics were recorded. Complete response rate was the primary outcome. Median time to best response and to complete response were evaluated. Treatment-related adverse events (TRAEs) and dose adjustments were recorded.

Results: Of 19 patients included in the study, 8 (42.1%) patients achieved a complete response. TRAEs occurred in 14 (73.6 %) patients with 8 (57.1%) reporting ≤ 2 TRAE categories and 6 (42.8%) > 2 . Overall, 78.9% of patients received a modified treatment schedule. 12.5% of patients that achieved complete response received full dosage from the beginning to the end of treatment compared to 27.3% of those with a non complete response.

Conclusion: The associations between the clinical outcome of interest (complete response vs non-complete response) and the clinico-pathological and treatment characteristics were evaluated. No statistically significant association was observed. Our analysis confirm the observation that there is no significantly statistic correlation between clinical response and sonidegib alternate dose regimen.

Second Line Cemiplimab for Locally Advanced Basal Cell Carcinoma – A Real World Multicenter Experience

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Background: Basal Cell Carcinoma (BCC) is the most common form of human malignancy. It is generally curable when caught early however, advanced cases can be difficult to treat, with possibly poor prognosis without systemic therapy. Cemiplimab is a human IgG4 anti-PD-1 monoclonal antibody that blocks the PD-1/PD-L1 pathway. Recent evidence from a multicenter, open-label, Phase II trial has suggested that Cemiplimab is a feasible and clinically effective treatment for advanced basal cell carcinoma (BCC), following HHi Hedge-Hog pathway inhibitor) therapy failure or intolerance. Here, we present a multicenter real-world experience from Israel.

Methods: Data from electronic medical records of patients from 5 academic centers was collected. All patients had a biopsy, proving locally advanced or metastatic BCC, and were previously treated with HHi therapy. Patients were provided with Cemiplimab via a managed access program. Treatment consisted of 350mg IV Cemiplimab every 3 weeks, until progression or unacceptable toxicity. Response was clinically or radiographically evaluated by the treating oncologist / dermatologist.

Results: Between April 2021 and February 2023, 12 patients received second line Cemiplimab following HHi failure or intolerance. Eight patients were male, with the median age during treatment being 77.5 years. Two patients aged 23 and 31 years old had Gorlin Syndrome. Eleven patients had a locally advanced or unresectable disease, and one patient had a metastatic disease. The median number of cycles administered was 11.5. Seven patients experienced partial response, and one patient had a stable disease. The rest had a progressive disease.

Conclusions: To our knowledge, this is the first real world multicenter case series published on Cemiplimab for the second line treatment of advanced BCC, following failure or intolerance to HHi therapy. Although the study is small in size, it suggests Cemiplimab may be a promising treatment option for patients with advanced BCC. Larger trials are still needed to confirm the efficacy and safety of this treatment in BCC patients.

Skin cancer risk factors based on the “EUSCAP” register

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Skin cancer risk factors based on the “EUSCAP” register

Introduction and Objectives: A better understanding of risk factors for melanoma and non-melanoma skin cancer (NMSC) would refine the framework for prevention and control strategies, aiming to reduce disease burden. Based on the detailed “EUSCAP” questionnaire, we created a registry allowing in-depth analysis of skin cancer (SC) risk factors. Preliminary results identified inter alia independent risk factors for the development of basal cell carcinoma.

Materials and Methods: Over 500 dermatology patients answered the “EUSCAP” questionnaire comprising constitutional, socio-familial, clinical and behavioural information. Sun exposure is recorded chronologically in temporal segments of 20 years each and a distinction is made between occupational sun exposure, incidental sun exposure and sunbathing. The questionnaire is supplemented by an extensive physical examination, analysis of personal and family history of skin cancer and any histological results. Retrospective multivariable analysis was performed on the first 327 patients in order to investigate risk factors for the development of basal cell carcinoma.

Results: Of the 327 patients analysed, 162 (49.5 %) were males and 165 (50.5 %) were females, with mean age of 60 (\pm 15). The results of our study showed that patients with \geq 1 NMSC were significantly older than participants reporting \geq 1 melanoma or no SC ($p < 0.001$). Participants with \geq 1 BCC reported ever recreational sun exposure significantly more often ($p = 0.01$) than others. Patients with \geq 1 SCC as well as patients with 2 or more different SC types were significantly more likely to be clinically immunosuppressed ($p < 0.001$). Furthermore, we identified 3 independent predictors of lifetime BCC risk: 1) freckles during summertime 2) sunburn during childhood and 3) family history of NMSC

Conclusions: The creation of the EUSCAP registry with over 500 dermatological patients provides a comprehensive and unparalleled opportunity to explore risk factors for all skin cancer types. The preliminary results based on 327 patients presented here are just the beginning of many more findings to come in the near future.

Surgery versus imiquimod 5% cream for nodular basal cell carcinoma: a randomized, controlled trial with 5 years follow-up

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Background: Interest for imiquimod 5% cream as treatment of basal cell carcinoma (BCC) increases. For superficial BCC, it has been demonstrated that imiquimod has high long-term efficacy, but for nodular BCC (nBCC) long-term evidence is sparse.

Objective: To compare the long-term effectiveness of superficial curettage followed by imiquimod 5% cream to that of surgical excision (SE) in nBCC.

Methods: Five-year follow-up data was collected from patients who participated in a non-inferiority trial, in which patients were randomized to 6 weeks imiquimod 5% cream preceded by superficial curettage or SE in a 1:1 ratio. The outcome of primary interest was the 5-year probability of remaining free from treatment failure.

Results: Data on 5-year outcome of 145 randomized patients with histologically verified nBCC were available for 107 patients (52/73 imiquimod and 55/72 SE). The 5-year probability of tumor-free survival was 77.8% after imiquimod (95% confidence interval (CI): 65.7-86.0%) and 98.2% after SE (95% CI: 88.0-99.8%, $p=0.007$). Investigator-reported cosmetic outcome after imiquimod was significantly better than after SE.

Conclusions: SE remains the most effective treatment for nBCC, but the 5-year response of imiquimod 5% cream is still substantial. Imiquimod can therefore still be considered as a valuable option for treatment of nBCC. In nBCC patients who highly value cosmetic outcome, burden from SE or have strong preference for a treatment at home, imiquimod 5% cream is a good treatment option.

The correlation between dermoscopic and histopathological findings as an important factor in the classification of subtypes of basal cell carcinoma

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Introduction: the correlation of dermoscopic and histopathological data leads to early diagnosis of basal cell carcinoma subtypes, allowing the right choice for treatment. Dermatoscope is a tool that allows us to see the key vascular structures and is able to increase the diagnostic accuracy of the classification of different subtypes of basal cell carcinoma.

Aim: The objective of this study is to establish an early diagnosis through data obtained from dermoscopic and histopathological correlation.

Materials and method: We retrospectively analyzed the dermoscopic images of 50 patients skin lesions, for more than 3 years. Based on clinical data, dermoscopic and histopathological finding, that received clinical diagnosis from 42 cases of BCC. Clinical data were obtained for each patient, including age and sex, location and clinical appearance of lesion. Each case was evaluated by presence of the following dermoscopic features: vascular pattern, ulceration, and additional dermoscopic features.

Results: Among the 50 lesions were collected, with 42 histopathologically proven of basal cell carcinoma. All lesions included in this study showed more than one of the following characteristics of basal cell carcinoma. We conducted a retro-prospective study to evaluate the presence of dermoscopic features in superficial, nodular, pigmented and infiltrative BCC.

Conclusion: The results of this study elucidate the specific dermoscopic criteria associated with different subtypes of basal cell carcinoma, based on data obtained from dermatoscopic and pathological correlation. Early detection contributes to the evaluation of preoperative dermoscopy as a great value in the accuracy of the preoperative diagnosis of basal cell carcinoma.

Keywords: dermoscopy, histopathological, basal cell carcinoma.

The role of line-field confocal optical coherence tomography in the differential diagnosis of infiltrative basal cell carcinoma with scar-like lesions

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Introduction and Objectives: Line-field confocal optical coherence tomography (LC-OCT) is an innovative non-invasive imaging technique. Previous LC-OCT studies described morphologic criteria of basal cell carcinoma (BCC) and suggested that this technique facilitates differential diagnosis with clinical and dermoscopic imitators.¹⁻² Some imitator features have already been described using LC-OCT, but scar-like lesions still need to be characterized with LC-OCT to differentiate them from infiltrative BCC (iBCC), as clinical and dermoscopic differential diagnosis between these two entities can be challenging.

Materials and methods: Herein, we report 4 scar-like lesions clinically and dermoscopically equivocal for iBCC. All lesions were imaged with LC-OCT prior to surgical excision and were confirmed as scars at histopathology. Based on these observations, LC-OCT criteria for scar-like lesions are proposed.

Results: The 4 scar-like lesions belonged to 2 women and 2 men (median age 67.5 (64-84) years) and showed white shiny structures and short-fine telangiectasias on dermoscopy (compatible with iBCC, Fig. 1a). However, for all lesions, LC-OCT examination showed no evidence of lobules with the typical triad of colours usually seen in BCC (inner grey millefeuille pattern, intermediate dark cleft-like spaces, and outer bright rim); instead, dense collagen fibres sometimes visualized as branched projections were seen in the dermis (Fig. 1b), which corresponded to dermal fibrosis at histopathology (Fig. 1c).

Conclusion: The presence of dense collagen fibres in the dermis could be considered as a LC-OCT criterion to rule out an iBCC in case of in lesions clinically/dermoscopically equivocal for this type of lesion. Although based on a limited sample, this case series seems to confirm that the differential diagnosis of BCC from imitators can be enhanced by LC-OCT compared to clinical/dermoscopic examination alone and that LC-OCT should be included in the diagnostic process and management of BCC.

Supporting Document 1

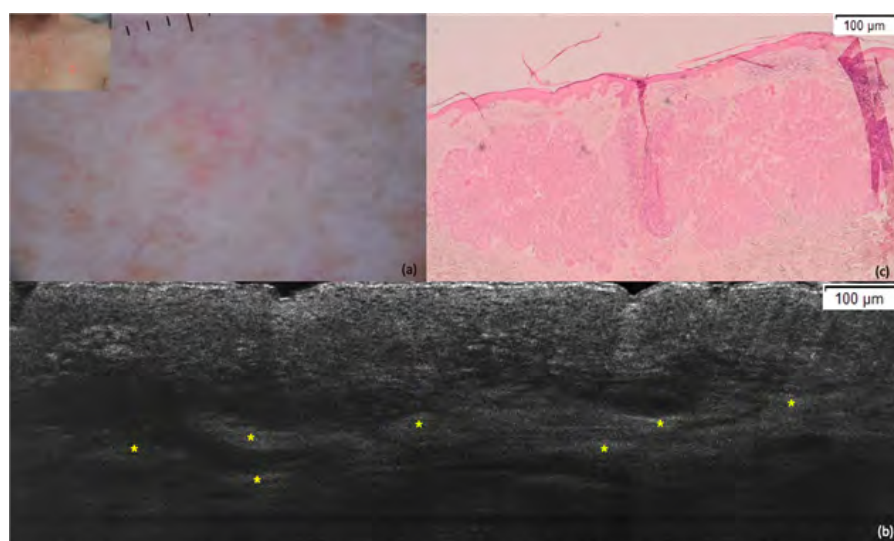


Figure 1. Erythematous macular (8 mm x 8 mm) lesion with white shiny structures and short-fine telangiectasias, located on the left pectoral region of a 65-year-old man (a). LC-OCT (b) showed no evidence of BCC lobules but, instead, dense collagen fibres in the dermis sometimes visualized as branched projections (yellow stars). Histopathology (hematoxylin and eosin, 40x) confirmed the presence of prominent dermal fibrosis (c).

Usefulness of the combination of reconstructive techniques in Mohs micrographic surgery

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Introduction and objectives: Mohs micrographic surgery is the gold standard procedure for histologically aggressive, persistent and high risk recurrence skin cancer, that offers the best cure rates and helps to spare non affected skin surrounding the tumour. The objective of the presentation is to expose the usefulness of the combination of different reconstructive techniques, compared with the use of a single reconstructive technique.

Materials and Methods: From January 2020 to October 2022, a total number of 180 Mohs surgeries were performed for the treatment of non-melanoma skin cancer. Of all the treated cases, 99% were located on the face and scalp, 0.5% in the cervical region, 0.5% in other areas. Considering reconstruction, 12.2% of cases were repaired with direct closure, 10% through a combination of multiple surgical techniques and 77.7% with the application of a single reconstructive technique,(single flap, total skin graft or secondary intention).

Results: In our experience the final surgical defect after Mohs micrographic surgery is commonly wide, asymmetric, unpredictable and it usually involves several aesthetic units. The election of a single large reconstructive technique requires a regimen of general anesthesia or sedation. This ends up widening the surgical time, opens to an increase of post surgical complications such as hematoma, nervous damage, infection and forces the patient through a period of hospitalization hardening the impact on its health and psychological integrity. Alternatively the usage of combinations of reconstructive techniques allows the surgeon to repair the defect in the same surgical session and generally under local anesthesia, decreasing surgical time, post surgical complications, patient hospitalization and estimate cost for health system.

Conclusions: The first objective of reconstruction after Mohs surgery is the functional restoration of the affected area and preservation of the appearance and aesthetic balance of the tissues and organs involved. The optimal result is to achieve functional reconstruction, place the sutures as much as possible on the natural lines of the skin and ease the most the path of the patient

Vismodegib Experience- effective treatment of locally advanced and multifocal Basal Cell Carcinoma – Case report

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Introduction: Basal cell carcinoma (BCC) is the most common skin cancer which develops predominantly in the head and neck region and commonly occurs in the geriatric patient population. The surgical excision with narrow safety margins has been considered to be the gold standard treatment for this type of skin tumor. However, this option is not always possible, either due to a critical advanced localization of the BCC in areas difficult to operate, the presence of multifocal BCC-lesions or due to patient reluctance against invasive treatments and accompanying patient multimorbidity.

Materials and methods: We report the case of a 90-year old female patient with multifocal BCCs of the head and neck, who showed clinical remission under treatment with Vismodegib.

Case Presentation: A 90-year old female patient presented in September 2019 at our clinic due to a pigmented ulcerated plaque 1x5 cm on the left supraclavicular area. On the clinical exam we found besides an ulcerated pigmented BCC, another four erythematous erosive plaques on the frontal, nose and neck regions. Both excisional (on the supraclavicular area) and shave (on the other lesions) biopsies were performed and showed evidence of nodular, infiltrative and pigmented BCCs. Microscopically controlled surgery would have been the therapy of choice. After having declined the further surgical procedures, the patient accepted the treatment with Vismodegib.

Our patient received the oral dosage of 150mg vismodegib daily for 12 months. This resulted in shrinkage of the tumors of the externally visible lesions. During the 18-months-follow up visit, no sign of recurrence of the BCCs could be seen. Adverse reactions occurred in the form of alopecia, muscle cramps and dysgeusia, which played no role for the patient, all known side effects of vismodegib therapy.

Conclusions:

Vismodegib not only stopped the progression of the BCCs, but cured the patient of his cancer. This case highlights the role of vismodegib treatment not only as an efficient drug, but also as an opening for treating an otherwise reluctant patient. The effect of vismodegib treatment should be further examined, especially its role as a neoadjuvant drug and its long-term risk of tumor recurrence.

Supporting Document 1



Supporting Document 2



EPIDEMIOLOGY OF NON-EPITHELIAL TUMORS IN THE REPUBLIC OF BELARUS

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Aim: to analyze the main epidemiological indicators and the state of early diagnosis of skin melanoma in the population of the Republic of Belarus for the period from 2018 to 2022.

Materials and methods.

The basis for studying the incidence of skin melanoma in the population of the Republic was the statistical data of the Belarusian Cancer Registry, as well as data on patients with a malignant neoplasm diagnosed for the first time in their life. Optical and digital dermatoscopy were used.

Results: In the period from 2018 to 2022, in the structure of the incidence of all malignant neoplasms (including hemoblastoses), skin melanoma was 2.0%. The highest incidence rate was observed in women living in the countryside. A pronounced upward trend in the incidence of skin melanoma in men and women begins at the age of 30-34 years, with a peak in the age group of 60-64 years. In the period from 2018 to 2022, skin melanoma in men most often developed on the skin of the trunk, and in women – on the skin of the lower extremities, of all registered cases.

Over the past 5 years, the diagnosis of stage I of skin melanoma has improved. At the same time, the number of cases in stages III and IV increased. Noteworthy is a rather high percentage of melanoma cases in which the stage of the disease has not been diagnosed.

The adjusted 5-year survival rate for all stages of skin melanoma increased by 3.8% from 2013 to 2022, and in 2022 it was 70.8% for melanoma.

Conclusions: In the Republic of Belarus, there is an increase in the incidence of melanoma of the skin. The main role in the increase in morbidity is played by demographic changes in the composition of the population over 30 years. A fairly high percentage of skin melanoma detection in stage II (38.1%) in 2022 indicates the need to strengthen the work on the diagnosis of melanoma by primary care physicians and improve the level of sanitary literacy of the population.

A CASE ON THE IMPORTANCE OF WIDE LOCAL EXCISION FOR REGRESSIVE LENTIGO MALIGNA

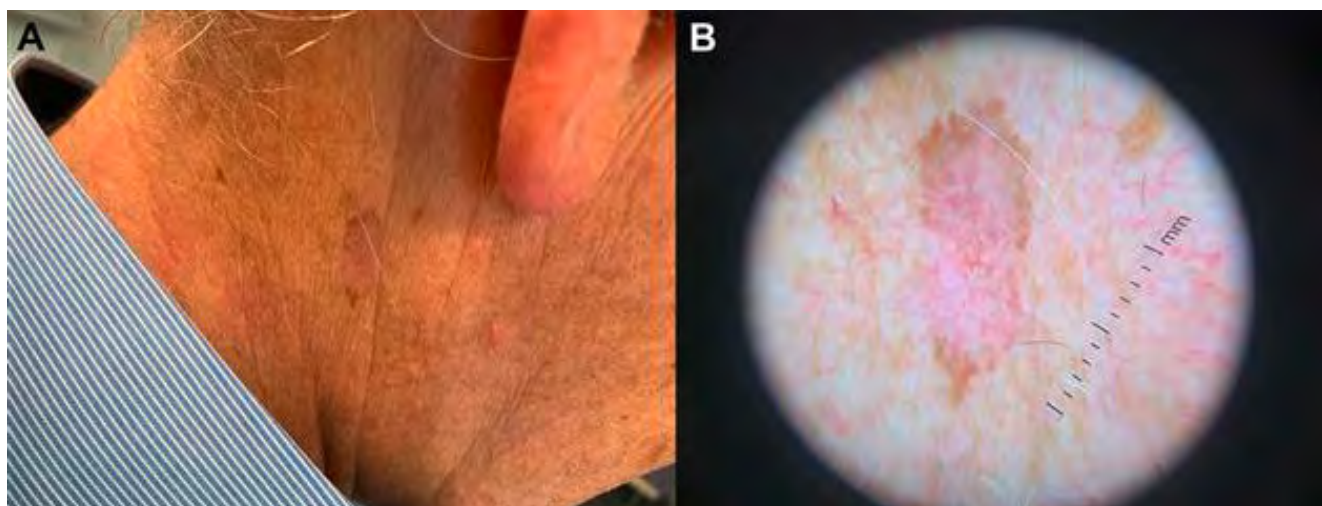
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Introduction and Objectives: Lentigo Maligna (LM) is a subtype of in situ melanoma (Mis) that develops in UV-exposed areas in older patients. The standard treatment for primary cutaneous melanoma is a first excisional biopsy with limited margins and a subsequent wide local excision (WLE) after histopathological confirmation. However, because of the unclear clinical margins of LM, which seem to have a subclinical extension, excision is often incomplete. This is supported by the fact that around 20% of LM recur. The rationale behind WLE is mainly recurrence avoidance by: 1) ensuring complete clearance of the "field", particularly in melanomas with a radial growth phase (such as LM) because of their propensity to recur as Mis in the immediate vicinity of the primary site, and 2) removing any micro-satellite metastasis. Some have questioned the necessity of a complete histopathological examination of melanoma WLEs or even performing a WLE at all. The prevalence and predictors of residual melanoma in WLE were investigated in retrospective studies and indeed, this event was found to be rare with rates ranging from 0% to 6%. Nevertheless, LM subtype was consistently found as a predictor of persistent disease.

We present an illustrative case of a LM with features of regression that appeared completely excised at first but showed residual disease in the WLE. With this case, we support WLE of LM, especially if large, with regression and on risky localizations (face, ears and neck) as well as a complete histopathological examination of the sample. As an alternative and in centres where it is available, Mohs surgery should be encouraged. If performed by trained operators, non-invasive imaging diagnostic techniques such as reflectance confocal microscopy can represent a useful tool for delineating margins in poorly defined lesions. In selected cases of LM where surgery can be disfiguring, imiquimod could constitute a fair alternative. When addressing excisional margins and their histological evaluation, clinicians should distinguish between melanoma subtypes. Special attention should be paid to LM, tricky localisations and possibly to regression. This needs to be confirmed in larger studies.

Supporting Document 1



A Comparison of Breslow Thickness Measurement Using Light and Digital Microscopy

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Introduction and Objectives: Histopathology services are transitioning from light microscopy to digital methods. Breslow thickness, as measured using a Vernier scale or eyepiece graticule on a light microscope, remains the strongest prognostic biomarker of cutaneous melanoma to date. Digital pathology affords opportunities to measure Breslow thickness digitally using a measurement tool within the viewing software, but the accuracy of digital Breslow measurements has not been evaluated.

This work aims to compare traditional Breslow thickness measurements on glass slides with digital measurements and assess their respective strengths as prognostic biomarkers.

Materials and Methods: Sixty-three specimens were selected at random from a sub-sample of a larger existing dataset, the Leeds Melanoma Cohort. Measurements were taken using a vernier scale on a light microscope and on the corresponding digital slide. Measurements were validated by a board-certified pathologist using an eyepiece graticule. Median difference between the two methods is presented, alongside a Bland-Altman plot for assessment of agreement. Multivariate cox proportional hazards regression models were conducted to assess overall survival and melanoma specific survival for the two measurements and their fit compared using Akaike's and Bayesian information criteria.

Results: The digital measurements were larger by a median of 0.03mm (95% CI: 0.02, 0.08). Most cases were within standard limits for agreement and had similar performance in modelling overall and melanoma specific survival, based on information criteria.

Conclusions: This small study has demonstrated similar measurements between each modality, with digital slide measurements being greater than glass measurements by 0.03mm. As such, digital slide measurements are unlikely to impact the current TNM8 AJCC staging system, which requires measurements to be provided to the nearest 0.1mm. This work does not provide evidence that digital measurement affects the strength of Breslow thickness as a prognostic biomarker.

Supporting Document 1

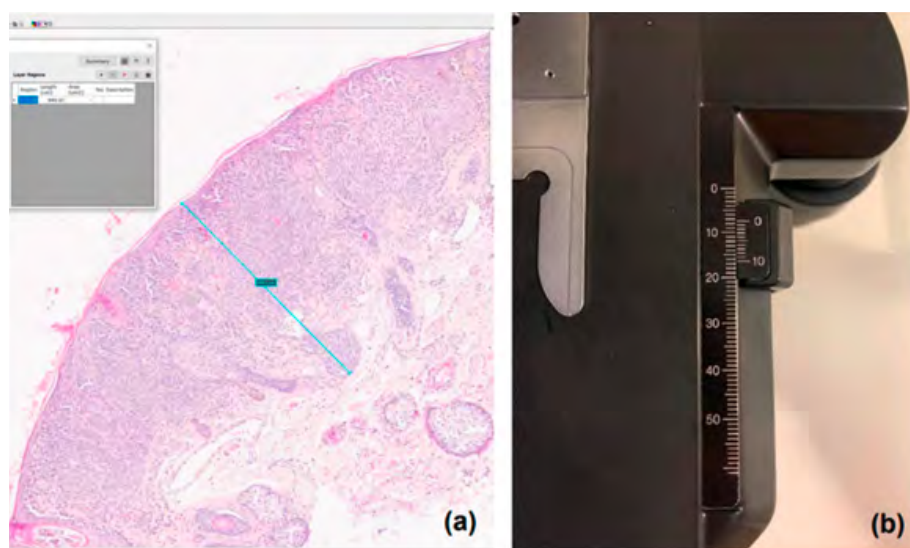
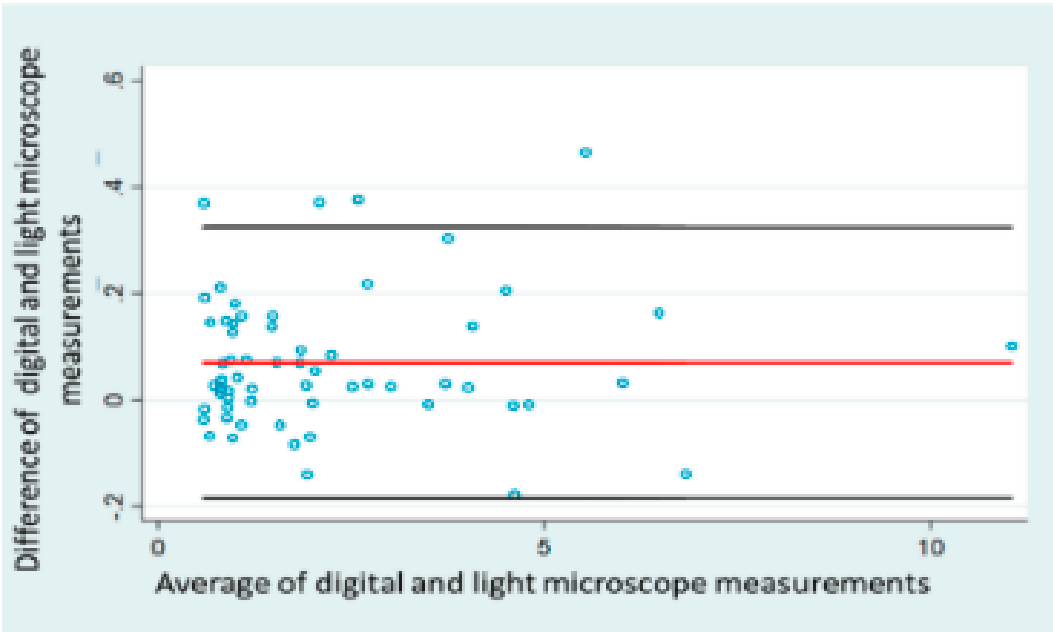


Figure 1 – (a) Whole slide image measurements in the software ImageScope (b) The Vernier Scale located on the stage of the light microscope.

Supporting Document 2

(a)



(b)

Number of cases	Sex (male, female)	Median age (IQR)	Median Breslow (IQR)	Subtype (%)				
				SSM	Nodular	LM melanoma	Acrail melanoma	Other
63	27, 36	59 (46-65)	1.65 (1-3)	54	25	2	2	17

(c)

	Overall survival		Melanoma specific survival	
	Univariable HR (95% CIs)	Multivariable HR (95% CIs)	Univariable HR (95% CIs)	Multivariable HR (95% CIs)
Glass measurement	1.46 (1.24-1.73)	1.47 (1.16-1.85)	1.49 (1.25-1.78)	1.43 (1.12-1.82)
Digital measurement	1.45 (1.23-1.71)	1.45 (1.15-1.84)	1.48 (1.24-1.76)	1.42 (1.10-1.81)

Figure 2 – (a) Bland-Altman plot showing the agreement between the two methods (b) Background demographics. IQR = Interquartile range, SSM = Superficial spreading melanoma, LM = Lentigo maligna (c) Survival data showing both overall and melanoma specific survival for the two methods. HR = Hazard ratio 95% CI = 95% Confidence interval

Analysis of cell-free tumor DNA in cerebrospinal fluid as a diagnostic biomarker for leptomeningeal melanoma metastasis: a case series

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Introduction: leptomeningeal metastases (LMM) in melanoma are associated with poor survival. Diagnosis is based on MRI findings and detection of melanoma cells with cytological examination of the cerebrospinal fluid (CSF). Ambiguous results often delay treatment initiation in this urgent medical setting. We report a single center case series in which detection of BRAFV600E/D- and NRASQ61R/K-mutations on cell-free tumor DNA (ctDNA) in CSF was used as a complementary diagnostic biomarker.

Materials and Methods: retrospective review of medical records of melanoma patients with clinical suspicion of LMM, in whom MRI of the brain, cytological/biochemical CSF analysis were performed and complemented with ctDNA analysis on 1 ml of CSF, using the fully automated Idylla® platform.

Results: 9 patients were included (7 female, median age 55.7y; 6 BRAFV600-, 2 NRASQ61-mutant, one mutational status was unknown prior to CSF analysis). At the time of first CSF analysis, patients had stage IV-M1c (n=4) and IV-M1d (n=5) melanoma. In all patients LMM were suspected clinically. The most frequent symptoms were headache (n=6), a focal neurological deficit (n=6), vertigo (n=4) and nausea (n=3).

6 patients had MRI abnormalities, indicative of LMM. CSF analysis revealed malignant cells in 2 patients (1 with MRI abnormalities). BRAFV600E/D- or NRASQ61R/K-mutant ctDNA was detected in the CSF analysis of 5 patients (4 of 6 with-, and 1 of 3 patients without MRI abnormalities and in both patients with positive CSF cytology). Progressive LMM were confirmed in all patients with positive CSF ctDNA analysis during follow-up. In one additional patient, a second CSF analysis revealed the known BRAFV600E -mutation and the emergence of an acquired NRASQ61-mutation during BRAF-/MEK-inhibitor treatment. During follow-up, in patients with a negative CSF ctDNA analysis, 1 displayed LMM, the other 2 were proven not to be affected by LMM.

Conclusion: analysis for BRAFV600- and NRASQ61-mutant ctDNA on CSF using the Idylla® platform holds promise as a sensitive and specific complementary biomarker for the diagnosis of LMM, especially in cases with ambiguous imaging or CSF cytology results. The rapid (90 min) analysis of 1 ml of CSF, offering same day results, can be of important benefit, facilitating urgent treatment decisions.

Clinical and pathological features of melanoma patients in COVID-19 era – experience of three University Centers in Serbia

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Introduction and objectives: Melanoma is an aggressive disease, therefore early detection is paramount to favorable disease-free and overall survival. As a result of Covid 19 pandemic, a shift toward more advanced disease was observed possibly due to diagnostic and therapeutic delays. In Serbia, melanoma is the eleventh most common cancer, with an incidence rate of 1.7%. Despite the fact that Serbia is a country with lower incidence rates per 100 000, a mortality rate among men is one of the highest worldwide. The aim of this study was to investigate the effects of the COVID-19 pandemic on the clinical and pathological features of melanoma patients.

Materials and Methods: In this retrospective study, 405 patients with a new diagnosis of melanoma were analyzed at three centers in Serbia over a period of two years. We compared the pre-COVID-19 era (01/MAR/2019–28/FEB/2020, n = 222) with the COVID-19 era (01/MAR/2020–28/FEB/2021, n = 183) by evaluating the demographic characteristics of patients such as gender and age, as well as Breslow thickness and stages of the tumor. Comparisons between groups were performed with the independent T test (age, Breslow thickness), Mann–Whitney-U test (Breslow index variables) or chi-square test (staging).

Results: The number of melanoma diagnoses decreased during the pandemic, with 39 (9.6%) fewer cutaneous melanomas being diagnosed in the first year of the pandemic when compared with the previous year. There were no relevant differences in patient characteristics between the two cohorts regarding gender or average age. The number of patients with Breslow thickness <1mm was significantly lower during the COVID-19 pandemic (p=0,036) with 35,2% of patients having Breslow <1mm in pre-COVID-19 era vs 24,7% in COVID-19, respectively. Our study found a difference regarding melanoma stage during the COVID-19 pandemic vs Pre-COVID-19 era (p=0.022) (Table 1)
Conclusion: Our findings suggest that the COVID-19 pandemic delayed the diagnosis of melanoma in Serbia, with the detection of the tumor at more advanced stages, potentially leading to a higher mortality, lower survival rates and higher costs for the healthcare system.

Table 1: Melanoma stage during the COVID-19 pandemic vs Pre-COVID-19 era

	Pre-COVID-19 era		COVID-19 era	
Stage 0	31	14%	9	4,9%
Stage I	78	35.1%	57	31,1%
Stage II	54	24,3%	62	34%
Stage III	44	19,8%	35	19,1%
Stage IV	15	6,8%	20	10.9%
P=0,022				

Clinicopathological data and melanoma risk of clinically atypical naevus subtypes

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Introduction and Objectives: Early detection of melanoma is a major determinant in disease outcome and drives the number of unnecessarily removed naevi in clinical practice. This study aimed to evaluate demographic information and melanoma risk of clinically atypical, predominantly flat naevus subtypes.

Methods: Based on the previously described methodology of ex vivo dermoscopy, derm dotting and targeted sectioning, 12 naevus subtypes were identified in a retrospective collection of more than 7000 excised naevi. Dermoscopic and histopathological features of these subtypes were described and their associated age, gender, location, diameter, co-occurrence and signature tendency were compared.

Results: Moreover, melanoma markers were identified based on frequency of a positive melanoma history, while melanoma precursors were identified based on histopathological atypia and frequency of melanoma within naevi. Notably, atypical lentiginous naevi and orange pulverocytic flat naevi were associated with higher proportions of (severe) atypia and melanoma. On the other hand, while representing about half of the collection, hyperpigmented naevi infrequently demonstrated atypia and melanoma.

Conclusions: We believe these subtypes may reflect different tumoural and/or germline genetic entities with different risk of melanoma development. Further research of these subtypes can lead to better follow-up of high-risk patients, less unnecessary excisions and new insights in melanoma pathogenesis.

Supporting Document 1

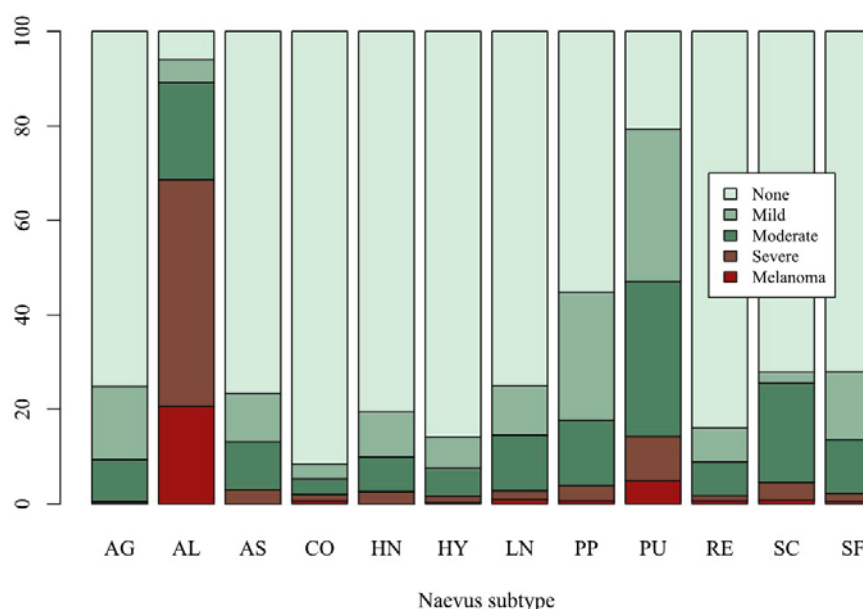


Figure 1: Histopathological atypia and melanoma association within lesions. Legend: AG: actively growing naevus; AL: atypical lentiginous naevus of the elderly; AS: naevus with asymmetrical shoulder; CO: combined naevus (with phenotypic heterogeneity); HN: hyperpigmented naevus, mainly nested; HY: hyperpigmented naevus, mainly lentiginous; LN: naevus with large nests; PP: orange pulverocytic naevus, partially papillomatous; PU: orange pulverocytic naevus, fully flat; RE: reactive naevus; SC: sclerosing naevus; SF: superficially fibrosing naevus. A three-tier system was used to divide lesions according to their histopathological atypia (mild – moderate – severe) and occurrences of melanoma within naevi were recorded. Melanoma was most often found within the naevus subtypes AL and PU, with melanoma occurring in 21% and 5% of cases respectively. The total sample size was 7364 naevi.

Combined immunohistochemical expression of epidermal AMBRA1 and Loricrin as a prognostic biomarker for non-ulcerated cutaneous AJCC stage I and II Melanoma: From discovery to validation

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Introduction and Objectives: Cutaneous melanoma continues to increase, with an increase in patients diagnosed with thin, <1mm tumours with reduced probability of recurrence-free survival (RFS). The inability of current AJCC staging criteria to identify genuinely low-risk subsets of patients with AJCC stage I/II tumours emphasises the acute need for credible prognostic biomarkers to stratify patient follow-up based on personalised risk. Following the identification of the combined expression of AMBRA1 and Loricrin (AMBLor) in the epidermis overlying non-ulcerated AJCC stage I melanomas as a prognostic biomarker and valuable pre Sentinel-lymph-node-biopsy (SLNB) test, the purpose of the present study was to extend the AMBLor evaluation as a prognostic biomarker for both AJCC stage I and II melanoma. Methods: Prospective analysis of AMBLor was performed in 4 retrospective cohorts of non-ulcerated AJCC (8th edition) stage I/II cutaneous melanomas derived from the USA and Australia (discovery cohort) and Spain and the UK (Validation cohort) following automated immuno-histological staining and binary scoring analysis to define 'at risk' or 'low risk' patient subsets.

Results: Data revealed retention of AMBLor in the discovery cohort of 541 melanomas correlated with significantly increased RFS of 96% compared to 87% for patients with stage I/II tumours in which AMBLor was lost ($P=0.06$; HR 3.6, 95% CI 1.99-6.84, NPV 96%). Subsequent AMBLor analysis in the validation cohort of 303 melanomas, further confirmed retention of AMBLor correlated with increased RFS of 98% compared to 81% for patients with stage I/II tumours in which AMBLor was lost ($P=0.01$; HR 8.16, 95% CI 3.68-18.07). Sub-cohort analysis of 311 SLNB-ve non-ulcerated stage I/II tumours further revealed a trend for decreased RFS for patients stratified as AMBLor at-risk compared to those defined as AMBLor low-risk.

Conclusions: Collectively data from this multi-international study confirm AMBLor as a prognostic biomarker marker able to identify genuinely low risk subsets of AJCC stage I/II melanomas. Inclusion of AMBLor into clinical melanoma management may therefore aid stratification of patient follow up and adjuvant treatment enabling significant savings on healthcare resources, and improvement in patient anxiety. In addition, data suggest AMBLor may guide use, and complement the prognostic information provided by SLNB.

Correlation and comparison of solar lentigo with lentigo maligna in line-field confocal optical coherence tomography and reflectance confocal microscopy.

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Background and objectives: Line-field confocal optical coherence tomography (LC-OCT) is a recently developed in vivo imaging technique which provides the cellular resolution of reflectance confocal microscopy (RCM) as well as the imaging depth of standard OCT.¹ It can produce real-time images in both the horizontal and vertical plane and display 3-dimensional (3D) pictures. Many skin lesions have already been studied in LC-OCT²⁻⁴ but no description has been reported comparing LC-OCT with RCM in solar lentigo (SL) and lentigo maligna (LM), one of the most crucial differential diagnoses in our daily practice. We aimed to describe the morphological features of typical solar lentigo and lentigo maligna in LC-OCT and to correlate them with RCM.

Methods: Both lesions were examined in-vivo with RCM and LC-OCT. For each lesion at least three 3D blocks were acquired with LC-OCT and a minimum area of 6x6mm was imaged with RCM Vivablock at four depths corresponding to the layers of the epidermis and dermis. These images were then matched to display the best correlations in vertical and horizontal frames between both techniques.

Results: An accurate correlation was observed between LC-OCT and RCM for both SL (Fig. 1) and LM (Fig. 2) and well-established diagnostic criteria⁵⁻⁶ in RCM were equally observed in LC-OCT. The regular honeycomb pattern characterizing SL was clearly visible in both techniques as well as the cord-like rete ridges in a lentiginous digitiform proliferation. The follicles showed no involvement by bright and dendritic cells, including in the deeper portion which was easily examined on the vertical and 3D pictures of LC-OCT. In both techniques the LM showed confluent atypical dendritic bright cells around the follicles as well as pagetoid spreading in the upper layers of the epidermis as clearly shown in the vertical frames produced by LC-OCT.

Conclusions: LC-OCT showed high and accurate correlation with RCM in examining the morphological criteria of both LS and LM with the additional advantage of displaying vertical and 3D pictures, allowing easy assessment of their architectural and cellular features. Further studies are needed to evaluate the added value of LC-OCT to pre-existing techniques in diagnostic performance.

Supporting Document 1

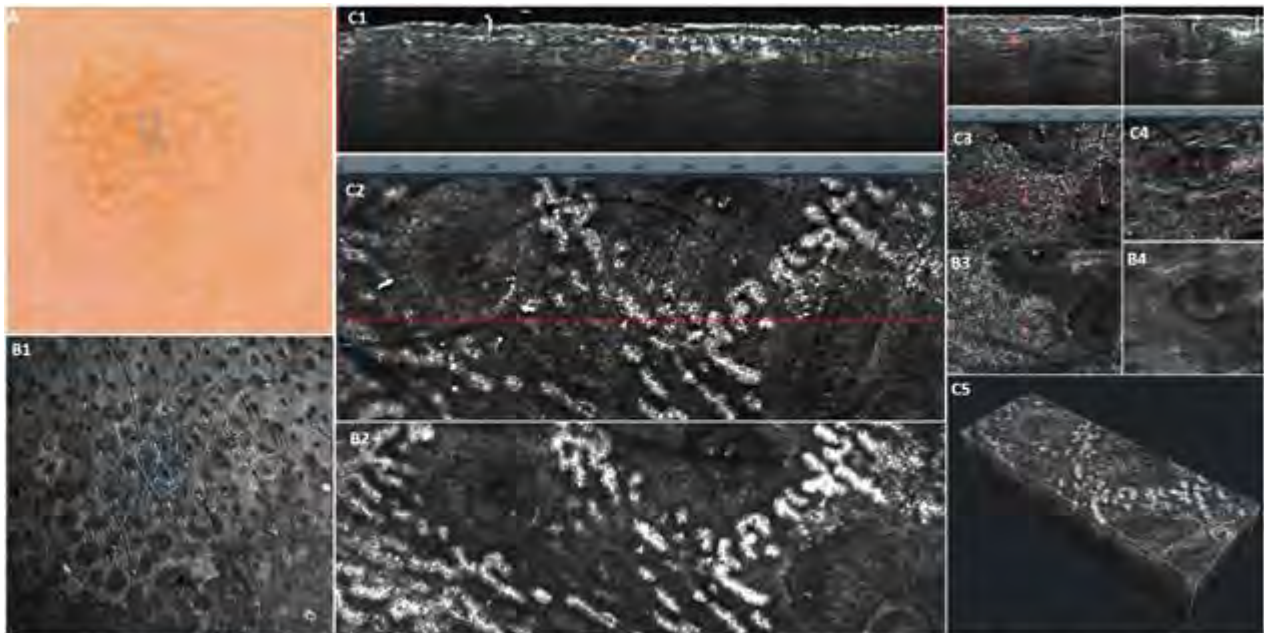


Figure 1. Dermatoscopic (A), RCM (B1-4) and LC-OCT (C1-5) presentation of solar lentigo with regular honeycomb pattern (orange stars), cord-like rete ridges in a lentiginous digitiform proliferation (yellow arrows) and follicles (green stars) free of bright and dendritic cells.

Supporting Document 2

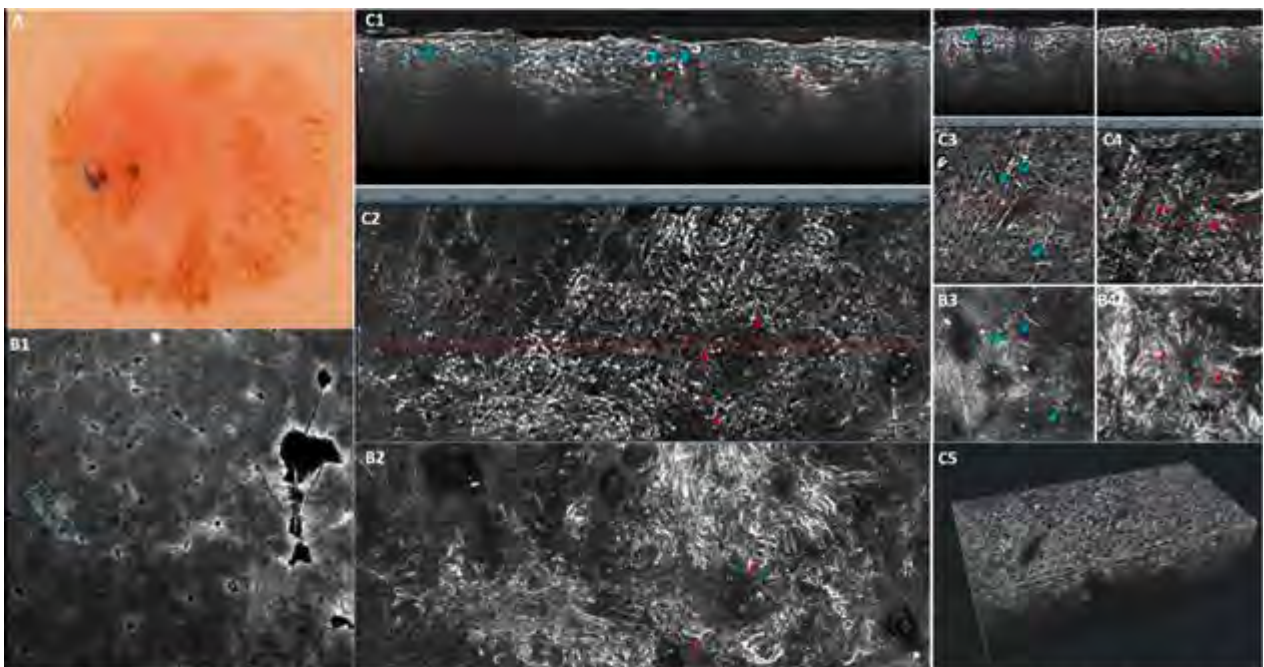


Figure 2. Dermatoscopic (A), RCM (B1-4) and LC-OCT (C1-5) presentation of lentigo maligna with confluent atypical dendritic bright cells (red arrows) around the follicles (green stars) and pagetoid spreading (blue arrows) in the upper layers of the epidermis.

Epidemiological and Histopathological Characteristics of Skin-Metastasizing Melanoma: An Observational Study in a Romanian Hospital

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Introduction and Objectives: Approximately 2–10% of melanoma patients develop cutaneous/subcutaneous metastases, and about half of the metastatic cases imply distant secondary tumors of the skin. The aim of this study is to assess the characteristics of the most frequent epidemiological and pathological features displayed by primary melanomas that later generate skin metastases.

Materials and Methods: We conducted a descriptive, retrospective study on cases with skin metastases deriving from cutaneous melanomas diagnosed in our hospital between 2018-2022. The melanoma subtype, Breslow index, mitotic rate, presence of regression, lymphovascular and perineural invasion were analysed at the time of diagnosis of the primary melanoma, using the collected tissue samples; moreover, BRAF molecular testing was also performed.

Results: In total, 10 patients were included in this study. Epidemiologically, the sex distribution was equal, the majority of patients lived in urban areas (80%) and were under 50 years old at diagnosis (70%). The most common localisation of the primary melanoma was encountered on the left calf (30%), closely followed by the anterior thorax (20%). The microscopical evaluation of the haematoxylin and eosin-stained specimens processed from the primary tumour revealed the prevalence of superficial spreading melanoma (80%), with the remainder of cases represented by the nodular subtype. Breslow index was mainly comprised between 2.01-4.00mm (40%), the ulceration status was equally present/absent, regression was highlighted in one case (10%), whereas the mitotic rate was ≥ 1 in all cases. One half of the examined samples presented lymphovascular invasion, and 40% of them exhibited perineural invasion. Only 20% of individuals were BRAF-positive and benefited from specific therapy.

Conclusions: Breslow index and the mitotic rate are essential prognostic markers, recte higher values are associated with greater potential occurrence of subsequent cutaneous metastases in patients with personal history of melanoma. Supplementarily, the BRAF-wild type cases are positively corroborated with a poorer metastatic evolution. These findings suggest that follow-up strategies should be tailored according to the epidemiological and pathological characteristics of the primary malignant melanocytic lesion.

Epidemiology of malignant melanoma based on Japan's National Cancer Registry 2016–2017

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Introduction and Objectives: Melanoma accounts for 1.7% of global cancer diagnoses and is common cancer in white population. However, the incidence of melanoma vary among different races and ethnic groups and is known to be less common in Asian population. This study aims to elucidate melanoma incidence in Japan based on the National Cancer Registry, a new nationwide integrated population-based registry.

Materials and Methods: Data of patients diagnosed with melanoma in 2016 and 2017 were extracted and classified by subtypes. The distribution of sex, age and primary site was analyzed. Tumor incidence was calculated as the number of 2016 new cases divided by the corresponding total person-years.

Results: Overall, 5,023 (2016: 2537, 2017: 2486) patients with melanoma were included. The mean age of the patients was 69.8 (range: 3–105) years and the median age was 73.0 years (Fig. 1). Slightly more than half (2660, 53.0%) were females. The percentage of each subtype was as follows: cutaneous, 71%; mucosal, 22%; eye, 5%; neural organ, 0.004%; and primary unknown, 2% (Fig. 2). Among cutaneous melanoma, 42% of the cutaneous melanomas were located in the lower limb followed by head and neck (22%). The overall age-adjusted incidence of melanoma was 1.07 per 100,000 persons for the Japanese population model and 0.89 per 100,000 persons for the World Health Organization (WHO) model.

Conclusion: This is the first report to provide comprehensive information on the epidemiological status of melanomas in Japan using population-based NCR data.

Cutaneous melanoma was the most frequently with nearly half of the cases occurring on the lower limbs.

False positive rate from PET-CT in cutaneous malignant melanoma – a systematic review and meta-analysis

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Cutaneous malignant melanoma (CMM) is increasing in prevalence and possesses the highest mortality rate associated with skin cancer (1). Diagnosis is based on primary excision, histology, and further staging investigations (2). Positron Emission Tomography and Computed Tomography (PET-CT) is used for staging, but false positive (FP) results lead to negative diagnostic and health economic consequence (3,4). No quantification of (FP) results has been performed. A systematic review and meta-analysis of FP results in prospective PET-CT studies for CMM with systemic distribution of FP results was performed.

The SR produced 14 trials for inclusion. Patient-based reporting had the lowest pooled proportion of FP results with 5.6% (95% CI = 3% to 9.1%), lesion-based was highest with 9.1% (95% CI = 3.4% to 1.7%) and combined was 7.1% (95% CI = 4.1% to 10.7%). Bias was low to unclear other than for FP reporting and heterogeneity (I²) was considerable for all analyses. FP findings were mainly lymphatic, dermatological, respiratory, or skeletal in nature. This study was the first attempt to quantify the pooled proportion of FP results from PET-CT in CMM. A small number of trials (n=14) were utilised due to the pre-dominance of retrospective methodology in this field. It is unclear whether this represents the true proportion of FP results due to inconsistent reporting. Recent focused study on FP results suggests it could be higher (5). Repeat meta-analysis using retrospective work should be carried out and future work should be prospective with clearly document FP results using a reference standard.

Full-body skin examination in screening for cutaneous malignancy: A focus on concealed sites and the practices of international dermatologists

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Background: Clinicians largely rely on full-body skin examination (FSE) as the mainstay of clinical detection of melanoma and NMSCs. The process of FSE is often suggested to entail a total examination of the skin, that is inspection of all skin including mucous membranes; however practice may vary between examiners. Notably, studies evaluating the practice of FSE including the examination of concealed sites have pointed to a lack of accepted standard of practice.

Objective: To determine the approach of international dermatologists to CSE during FSE and examine influencing factors, barriers and attitudes towards CSE.

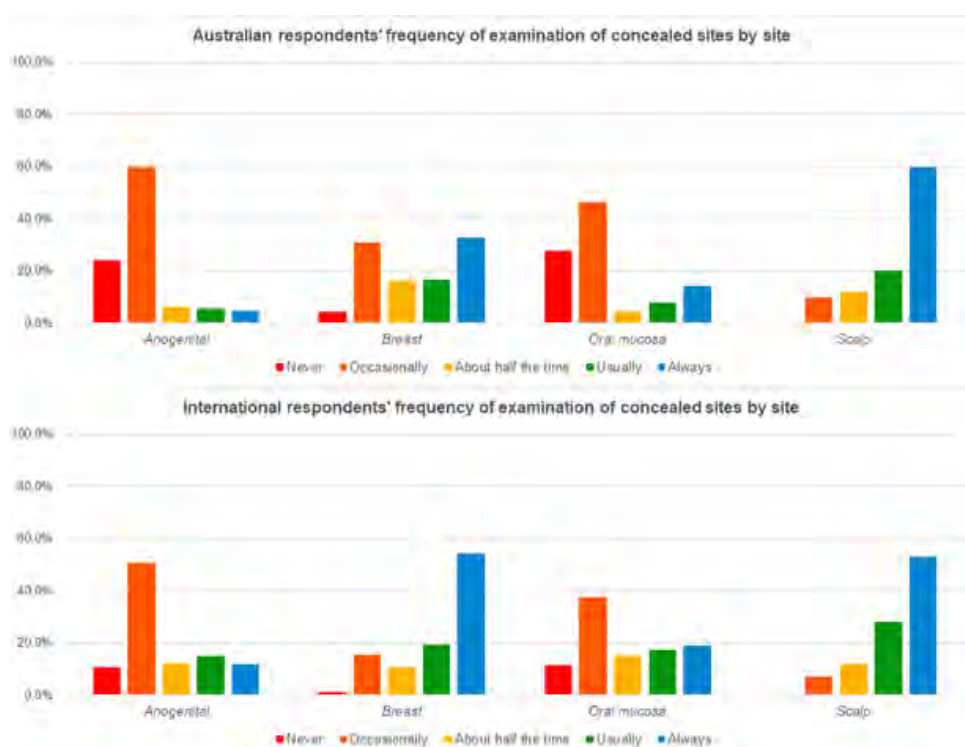
Methods: Members of the International Dermoscopy Society were surveyed using an online twelve-question survey disseminated via email. Primary outcomes were clinician-reported frequency, practice and attitudes regarding the inclusion of concealed sites in the FSE. Descriptive statistics regarding responses to each question were extracted from Google Forms.

Results: Among 1249 unique clicks to the emailed survey link, there were 706 completed responses (completion rate 56.5%). Among 699 international respondents, 54.0% reported always examining the breasts, while 52.3%, 18.8% and 11.8% always examined the scalp, oral and anogenital mucosa, respectively. The most frequent reason for examining concealed sites was patient concern, whilst common reasons for not examining concealed sites included low incidence of pathology and fear of sexual misconduct.

Conclusion:

Dermatologists' concerns of missing cutaneous malignancy, possible medicolegal ramifications, and inconsistencies in approaches toward concealed site examination dictate the need for consensus guidelines to instruct best practice. This is necessary to define the responsibilities of clinicians and inform patient expectations of care to avoid medicolegal repercussions arising from the absence of a consensus approach.

Supporting Document 1



Impact of the COVID-19 Pandemic on Melanoma Diagnosis in Serbia: Increased Breslow Thickness in Primary Melanomas-A Single Center Experience

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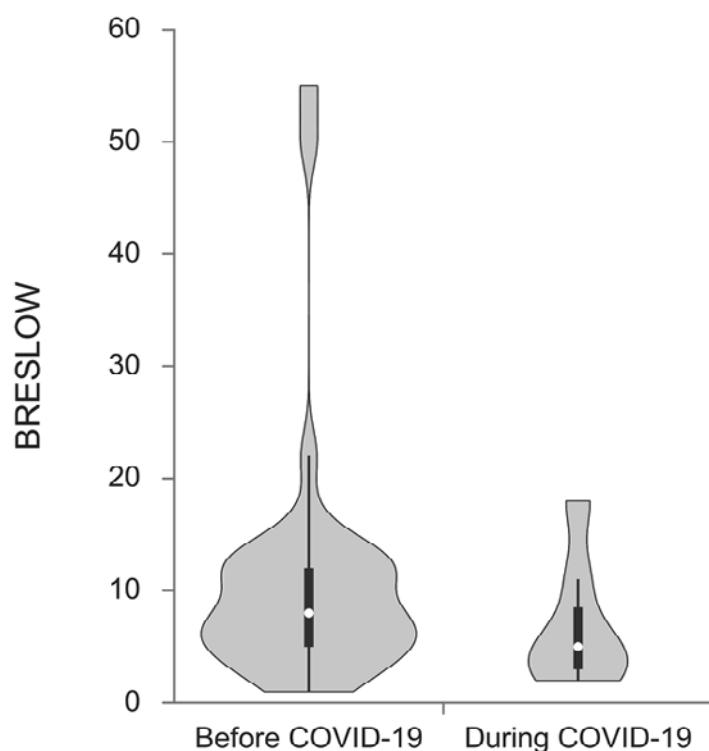
Higher Breslow index and present ulcerations indicate a more aggressive form of melanoma and thus an early diagnosis plays a key role in ensuring the best prognosis with good survival rates. The ongoing global COVID-19 pandemic has greatly impacted global and national healthcare systems, leading Europe and the rest of the world to reduce elective hospital activities for nonurgent and non-COVID-related cases, making melanoma diagnosis a real challenge. Our study aimed to evaluate the pandemic's impact on diagnostic delay in melanoma patients in Serbia.

In this retrospective study, we included 393 subsequent melanoma patients treated at the university hospital in Serbia's capital over a period of five years and three months. We compared the prepandemic (01/JAN/17-14/MAR/20) and pandemic periods (15/MAR/20-31/MAR/22) by evaluating patient files for demographic data, melanoma subtype, Breslow thickness, Clark level, ulceration status, mitotic index rate, and pT staging, all categorized according to the current AJCC 2017 guidelines.

We observed a significant reduction in the number of diagnosed patients (86.3 vs. 13.7%; $p = 0.036$). The pandemic cohort had an increased percentage of head, neck, and torso melanomas with a decrease in upper and lower extremity melanomas (74.1% vs. 25.9%; $p = 0.021$). These lesions in both cohorts occurred more often in men than in women (69.4% vs. 47.7%, $p < 0.001$). Melanomas diagnosed during the pandemic had an increased median Breslow thickness (1.80 vs. 3.00; $p = 0.010$), a higher percentage of Clark IV–V level lesions (44.0% vs. 63.0%; $p = 0.009$), increase in median mitotic index rate (2 vs. 5; $p < 0.001$) and increase in primary lesions thicker than 2 mm (37.8% vs. 53.7%; $p = 0.026$).

The study could be an important scenario guide in the case of similar events in the future. The long-term focus regarding melanoma diagnosis and treatment should be on telemedicine and preventive measures such as national screening programs, self-examination guides, and education on the impact of melanoma on general population health.

Supporting Document 1



LC-OCT ex vivo: a promising new imaging technique in dermatological diagnosis

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Introduction and Objectives: New imaging technologies, such as ex vivo confocal microscopy, have radically changed the way tissues are processed and visualized. Through techniques like this, it is possible to visualize microscopic images of excised tissues in real-time. Recently, a new technology called "line-field confocal optical coherence tomography (LC-OCT)" has been developed. This imaging technique combines concepts of reflectance confocal microscopy (RCM) and optical coherence tomography (OCT). In addition, it allows us to see real-time vertical and horizontal cuts of the skin with an isotropic resolution of approximately 1 μm and a penetration depth of approximately 400 μm . It can also offer three-dimensional reconstructions of the skin's architecture. The objective of this study is to evaluate the ex vivo images in horizontal, vertical, and 3D cuts that LC-OCT can offer and correlate them with RCM and histology.

Material and Methods: Five patients and a total of 5 cutaneous tumor lesions were included. The following protocol was performed in each tumor: in vivo RCM (with images at 3 different depths), LC-OCT of a representative sector of the lesion chosen by dermoscopy and, finally, ex vivo 3D LC-OCT of the entire lesion after being excised. The samples were subsequently evaluated in the dermatopathology laboratory.

Results: We were able to describe for the first time 3D reconstructions of 5 cutaneous tumors using ex vivo LC-OCT technology. Additionally, we were able to perfectly correlate these images with in vivo RCM, in vivo LC-OCT and histology.

Conclusions: LC-OCT is a non-invasive imaging technique that can evaluate ex vivo the architecture of the skin and provide similar images to conventional histology. Additionally, we were able to evaluate and describe for the first time 3D reconstructions of different cutaneous tumors using this ex vivo technology.

Line-field confocal optical coherence tomography of seborrheic keratosis: a case series

MD Clément Lenoir

Introduction and Objectives: Line-field confocal optical coherence tomography (LC-OCT) is a recently developed non-invasive imaging technique combining the high penetration depth of conventional OCT with the high isotropic resolution of reflectance confocal microscopy.¹ Seborrheic keratosis (SK) is one of the most common benign lesions encountered in daily practice. Although it is often easy to diagnose, it may sometimes resemble a melanoma, basal or squamous cell carcinoma (BCC and SCC).² We believe that LC-OCT could be an asset in these situations, and we aim to describe the most characteristic morphologic features of SK upon LC-OCT to help differentiate it from its clinical lookalikes.

Materials and Methods: LC-OCT examination was performed on 29 lesions which were thereafter excised for histopathological analysis and diagnostic confirmation of SK. LC-OCT pictures were compared to histology and the best-correlated and most commonly found morphologic features were described and illustrated in Fig. 1.

Results: The following morphological features were identified and showed clear correlation with histology: (i) acanthotic proliferation of non-pleomorphic keratinocytes in the epidermis; (ii) presence of pseudo-horn cysts in the shape of roundish hyperreflective structures in the epidermis; and (iii) extension of the rete ridges in the dermis, limited by a straight horizontal line. Upon LC-OCT examination, those features can show variable prominence and translate into different architectural patterns which appear to correlate well with histopathological subtypes (flat SK, Fig. 1a-b, acanthotic SK, Fig. 1c-d, hyperkeratotic SK, Fig. 1e-f, pigmented reticulated SK, Fig. 1g-h).

Absence of large, pleomorphic, and irregularly shaped bright cells in the epidermis or underneath, keratinocyte pleomorphism, and lobular structures appended to the epidermis or located in the dermis allow to rule out the frequent malignant lookalikes of SK (respectively melanoma, SCC and BCC) as shown in Fig. 2.3-5

Conclusion: In conclusion, LC-OCT seems able to detect the main histopathological features of SK and to possibly differentiate it from its clinical imitators. Larger studies are needed to confirm these preliminary data, particularly in terms of association of LC-OCT criteria with different SK subtypes as well as the diagnostic performance in discriminating SK from its imitators.

Supporting Document 1

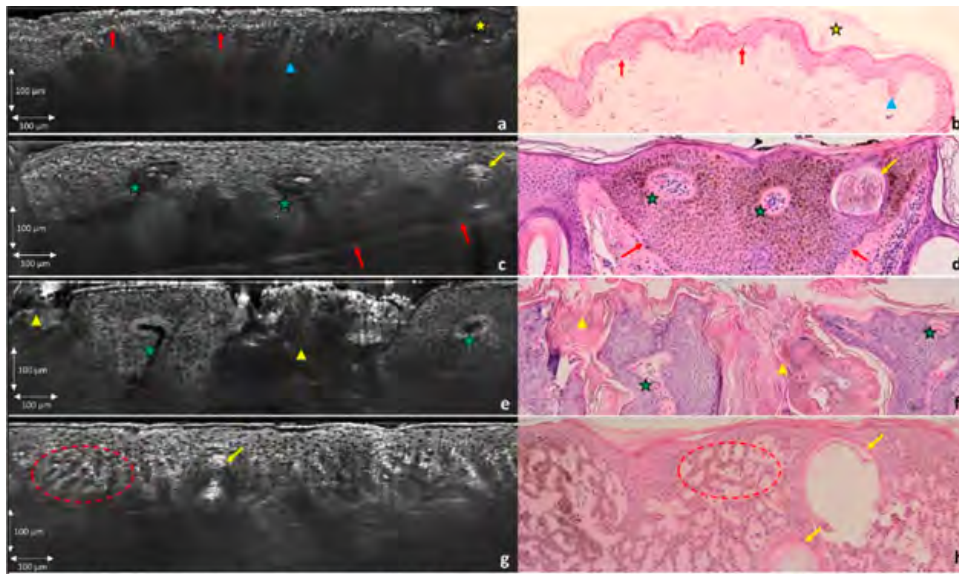


Figure 1. LC-OCT and histopathological presentation of four different subtypes of seborrheic keratoses (SK): flat (a-b), acanthotic (c-d), hyperkeratotic (e-f), and pigmented reticulated (g-h).
(a-b) Flat SK: dermal-epidermal junction (DEJ) (red arrows), lentiginous elongation of rete ridges (blue triangle), mild hyperkeratosis (yellow stars).
(c-d) Acanthotic SK: DEJ (red arrows), dermal papillae (green stars) can be seen inside the acanthotic epidermis, which also contains some pseudo-horn cysts (yellow arrows).
(e-f) Hyperkeratotic SK on the right temple of a 72-year-old woman. LC-OCT examination shows thick layers of keratin (yellow triangles) over a papillomatous epidermis, which encompasses dermal papillae (green stars).
(g-h) Pigmented reticulated SK on the right cheek of a 70-year-old man. LC-OCT examination shows fine strands of keratinocytes intermingling in a clearly defined reticular pattern around the basal layer (red circle), as well as some pseudo-horn cysts (yellow arrow).

Supporting Document 2

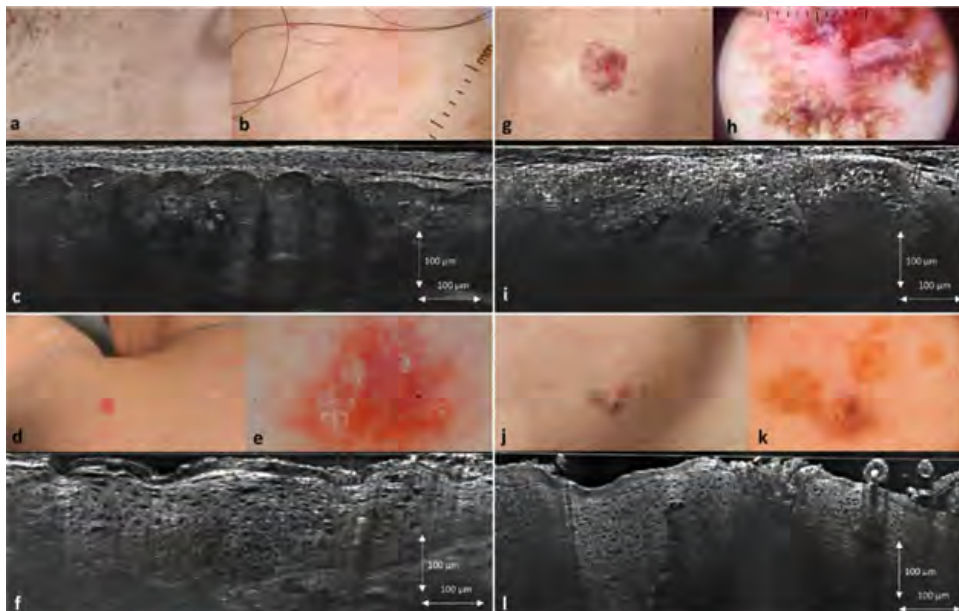


Figure 2. Clinical, dermoscopic and LC-OCT presentation of basal cell carcinoma (BCC), melanoma, squamous cell carcinoma (SCC) and seborrheic keratosis (SK).
(a-c) Nodular BCC on the right chest of a 48-year-old man. LC-OCT examination shows lobular structures in the dermis with the typical *mallefeuille* pattern (laminated structure prevalently parallel to the epidermis, resembling the arrangement seen in the eponymous French delicacy and corresponding to dense cellularity prevalently orientated along the same axis).
(d-f) Melanoma on the right leg of a 45-year-old man. LC-OCT examination shows a poorly defined architecture and the presence of large bright pleomorphic cells in the epidermis and beneath.
(g-i) In situ SCC on the left scapular region of an 82-year-old woman. LC-OCT examination shows pleomorphic atypical keratinocytes in the whole thickness of the epidermis.
(j-l) SK on the right mandibula of a 58-year-old woman. LC-OCT examination shows monomorphic keratinocytes in an acanthotic epidermis with mild hyperkeratosis.

Malignant Neoplasms in Patients Diagnosed with Melanoma and Non-Melanoma Skin Cancers — Analysis of a Large Single-Center Database of 184,766 Patients Diagnosed Between 2000 and 2020

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Introduction and Objectives: Limited publications postulates the role of both melanoma (MM) and non-melanoma skin cancer (NMSC) diagnosis as a risk factor for the occurrence of another malignant neoplasm. Our aim was to determine the prevalence and temporal relationships of MM, NMSC and other malignancies.

Materials and Methods: We conducted a retrospective analysis of medical records of patients who had been admitted to National Research Institute of Oncology, Gliwice, Poland, between January 1, 2000, and December 31, 2020. The MedStream Designer™ software was used to search the database and export data. We identified 238,563 patients diagnosed with malignant neoplasm according to ICD-10 (all codes starting with the letter C). In the final analysis 184,766 patients was included. Table 1 shows the clinical characteristics of the analyzed subpopulations.

Results: The most prevalent primary cancers were: breast (26,749; 14.48%), thyroid gland (26,225; 14.19%), prostate (15,991; 8.65%), lung (14,985; 8.11%), corpus uteri (9,580; 5.18%), NMSC (C44; 7,652; 4.14%), cervix uteri (7,356; 3.98%); rectal (6,636; 3.59%), brain (5,835; 3.16%) and melanoma (C43; 5,627; 3.05%). There were 20,472 patients in total with diagnoses of more than one cancer. Figure 1 presents cancers' profiles for patients with at least two cancer diagnoses and one of them being C43 or C44. 772 patients diagnosed with melanoma as primary cancer was further diagnosed with NMSCs (330; 42.75%), breast (54; 6.99%), prostate (53; 6.87%), connective tissue (52; 6.74%) and lung (32; 4.15%). In the case of 659 patients, melanoma was diagnosed as secondary cancer and the most frequent primary cancer was NMSCs (245; 37.18%).

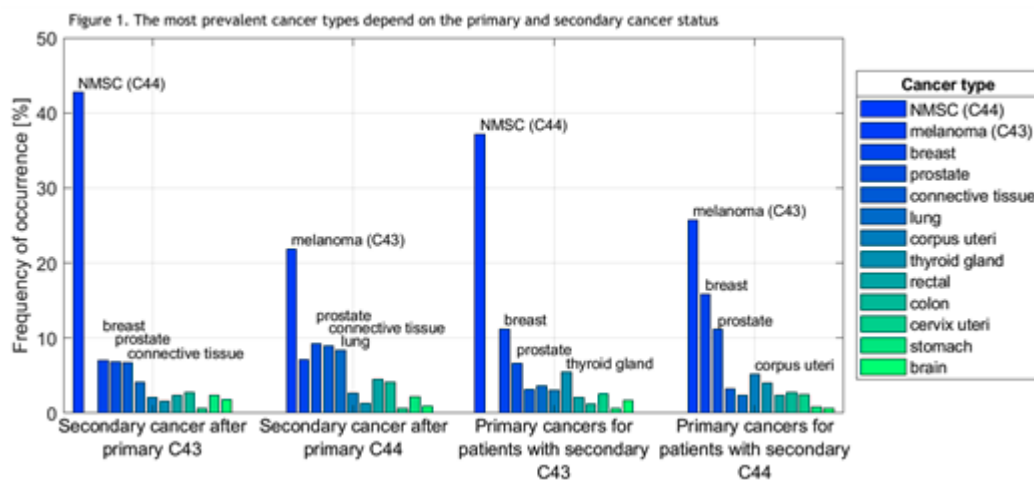
1,120 patients were initially diagnosed with NMSC and subsequently had other (secondary) cancer. Among them, the most frequent were: melanoma (245; 21.88%), prostate (104; 9.29%), connective tissue (100; 8.93%), lung (94; 8.39%), breast (80; 7.14%), rectum (50; 4.46%) and colon (46; 4.11%). The reverse sequence (diagnosis of NMSC as a second malignancy) was found in 1,281 patients. The most common primary tumour was melanoma (330; 25.76%).
Conclusions: MM and NMSC seem to be the predictors of the occurrence of other malignancies. This finding supports the necessity of multidisciplinary surveillance of patients with such diagnoses.

Supporting Document 1

Table 1. Clinical characteristics of subpopulations of patients.

Patient subpopulation		N	Mean age at primary diagnosis ± SD [year]	Median time of follow-up or to the secondary diagnosis [day]	Males [%]	
Primary diagnosis with C43 (single cancer and multiple cancers with secondary other than C44)		5,297	56.39 ± 15.29	697.00	45.52	
Primary diagnosis with C44 (single cancer and multiple cancers with secondary other than C43)		7,407	68.53 ± 12.70	490.00	51.68	
Primary diagnosis with cancer other than C43 and C44 (single cancer and multiple cancers with secondary diagnosis other than C43 and C44)		170,122	58.17 ± 14.17	506.97	41.65	
Patients with at least two cancers (N = 20,472 in total)						
Primary	Secondary	N	Mean age at primary diagnosis ± SD [year]	Mean age at secondary diagnosis ± SD [year]	Median time to the secondary diagnosis [day]	Males [%]
C43	Other than C44	442	60.65 ± 12.92	64.13 ± 12.74	476.04	50.45
C44	Other than C43	875	66.23 ± 12.25	69.74 ± 12.33	511.51	60.00
Other than C43	C44	951	65.82 ± 11.51	70.69 ± 11.12	1,129.00	49.11
Other than C44	C43	414	60.43 ± 12.90	63.61 ± 12.93	308.30	42.51
C43	C44	330	65.91 ± 13.61	68.42 ± 13.52	132.63	50.91
C44	C43	245	60.70 ± 14.96	62.34 ± 15.24	74.00	48.16
Other than C43/ C44	Other than C43/C44	17,215	59.81 ± 12.80	62.23 ± 12.79	121.64	45.88

Supporting Document 2



Melanoma growth in Lithuania: analysis of 5-year trend changes

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Introduction and Objectives: Every year skin cancer has been diagnosed more than all the other cancer forms [1]. Melanoma still remains potentially fatal skin cancer. Furthermore, morbidity of melanoma has been raising tremendously over the years [2]. Hence, the aim of this study is to determine the rate of melanoma cases in Lithuania from 2017 to 2021.

Materials and Methods: Data were collected from the Institute of Hygiene of Lithuania. Statistical analysis was performed using IBM SPSS statistics 23.0 software. Mann-Whitney U criteria was used to create comparison between the percentage distributions of melanoma incidence.

Results: An increase in the total number of melanoma cases is observed from 18.4% up to 21.8%, with a statistically significant difference between different age groups ($p < 0.05$).

In the group of children (age 0-17) a trend of consistency in incidence of melanoma was observed (19.2%). Number of cases remained the same for boys – 16,7% and girls – 21,4%.

In the adults group (age 18+) increase of melanoma cases was detected from 18.4% up to 21,8%. An increase of cases from 18.4% to 21.8% was observed in the group of women. In the group of men the total number increased from 18.6% to 21.7%. The morbidity of melanoma is higher in women's group. There was a statistically significant difference between women and men ($p < 0.05$).

In the senior group (age 65+) a trend of increase was observed from 18.4% to 21.9%. Melanoma cases increased from 18.2% to 22.1% in the group of senior women. In the group of senior men the total number increased from 18.6% to 21.7%. The morbidity of melanoma is higher in senior women's group. There was a statistically significant difference between senior women and men ($p < 0.05$).

Conclusions: During 5-year study period, an increasing trend of melanoma cases was observed in Lithuania. The morbidity of melanoma is highest in the senior group. Most of the patients with diagnosis of melanoma were women. In summary, melanoma is a growing issue in Lithuania. Nevertheless this illness can be prevented, as more people should follow safety measures, such as sun protection and early detection.

Melanoma in situ occurrence distribution by localization and morbidity patterns over the course of 8 years

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Introduction and Objectives: Melanoma cases are rising rapidly posing issues for public health. Early detection significantly lowers both short and long-term morbidity and mortality [1]. An important independent predictor of prognosis is the primary melanoma's anatomic location [2]. Study aim is to identify the frequency of melanoma in situ cases and their most prevalent location in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics from 2014 to 2021.

Materials and Methods: Data was obtained from the Health Information Center of the Institute of Hygiene in Lithuania. IBM SPSS statistics 23.0 software was used for data processing. The site and years of melanoma in situ occurrence was compared using chi-square (χ^2) statistic criteria and the statistical significance was determined using Pearson chi-square or likelihood-ratio depending on expected values.

Results: The morbidity pattern remained inconsistent over the years, however the site of occurrence stayed constant between different genders. The total of 226 instances, with the highest amount of cases in 2018 (12.8 %), 2019 (19.5 %) and 2020 (17.3 %) were observed. Melanoma in situ of face (42.0%) and trunk (12.4%) regions were the most common. Statistically significant difference was found between year and site of occurrence between different sex groups ($p < 0.05$).

Analysing the group of men, the overall incidence, remained variable throughout the years. Melanoma in situ of face (29.9 %), as well as scalp and neck (16.4 %), accounted for the majority of the cases. 2020 was the year with the most incidents – 20.9 %, however, there was no statistically significant difference between the site and year of occurrence ($p > 0.05$).

Consequently, analysing the group of women the incidence rate also remained inconsistent throughout the years. The majority of cases (47.2%) belong to face area. The most instances occurred in 2019, accounting for 17.6% of total incidents, however there was no statistically significant difference between the site and year of occurrence ($p > 0.05$).

Conclusions: Melanoma in situ morbidity pattern at the Hospital of Lithuanian University of Health Sciences Kaunas Clinics remained inconsistent over the period of eight years. Hence, the most common localization was face among different sex groups.

Prospective Clinical Trial with Total Body dermoscopy for the detection of melanocytic lesions with an autonomous scanner

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Introduction: Digital follow-up for early melanoma detection in high-risk patients is time-consuming. In an attempt to facilitate the workload of dermatologists our team has designed and developed for the first time a new imaging device that combines total body photography with total non-contact dermatoscopy photography in an autonomous scanner.

A prospective multicentric non-inferiority study has been initiated to compare the quality of our autonomous dermoscopic images with the images obtained using a standard digital dermatoscope.

Methods: The multicentric prospective clinical study approved by the Ethics and IRB of the Hospital Clinic of Barcelona includes 300 patients with atypical mole syndrome. Two clinical sites will recruit a wide variety of patients: Diagnosis Dermatologica, Barcelona, (specialized melanoma clinic) and Hospital de Figueres, Girona, (general dermatology department, regional hospital).

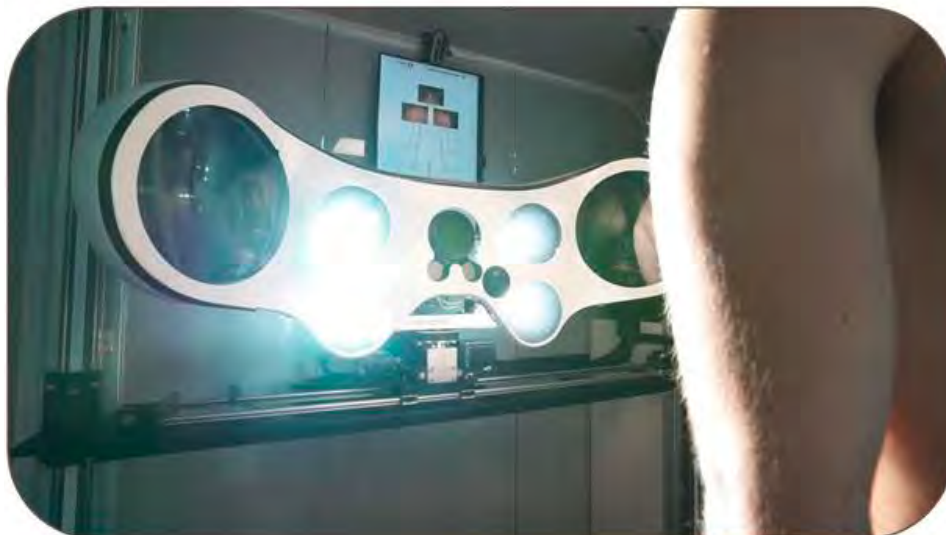
In a non-inferiority trial, patients will get scanned by the new device, and all pigmented lesions with a diameter above 3mm (maximum of 50 per patient, homogeneously distributed) will get non-contact dermatoscopy images (distance of 30-50cm). Afterwards, a technician will capture the same lesions manually using a contact handheld dermatoscope. Then all images will be evaluated independently and blinded for the type of device by 10 dermatologists that will assess the quality of the image (low, acceptable, optimal) and one of the following diagnostics for each image: melanocytic nevus, melanoma, basal cell carcinoma, squamous cell carcinoma, actinic keratosis, benign keratosis, dermatofibroma, vascular lesion and none of the others.

Results: Results are expected to behave in a similar manner than in previous research where there was a 94% concordance in diagnostic classes between the two image sources. In this study, having more patients with a potential for more diverse typology of lesions, results regarding previously underrepresented classes are expected. In total between 9.000-15.000 pairs of images will be included in this study. Additionally, performance metrics will assess mean and range of time per scan.

Conclusions: A new imaging autonomous scanner for total non-contact dermatoscopy photography will be assessed in a multicenter prospective trial. This new technology may facilitate the access to digital dermatoscopy by expanding the efficiency of the imaging procedure and incorporation of future development of AI solutions.

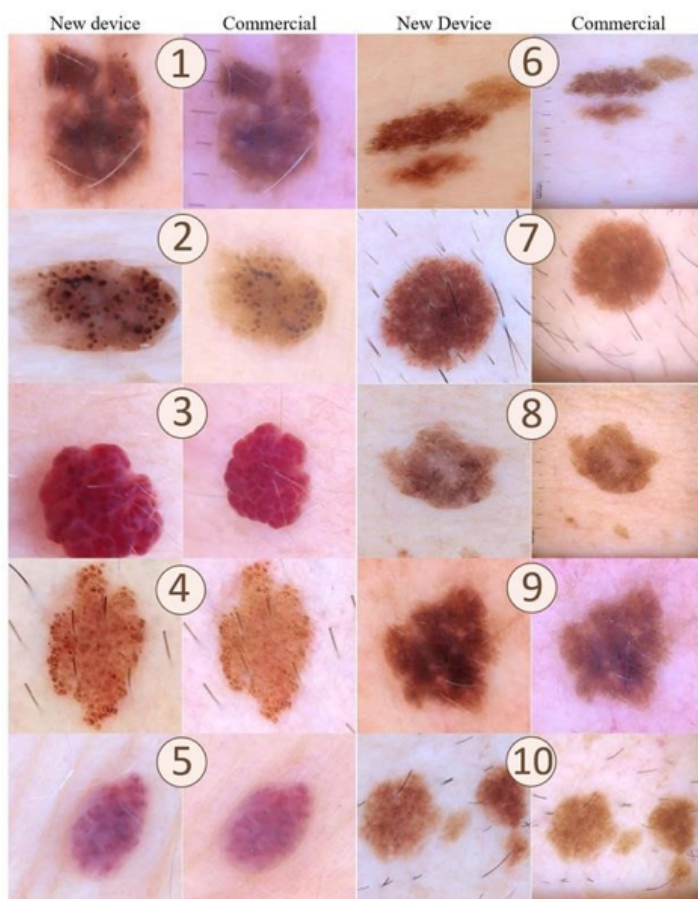
Supporting Document 1

Figure 1. Device for the autonomous scanning with digital cameras that move and in different body sites to image individual lesions with non-contact polarised dermoscopy. A booth with fixed illumination and a screen with verbal instructions provided by a computer guide the patient during the scanning.



Supporting Document 2

Figure 2. Images taken by device (left image) and by the commercial contact polarized dermoscope attached to a digital camera. No significant differences are observed. 1: Seborrheic keratosis, 2: Seborrheic keratosis, 3: Vascular lesion, 4: Melanocytic Nevus, 5: Vascular, 6: Melanocytic Nevus, 7: Nevus, 8: Seborrheic keratosis, 9: Melanoma, 10: Melanocytic Nevus



Significant improvement in melanoma survival over the last decade: A Hungarian nationwide study between 2011–2019

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Background: Recent real-world studies have reported significant improvements in the survival of malignant melanoma in the past few years, mainly as a result of modern therapies. However, long-term survival data from Central Eastern European countries such as Hungary are currently lacking.

Methods: This nationwide, retrospective study examined melanoma survival in Hungary between 2011–2019 using the databases of the National Health Insurance Fund (NHIF) and Central Statistical Office (CSO) of Hungary. Crude overall survival and age-standardized 5-year net survival as well as the association between age, sex, and survival were calculated.

Results: Between 2011 and 2019, 22,948 newly diagnosed malignant melanoma cases were recorded in the NHIF database (47.89% male, mean age: 60.75 years (SD: ± 16.39)). 5-year overall survival was 75.40% (women: 80.78%; men: 69.52%). Patients diagnosed between 2017–2019 had a 20% lower risk of mortality compared to patients diagnosed between 2011–2012 (HR 0.80, 95% CI 0.73–0.89; $p < 0.0001$). Age-standardized 5-year net survival rates in 2011–2014 and 2015–2019 were 90.6% and 95.8%, respectively (women: 93.1% and 98.4%, men: 87.8% and 92.7%, respectively). The highest age-standardized 5-year net survival rates were found in the 0–39 age cohort (94.6% in the 2015–2019 period). Conclusion: Hungary has similar melanoma survival rates to Western European countries. Based on net survival, the risk of dying of melanoma within 5 years was cut by more than half (55%) during the study period, which coincides with the successful implementation of awareness campaigns and the wide availability of modern therapies.

This work was supported by the Hungarian National Laboratory (under the National Tumorbiology Laboratory project (NLP-17))

This article has been accepted for publication in the Journal of the European Academy of Dermatology and Venereology

Simultaneous melanomas in the setting of multiple primary melanomas

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Background: It is estimated that about 1-13% of melanoma patients will develop multiple primary melanomas. Although the occurrence of subsequent tumors has been described during the last few years, the development of simultaneous melanomas has not yet been extensively studied.

Objectives: To study histological and clinical characteristics of simultaneous melanomas and define potential differences with non-synchronous multiple primary melanomas.

Methods: We reviewed our registries to identify patients with multiple primary melanomas. We studied epidemiological, clinical, and histological characteristics of patients who were diagnosed with simultaneous melanomas and compared them with those of patients who developed non-synchronous multiple primary melanomas. As simultaneous were defined subsequent melanomas that were diagnosed either at the same visit or within a time-period of maximum 1 month.

Results: Between 2000 and 2020, 2500 patients were diagnosed with melanoma at Andreas Syggros Hospital. 86 (3.4%) patients presented multiple primary melanomas and among them 35 (40.7%) developed simultaneous melanomas. Patients with simultaneous melanomas developed more frequently more than 2 tumors. First tumors of patients with non-synchronous melanomas were significantly thicker than second tumors while those of patients with simultaneous melanomas did not differ significantly. Slight differences in the tumor localization, staging and histologic type were observed between the two groups. However significant differences were ascertained between first and second tumors in both groups.

Conclusion: Simultaneous melanomas occupy an important proportion of multiple primary melanomas, affecting a non-negligible number of patients. Slight differences between simultaneous and non-synchronous multiple primary melanomas seem to define a distinct subcategory of multiple primary melanomas.

Supporting Document 1

	SM	nsMPM	P-value
Breslow index (range)	0.45 (0-4.50)	0.89 (0-7.80)	0.800
Localization			0.766
Trunk	49.5%	43.4%	
Upper limbs	28.4%	17.7%	
Lower limbs	14.7%	15.0%	
Head	7.4%	17.7%	
Missing data	0	6.2%	
Melanoma Type			0.557
SSM	80.0%	63.7%	
NM	0	10.6%	
ALM	0	1.8%	
LMM	16.8%	10.6%	
Other	0	2.7%	
Missing data	3.2%	10.6%	
Stage			0.789
0	42.1%	31.9%	
I	47.4%	45.1%	
II	6.3%	14.2%	
III	1.1%	3.5%	
IV	0	0	
Missing data	3.1%	5.3%	

	SM			nsMPM		
	1st SM	2nd SM	p-value	1st nsMPM	2nd nsMPM	p-value
Breslow index (mean)	0.83	0.42	0.164	1.31	0.45	<0.001
Breslow index 1st SM vs ns MPM: p-value 0.516						
Melanoma localization	1st SM	2nd SM	p-value	1st nsMPM	2nd nsMPM	p-value
trunk	20	19	<0.001	23	22	<0.001
lower limbs	4	5		11	6	
upper limbs	5	10		8	10	
head	5	1		6	11	
Unknown primary	1	0		0	0	
Missing data	0	0		4	3	
Localization 1st SM vs 1st nsMPM: p-value 0.420						
Melanoma stage	1st SM	2nd SM	p-value	1st nsMPM	2nd nsMPM	p-value
0	8	7	0.005	9	24	0.022
I	20	22		24	21	
II	4	4		12	2	
III	1	1		3	1	
IV	0	0				
Missing Data	2	1		4	4	
Stage 1st SM vs 1st nsMPM: p-value 0.230						
Same stage	1st and 2nd SM			1st and 2nd nsMPM		p-value
	18 (51.4%)			12 (23.1%)		0.595
Histologic type	1st SM	2nd SM	p-value	1st nsMPM	2nd nsMPM	p-value
Superficial Spreading Melanoma (SSM)	29	32	<0.001	34	31	0.001
Nodular Melanoma (NM)	0	0		8	3	
Lentigo Maligna Melanoma (LMM)	3	2		4	7	
Acral Lentiginous Melanoma (ALM)	0	0		0	2	
Other	0	0		0	2	
Unknown	3	1			7	
Histologic type 1st SM vs 1st nsMPM: p-value 0.912						

Data on melanoma from the majority of countries show a rapid increase of the incidence of this cancer, with a slowing of the rate of incidence in the period 1990–2000.

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Abstract: This article reviews epidemiology, risk factors, pathogenesis and diagnosis of melanoma. Data on melanoma from the majority of countries show a rapid increase of the incidence of this cancer, with a slowing of the rate of incidence in the period 1990–2000. Males are approximately 1.5-times more likely to develop melanoma than females, while according to other studies, the different prevalence in both sexes must be analyzed in relation with age: the incidence rate of melanoma is greater in women than men until they reach the age of 40 years, however, by 75 years of age, the incidence is almost 3-times as high in men versus women. The most important and potentially modifiable environmental risk factor for developing malignant melanoma is the exposure to ultraviolet (UV) rays because of their genotoxic effect. Artificial UV exposure may play a role in the development of melanoma. The most important host risk factors are the number of melanocytic nevi, familiar history and genetic susceptibility. A patient with a personal history of melanoma must be considered at greater risk for subsequent melanoma. Indeed approximately 1–8% of patients with prior history of melanoma will develop multiple primary melanomas. We herein review the dermatological diagnosis and classification of melanoma.

Using a clinicopathologic and gene expression model to predict sentinel lymph node metastasis in primary cutaneous melanoma could reduce the rate of sentinel lymph node biopsies with >70%: a multicentre Danish cohort study

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Background: Sentinel lymph node biopsy (SLNB) is the standard procedure for staging in primary cutaneous melanoma and is used to guide subsequent management. It is, however, an invasive procedure with associated risks and proper patient selection for SLNB remains a challenge; approx. 80% of all SLNB are negative, with even higher negative rates when looking only at thin melanoma (T1) which account for the vast majority of cases. The clinicopathological and gene expression profile (CP-GEP) model was developed to identify low risk melanoma patients who may safely forgo SLNB. The CP-GEP model combines Breslow thickness and patient age with the expression of eight genes to classify patients as high or low-risk for nodal metastasis.

This study presents data from an independent validation of the CP-GEP model in a multicenter Danish cohort.

Materials and Methods: Archived formalin-fixed paraffin-embedded primary melanoma tissue from 537 T1-T3 cutaneous melanoma patients was collected and analysed with CP-GEP in a prospectively designed study. The patients had undergone SLNB between 2010 and 2015 at either of two university clinics in Denmark. The CP-GEP result was compared with the SLNB result, calculating the diagnostic value of CP-GEP for SLNB metastasis.

Results: Median age at diagnosis was 58 years (interquartile range [IQR] 44-70) and median Breslow thickness was 1.3mm (IQR 0.95-1.82). The distribution of T1, T2 and T3 melanoma was 32.8%, 46.9% and 20.3%, respectively. The SLNB positivity rate was 18.1%. The CP-GEP model identified 219 (40.8%) patients as having a low risk for nodal metastasis with a NPV of 91.3%. When analysing the T1 subgroup (n=176) the CP-GEP low risk rate was 72.7% with an NPV of 94.5%.

Conclusion: The CP-GEP model accurately identifies patients at low risk for SN metastasis, and especially in patients with T1 melanoma. Results are in line with previous retrospective validation studies on European and US cohorts, however, this study contain the largest T1 subgroup validation with a potential very high SLNB reduction rate found for this subgroup. The CP-GEP is a promising risk stratification tool for melanoma patients, potentially preventing unnecessary surgery in a large group of patients.

What is the fidelity to risk-tailored screening and surveillance skin check schedules for melanoma? A prospective mixed-methods implementation study

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Introduction and Objectives: Skin cancer screening is not currently recommended in most countries due to insufficient evidence of a reduction in mortality and lack of data on cost-effectiveness. However, many guidelines recommend opportunistic screening guided by personal melanoma risk. We aimed to evaluate the implementation of a model of risk-tailored screening and surveillance based on personal melanoma risk, including assessing the fidelity (adherence) to risk-tailored surveillance recommendations and exploring factors influencing adherence or deviation.

Materials and Methods: We used a mixed-methods study design. Patients with or without melanoma attending tertiary dermatology clinics at the Melanoma Institute Australia, Sydney, Australia, were invited to complete an online melanoma risk assessment questionnaire via iPad and were provided with personal risk information alongside a risk-tailored skin check schedule. Clinic record data were collected from the risk tool, clinician-recorded data on deviations, and appointment booking system. Post-consultation, we collected patient surveys and conducted semi-structured interviews with patients and clinic staff. Interviews were audio recorded, transcribed and data were analysed thematically.

Results: Data included clinic records (247 patients), surveys (202 patients) and interviews (29 patients, 11 clinic staff). Overall, recommended skin check intervals were followed in 62% of cases. In cases of non-adherence, skin checks were more likely to occur more frequently than recommended. Decisions to deviate from recommended schedules were similarly influenced by patients (44%) and clinicians (56%). From the interview data, themes driving adherence among patients included trust in health professional advice and among clinicians included trust in the risk estimate. Themes driving patient's non-adherence included anxiety and autonomy around decision-making. Among clinicians, themes included concern around specific lesions, patient risk factors, and risk estimate accuracy.

Conclusions: This study showed reasonable fidelity to a program of risk-tailored skin check recommendations for people with and without melanoma. Further adherence may be gained by incorporating strategies to identify and assist patients with high levels of anxiety, promoting effective self-surveillance checks, improving clinicians' confidence in recommending risk-tailored skin check schedules, and further improving the risk prediction tools.

Androgen Receptor is a Determinant of Melanoma targeted drug resistance

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Introduction and Objectives: Melanoma provides a primary benchmark for targeted drug therapy. Most melanomas with BRAFV600 mutations regress in response to BRAF/MEK inhibitors (BRAFi/MEKi). However, nearly all relapse within the first two years, and there is a connection between pathways involved in BRAFi/MEKi-resistance and poor response to immune checkpoint therapy.

Materials and Methods: We recently showed that androgen receptor (AR) activity is required for melanoma cell proliferation and tumorigenesis. Here we find that AR expression is markedly increased in BRAFi resistant melanoma cells as well as in sensitive cells soon after BRAFi exposure. Increased AR expression is by itself sufficient to render melanoma cells BRAFi-resistant, eliciting transcriptional changes of BRAFi resistant subpopulations and elevated EGFR and SERPINE1 expression of likely clinical significance. Inhibition of AR expression and activity blunts changes in gene expression and suppresses proliferation and tumorigenesis of BRAFi-resistant melanoma cells, enhances MHC I expression and CD8+ T cells infiltration.

Results: Our findings point to targeting AR as a possible co-adjuvant approach for the prevention and management of the disease.

Association of miR-146a-5p and miR-21-5p with prognostic features in melanoma subtypes

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Introduction and Objectives: In cutaneous melanoma, Breslow thickness evaluation (BT) is the main parameter used to define the tumor stage, but also other tumor characteristics are relevant in prognostications. Indeed, specific features have been associated with a worse cutaneous melanoma prognosis, including defined histological parameters (greater Breslow thickness, presence of ulceration or higher mitotic index), and the tumor localization. Discrepancies in definition or other obstacles/difficulties in correctly assessing these parameters could lead to tumor misclassification. MicroRNAs (miRNAs) play a role in melanoma carcinogenesis. Given that their expression can be easily measured in archive samples, they could be valid prognostic biomarkers, since from the early stages of disease diagnosis, also paying attention to the different tumor subtypes and localization.

Materials and Methods: We quantified the expression of miR-146a-5p and miR-21-5p in 170 FFPE samples of melanoma patients with different Breslow thickness (BT) and prognostic histologic features, including subtype, presence/absence of ulceration and regression, mitotic index and tumor localization, to verify its association with melanoma characteristics that are associated with patients' prognosis.

Results: MiR-146a-5p and miR-21-5p expression was significantly higher in all tumors with higher mitotic rate ($\geq 1/\text{mm}^2$) as well as in ulcerated melanomas compared to those without ulceration. Furthermore, when we examined the miRNA combined expression in association with ulceration status in the same anatomical area, we found a significantly higher miRNA expression in ulcerated melanomas localized in the trunk and limbs. As for the presence of regression, no difference was observed in miRNA expression when considering all melanomas subtypes, but miR-21-5p expression was higher in LMM subtype with regression.

Conclusions: miR-146a-5p and miR-21-5p expression has shown to be different in melanoma with different histological parameters and the findings of the study can provide further insights for the diagnosis and treatment of melanomas with specific adverse prognostic features.

BAP1 mutations in two melanoma cases; synchronous cholangiocellular carcinoma and chromophobe renal cancer

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Introduction: The rapid advances in molecular genetics diagnostics have led to a better understanding of the background of melanoma. However, we do not have sufficient knowledge about the impact of germline mutations.

Materials and Methods: We selected and studied 37 patients cared at the Oncodermatology Department, National Institute of Oncology, Budapest, Hungary. In 26 patients, double synchronous tumours (melanoma and other) while in 11 patients triple tumours (melanoma and two others) were detected. Their genetic analysis was performed using a multigene NGS panel covering 113 genes associating with hereditary cancer predisposition syndrome on Illumina MiSeq instrument. All pathogenic, likely pathogenic and variant with unknown significance were validated in a second sample by Sanger sequencing.

Results: Two cases harboured germline BAP1 mutations. One patient (harboring the BAP1:c.442G>Tlp.Glu148Ter, splice mutation) is a 50-year-old female patient who was diagnosed with cholangiocellular carcinoma in the autumn of 2020. She has received systemic treatment for several lines. She underwent enucleation for choroidal melanoma in March 2022. Currently, she is receiving active oncological therapy for cholangiocellular carcinoma, her choroidal melanoma is being observed.

The other patient (harboring the BAP1:c.1251-11G>A, splice mutation) is a 64-year-old male patient who underwent a right nephrectomy for chromophobe cell renal cancer in February 2016. At the same time, a melanoma metastasis on the left side of the neck was detected. A left cervical block dissection was performed, followed by postoperative irradiation. PET/CT scan in August 2016 showed metastases in bone, muscle and several subcutaneous nodules. Based on her BRAF positivity, she received first-line BRAF-Mek inhibitor therapy, which was then suspended after 16 months due to progression and switched to PD-1 inhibitor immunotherapy. He is now in complete remission.

Conclusions: Hereditary causes in patients with melanoma are rare. However, in patients where melanoma occurs together with other tumours, genetic causes can be found. In our cohort two patients were identified with germline BAP1 mutation. Their clinical course seems better compared to mutation negative cases.

This work was performed within the frame of the Development of innovative tumor diagnostic and therapeutical interventions at National Institute of Oncology (grant NKFIH 2020-1.1.6-Jöv -2021-00008)

Copy-number variations and CDK4 amplification as a prognostic factor in acral lentiginous melanoma

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Introduction and Objectives: Acral lentiginous melanoma (ALM) is a cutaneous melanoma (CM) with poor prognosis due to the diagnosis in advanced stages and poor response to conventional antitumor therapy. ALM is an uncommon clinicopathological variant of CM, which arises on palms, soles and nail bed. Most ALM (more than 50%) belong to the triple wild-type (TWT) melanoma subtype for BRAF, NRAS, and NF1 genes, that are mutated in only 42-55% of ALM tumours. Furthermore, ALM with mutations in KIT (3-36%), GNAQ (11%) and TERT activating mutations (9-41%) have been identified. Copy number variations (CNVs) are numerous in ALM; amplifications have been described in KIT, TERT, CDK4, MDM2 and CCND1, and deletions in CDKN2A, PTEN and NF1.

Materials and Methods: In order to describe the ALM genetic profile, we conducted a retrospective review of patients newly diagnosed with ALM in the Hospital Universitari Arnau de Vilanova (Lleida) during the period 2010-2020. Paraffin-embedded biopsies from this series were reviewed and a microscopic analysis of ALM samples was performed in order to select tumour regions to extract DNA. Then, we analysed variations in gene dose, also known as CNVs (amplifications/deletions) of oncogenes by Multiplex Ligation-dependent Probe Amplification (MLPA), and we performed an analysis of clinical data to identify possible biomarkers in biopsies from our patient cohort.

Results: Our findings reveal that the total number of CNVs (total number of amplifications and deletions of oncogenes per patient) we have found that patients with high CNVs (≥ 7) have significantly a higher risk and poor outcome than patients with low CNVs (< 7). Furthermore, patients with CDK4 amplification have worse prognosis, and most of them have high CNVs compared to wild-type CDK4 patients. On the other hand, we confirmed that an increase in CDK4 copy-number correlates with an increase in CDK4 expression by immunohistochemistry.

Conclusions: The implication of these pathways in tumour progression and therapeutic response will be investigated to describe a characteristic molecular profile of ALM. These results will allow us to determine target molecular alterations to improve early diagnosis and personalized therapy of ALM patients.

Discovery of potential biomarkers of melanoma metastasis by lipidomic profiling

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Introduction and Objectives: Melanoma is the most lethal form of cutaneous cancer because of ability to metastasize to other organs. The 5-year survival rate of primary melanoma is over 98%. However, if it spreads to distant sites the survival rate declines to 17%. Thus, early detection of the disease as well as detection of its metastatic potential is important. Accordingly, there is a need for new molecular biomarkers that can be used to predict the progression of the disease. Metabolomics has emerged as a powerful tool for the discovery of metabolic biomarkers in various cancer types, because closely reflect the environmental impact, stage of diseases, and response to therapy.

Materials and Methods: In the present study, we applied a state-of-the-art quantitative lipidomics profiling platform Lipidizer to conduct the most comprehensive search to date of the plasma lipidome in melanoma patients. Blood sampling was performed after surgical removal of the primary tumour in 83 patients, while 69 patients had metastatic melanoma at the time of blood sampling. In total, 13 lipid classes and more than 1100 lipid species, including sphingolipids, neutral, polar glycerolipids, were covered by the analysis. Logistic regression was used to analyse the association between lipid species and metastasis formation. A p value <0.05 was considered statistically significant.

Results: The lipidome profile of patients with metastatic melanoma at the time of blood sampling showed significant differences compared to individuals without cancer. Three lipid classes (dihydroceramide: DCER; lactosylceramide: LCER; free fatty acid: FFA) showed significant decrease in patients with metastasis, while the triacylglycerol (TAG) class lipids increased remarkably. Significant differences were found on 170 lipid compounds between the two groups of patients. After correction for sex/age with logistic regression this number was reduced to 5 lipid species. The cholesterol ester CE(12:0), FFA(24:1), TAG46:3-FA12:0, TAG58:8-FA20:3 lipids negatively correlated with the presence of metastatic tumour; while TAG48:4-FA12:0 positively predicted the presence of metastasis.

Conclusions: Overall, the Lipidizer platform has helped us to identify several lipid molecules whose quantitative variation helps to predict the presence of metastasis in melanoma patients and contributes to a better understanding of the disease and possible future therapies.

Expression of cytokine and chemokine receptors in melanoma cell lines in response to liver endothelial cells

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Introduction and Objectives: Organ specific metastasis of primary tumours has been the subject of research for a long time. Metastasis formation has been shown to result from the interaction between the tumour cell and the target organ microenvironment. The endothelial cells covering the vascular walls of organs produce various chemo-attractants and adhesion molecules that can bind to receptors expressed on the surface of tumour cells and control the site of metastasis formation. Because melanoma has a fully comprehensive metastatic potential, our aim was to investigate receptor/ligand expression which could contribute to the increased invasive potential in melanoma cell lines after co-culturing with hepatic endothelial cells.

Materials and Methods: Matrigel Invasion Chambers were used for co-culturing, in which melanoma cells (WM983A, WM278, WM793B, WM1361, WM1366, and WM278) were seeded into the upper chamber, while endothelial cells were cultured in the lower chamber. After the incubation, invasive and non-invasive melanoma cells were selected, and hepatic endothelial cells were also recovered for further analyses. Real-time qRT-PCR were performed to determine the expression of cytokine and chemokine receptors, while the expression of cytokine and chemokine ligands in the endothelial cells was examined using Proteome Profiler Array.

Results: According to our results, WM983A, WM1361 and WM3248 melanoma cell lines showed significantly increased invasive potential after co-culturing compared to the control. On the other hand, we found increased CXCL8 and CXCL1 chemokine expression in the endothelial cells. Interestingly, both compartments of the CXCL8/CXCR2 ligand/receptor system were overexpressed as the result of co-culturing hepatic endothelial cells with WM3248 cell line, which was associated with increased invasive potential.

Conclusions: Our findings suggest that several cytokine and chemokine receptors can play a role in melanoma invasion, and the CXCL8/CXCR2 ligand/receptor system possibly contribute to the invasion targeting the liver.

First-in-human intratumoral administration of AS01B in combination with autologous CD1c (BDCA-1)+ / CD141 (BDCA-3)+ myeloid dendritic cells plus ipilimumab and IV nivolumab in patients with refractory advanced melanoma

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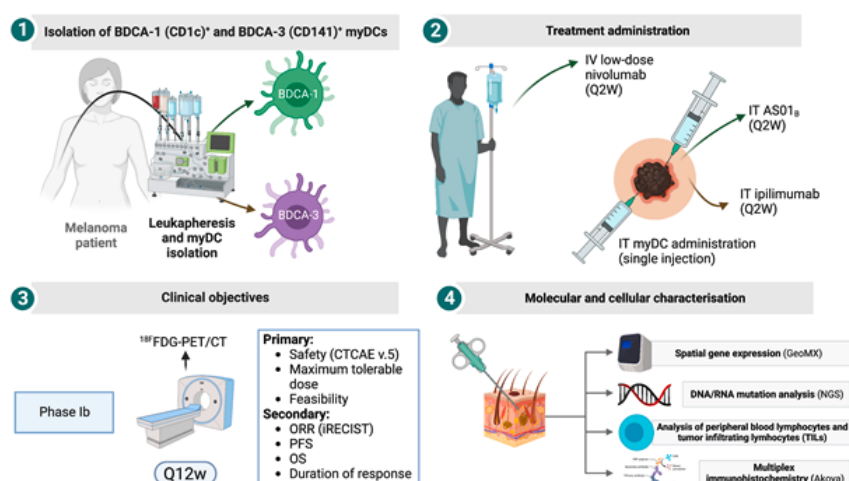
Introduction and Objectives: The presence of CD1c (BDCA-1)+ (cDC2) and CD141 (BDCA-3)+ (cDC1) myeloid dendritic cells (myDC) in the tumor microenvironment is necessary to induce an effector CD8+ T cell response and for response to immune checkpoint blockade (ICB). AS01B is an adjuvant component of a prophylactic vaccine demonstrated to induce adaptive immunity. Intratumoral (IT) injection of myDC is both safe and feasible (Schwarze et al. Vaccines 2020, JITC 2022).

Materials and Methods: In this first-in-human clinical trial (NCT: 03707808), patients with metastatic melanoma refractory to ICB and BRAF/MEK inhibitors (when eligible) were recruited. Patient's white blood cells were collected by leukapheresis for subsequent isolation of CD1c (BDCA-1)+ and CD141 (BDCA-3)+ myDC. Patients were treated with a low dose of intravenous nivolumab (10mg, q2w) plus IT administration of ipilimumab (10mg, q2w) and AS01B (50µg, q2w) for up to one year. Isolated myDC were administered (clinical or ultrasound-guided) as a single injection into a metastatic lesion on day 2. When feasible and safe, baseline and on-treatment core-needle biopsies were taken for analysis of immune cell markers using multiplex immunohistochemistry (mIHC).

Results: Eight patients were enrolled, and treatment was well tolerated without any unexpected adverse events. Six patients were evaluable for response with two of them achieving a durable CR (ongoing 12 and 9 months after the initiation of study therapy). One additional patient obtained a PR (ongoing after 9 months). One patient had an SD as their best objective response. Treatment is continuing for two patients. Preliminary mIHC analyses comparing baseline with on-treatment biopsies reveal an increase in tumor infiltrating lymphocytes and decrease in the mean distance between SOX10+ tumor cells and CD8+ T cells in a responding patient.

Conclusions: Intratumoral injection of CD1c (BDCA-1)+ / CD141 (BDCA-3)+ myDC in combination with repeated IT administration of ipilimumab and AS01B and systemic low dose nivolumab shows promising clinical results and no unexpected safety issues, meriting further investigation.

Supporting Document 1



Generating High-Quality Dermoscopic Images using Diffusion Models

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1. Combalia M, Codella N, Rotemberg V, et al. Validation of AI Prediction Models for Skin Cancer Diagnosis Using Dermoscopy Images. *Lancet Digital Health*. 2022;4(5):e330-e339.
2. Combalia M, Codella NCF, Rotemberg V, et al. Bcn20000: Dermoscopic Lesions in the Wild. *arXiv*. 2019.
3. Ronneberger O, Fischer P, Brox T. Convolutional Networks for Biomedical Image Segmentation. *arXiv*. 2015.

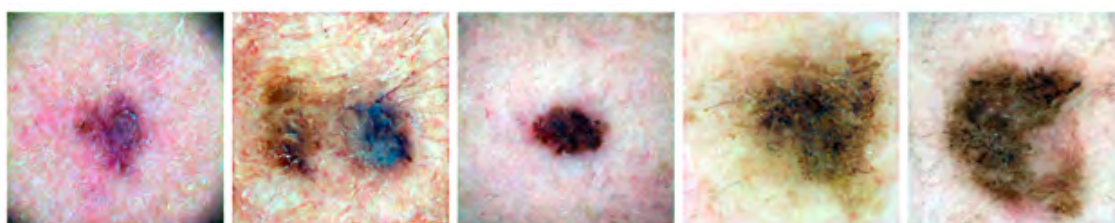
Introduction and Objectives: Access to labeled training data remains a challenge in healthcare for deep learning applications. To overcome this limitation, existing data augmentation techniques such as image manipulation in the pixel or feature space can increase the diversity and quantity of training data. However, these techniques may not generate high-quality images that represent real-world scenarios.

Materials and Methods: In this paper, we propose the use of diffusion models to generate high-quality images for healthcare applications. Diffusion models add noise to training data, denoise the data to recover it, and generate new related data. We trained a diffusion model on the melanoma class of the ISIC 2019 dataset, consisting of 4522 images. The model added noise to the data at each step of the chain, and the neural network had to learn how to remove the noise and create new information coherent with the melanoma images. The architecture of the neural network was based on a simplified Unet model, and we used the Adam optimizer with a learning rate of 1e-4 to train the diffusion model for 100 epochs.

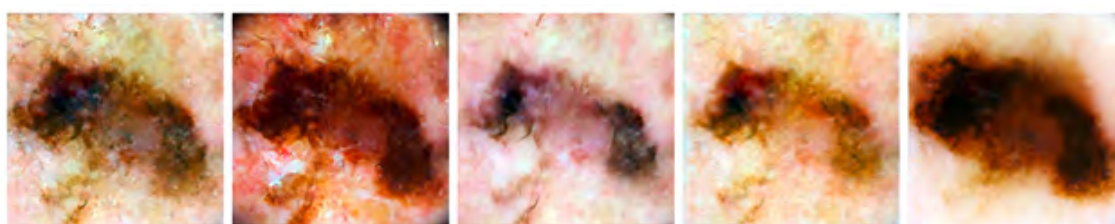
Results: Our results demonstrated that diffusion models can generate realistic, high-quality images and representative of real-world scenarios, as demonstrated by the images presented in figures 1 and 2. These images can be used for education, privacy, and data augmentation purposes in the healthcare domain.

Conclusions: In conclusion, diffusion models are an effective way to generate high-quality images for healthcare applications, especially when labeled training data is limited. Our results show that diffusion models can generate realistic images that represent real-world scenarios. Future work will explore the use of conditional diffusion models, starting with text prompts and later incorporating patient details such as genetic information. The use of diffusion models can be a valuable tool, providing high-quality images for education, privacy, and data augmentation purposes.

Supporting Document 1



Supporting Document 2



Identification of miRNA-gene networks affecting melanoma plasticity in response to immunotherapy

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Introduction and Objectives: MicroRNAs are essential modulators of gene expression either at the transcriptional or translational level. Since they fine-tune several important gene networks and pathways, they are often found deregulated in cancer and they serve as important indicators of prognosis, diagnosis, tumor staging and response to current therapies. In this study, we explore how such networks control responses to immune checkpoint blockade therapies in melanoma.

Materials and Methods: Previously, we have developed four mouse melanoma models, M1 (UV-induced, Braf-mutated), M2 (UV-induced, Braf-mutated), M3 (DMBA-induced, Gna11-mutated), and M4 (UV induced, Kras/Gnaq-mutated) that represent neural crest-like, undifferentiated, melanocytic, and transitory subtypes of human melanoma, respectively. In preclinical clinical studies of immune checkpoint blockade (ICB), melanomas expressing higher level of melanocytic plasticity signature, such as M1 and M2, were more resistant than those expressing lower level of MPS, such as M3 and M4 melanomas.

Results: By paired sequencing analyses of the four melanoma models subjected to anti-CTLA-4 treatment, we found that anti-CTLA-4 induced significant changes of mRNA and miRNA expression in the sensitive models (M3 and M4), but not in the resistant models (M1 and M2). In the M4 melanoma, anti-CTLA-4 treatment reduced the expression of miR-203, miR-205, and miR-200 family that counteract Zeb1 for mesenchymal-epithelial transition (MET). However, the early recurrent tumors exhibited higher expression of microRNAs that targeted inflammatory cytokines such as CCL2 and CCL8. In the M3 melanoma, anti-CTLA-4 treatment reduced the expression of miRNAs that targeted inflammatory cytokines such as CCL5 and CCL8. However, the early recurrent tumors exhibited lower expression of microRNAs that targeted corticosteroid-inducible genes, such as Tsc22d3 and Dusp family, and immune checkpoints, including LAG3 and TIM-3.

Conclusions: These results suggested that melanomas of low MPS expression could develop multiple mechanisms to escape the ICB-induced immune responses, including (1) switching to mesenchymal-like state; (2) adapting by suppressing inflammatory responses; and (3) increasing the expression of other immune checkpoints. Currently, we are performing the studies to validate these results and investigate detailed mechanisms.

Joint modeling of safety and peripheral Mode-of-Action biomarkers to support RP2D identification in Phase 1 study of SAR444245 as monotherapy or combined with pembrolizumab in patients with advanced solid tumors

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Introduction and Objectives: SAR444245 (SAR'245) a clinical-stage site-specific pegylated human IL-2, blocks IL-2 alpha receptor binding but retains near native binding affinity for beta/gamma IL-2 receptor subunits. Previously, we reported results of Phase 1 HAMMER study (NCT04009681); herein, we describe an innovative integrative approach that considers peripheral key mode-of-action (MoA) biomarkers with objective response and dose-limiting toxicity (DLT) rate to help identify the recommended Phase 2 dose (RP2D) for SAR'245.

Materials and Methods: SAR'245 was given IV as monotherapy Q2W [Cohort A], monotherapy Q3W [Cohort B] or Q3W + IV pembrolizumab 200 mg Q3W/400 mg Q6W [Cohort C] and Q3W + Cetuximab [Cohort D]. Joint modeling was carried out to account for relationship between dose and 1) MoA biomarkers, and NK cells in blood measured by flow cytometry; 2) response surrogate biomarker: Circulating tumor DNA (ctDNA) measured by Guardant Omni 500 panel; and 3) DLTs. A latent variable was used to model correlation between DLT and MoA or response surrogate biomarkers, Bayesian approach derived posterior probabilities (PP) at each dose level of the target region (defined by >20% probability of fold change of biomarker values post-treatment above a predefined threshold and DLT rate <33%) and the PP of overdose region (defined by DLT rate ≥33%). RP2D was determined by maximizing the PP of target region among doses with PP of the overdose region probability <40%.

Results: A total of 136 patients, including melanoma patients were analyzed. The CD8/CD4 ratio and concentrations of NK, CD8, and CD4 achieve maximum probability of reaching meaningful modulation around 32 µg/kg. When SAR'245 was combined with pembrolizumab, the results with PoM biomarkers and with ctDNA showed the best performance at 24-32 µg/kg and at 16-24 µg/kg respectively. When all parameters were considered, either 24 or 32 µg/kg could serve as an adequate dose at Q3W scheduling.

Conclusions: In early oncology studies, joint modeling using non-invasive biomarkers, including MoA and response biomarkers, and a safety profile can inform dose-response relationships and support RP2D selection. This innovative integrative modeling will guide clinical study design. Studies of SAR'245 that further explore the dosing and scheduling are on-going.

miRNA-195-5p-enriched small extracellular vesicles enhances BRAF-mut melanoma response to MAPK inhibitors

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Introduction: Although the use of MAPK inhibitors has considerably improved BRAF-V600E mutant melanoma prognosis, drug resistance remains an unsolved clinical challenge, with the majority of advanced patients relapsing within a few months after treatment initiation. Tumor-derived Extracellular Vesicles (EVs) have been raised as important regulators of tumor resistance, and modulation of their cargo, with enrichment of antitumoral molecules, represents a promising strategy to improve therapy response and clinical outcomes. As miR-195-5p down-regulation is associated with cutaneous melanoma growth and resistance, we aimed to analyze whether restoring its expression could modulate EVs cargo and increase bystander cells response to MAPK inhibitors (MAPKi).

Methods: BRAF-mutant A375, SKMel-5 and SKMel-28 human melanoma cells were transfected with miR-195-5p or control mimics (10nM), and treated or not with the MAPK inhibitors (BRAFi and MEKi, 1:1uM). After 72 hours, EVs were isolated by differential ultracentrifugation, resuspended in PBS and characterized by NTA analysis, electron microscopy and western blot. Characterization of EVs miRNA profile was performed by digital barcode technology. For in vivo experiments, EVs were exogenously loaded with miR-195-5p by electroporation and cells were incubated with these EVs in the presence of MAPKi before inoculation in nude mice.

Results: miR-195-5p overexpression resulted in increased small EVs release by melanoma cells. Analysis of miRNA profile showed that EVs derived from cells overexpressing miR-195-5p presented a higher content of this miRNA, along with increased levels of the tumor suppressors miR-152-3p and miR-202-3p. Uptake of miR-195 enriched vesicles by bystander tumor cells resulted in decreased proliferation and viability. Interestingly, upon MAPKi treatment, miR-195 EVs boosted tumor cell death and also decreased their clonogenic potential. Moreover, using a tumor xenograft model, EVs exogenously loaded with miR-195-5p impaired melanoma growth in vivo, reducing the repopulation capacity of cells previously exposed to MAPK inhibitors.

Conclusions: restoring miR-195-5p expression in cutaneous malignant melanoma significantly increases MAPKi treatment efficacy through the secretion of EVs enriched in tumor suppressors microRNAs and uptake by bystander cells. Our findings also suggest that EVs preparations can be translated into clinical product to be used as adjuvants in melanoma patients. Funding: FAPESP (process number 2019/07278-0).

Multiomics analysis of immune-related adverse events in melanoma patients treated with anti-PD1-based immune checkpoint inhibitors

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Introduction and Objectives: Immune checkpoint inhibitors (ICIs) are standard-of-care in advanced melanoma, but their use is associated with immune-related adverse events (irAEs). We performed multiomics analysis to unravel the underlying immunobiology.

Materials and Methods: 82 patients treated with anti-PD1/anti-CTLA4 (84%) or anti-PD1 (16%), with (74%) irAEs, were retrospectively analyzed (discovery cohort [DC]; n=9) or prospectively collected in a main (MC; n=54) and an internal validation set (VC; n=19). The results were confirmed in an external validation cohort (n=30). Serum was collected at baseline (BL) and at irAE onset (AE) or 2nd infusion. Serum proteins were analyzed using the Olink Proteomics 384 immuno-oncology assay and validated with a Mesoscale multiplex assay.

Results: Proteomic analysis and multiplex cytokine/chemokine assay from serum at baseline and at irAE onset indicated aberrant T-cell activity with differential expression of Type I and Type III immune signatures. CXCL-9, CXCL-10, IL-10, IL-17A, IFN γ , TNF α , TNF β (LTA) and IL-21 were increased at irAE onset in the DC and MC cohorts in both assays. This significant increase was absent in patients without irAEs. A logistic regression model assessed the predictive value of these 8 cytokines for irAEs development. AUC was 0.87 (95% CI 0.77-0.97) in MC and 0.71 (95% CI 0.45-0.97) in VC. Validation of these results with 5 cytokines/chemokines (CXCL-10, IL-10, IL-17A, IFN γ , TNF α) in the external cohort showed an AUC of 0.74 (95% CI 0.47-0.91). Single cell RNA sequencing from peripheral blood samples in patients with and without irAEs showed early decrease in naïve CD4⁺ T-cells, increase in monocytes and decrease in CD4⁺ T-cells with IL-17A expression. Multiplex immunohistochemistry of skin rash and colitis tissue showed increase in the proportion of CD4⁺ T-cells with IL-17A expression. Based on these findings, anti-IL17A (Secukinumab 300mg, s.c.) was administered in a pilot cohort of 2 patients with severe myocarditis, colitis and skin rash, with irAE resolution within 20, 40 and 43 days, respectively.

Conclusions: This study demonstrates the role of Type III CD4⁺ T-cells in irAEs development and provides proof-of-principle evidence to support a clinical trial examining anti-IL17A for the management of irAEs.

Optimising Deep Learning Models for Histopathological Classification of AMBLor in melanoma

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Introduction and Objectives: The worldwide annual incidence of cutaneous melanoma is over 200,000 and increasing. We have previously identified the combined immunohistochemical expression of two epidermal proteins, Autophagy and beclin 1 regulator 1 (AMBRA1) and Loricrin overlying primary non ulcerated AJCC stage I/II as a novel prognostic biomarker. However, the process of scoring histological images remains labour intensive and influenced by subjectivity. Artificial intelligence (AI) has improved the accuracy of several pattern recognition tasks, such as classification of objects and various other entities in digital images and has shown good results even for tasks previously considered too challenging to be accomplished with conventional image analysis methods. Moreover, AI has the potential to decrease dermatologist workloads, eliminate repetitive and routine tasks, and improve access to dermatological care.

Materials and Methods: The aim of the present study was to investigate the potential use of AI for melanoma stratification and disease subtyping using digitised immunohistochemical images of early-stage melanoma stained for AMBRA/Loricrin (AMBLorR) expression. A dedicated training algorithm was created to quantify IHC expression of AMBLorR using Visiopharm image analysis. DeepLab V3 architecture on 216 Leica Biosystem's Aperio scanner was used to derive images of AMBRA 1, Loricrin and corresponding Haematoxylin and eosin stains from 72 anonymous non-ulcerated AJCC stage I/II melanomas.

Results: Image alignment was successfully performed to create serial digitised images using Visiopharm. Multiple auxiliary Analysis Protocol Packages were then used to identify Regions of Interest with subsequent quantitative analysis to stratify patients into risk categories. We demonstrated that Visiopharm was able to correctly distinguish between lost and maintained AMBRA1 expression (Pearson r Correlation = 0.9558, p value<0.0001), but was unable to determine loss of epidermal Loricrin expression based on gaps in epidermal staining.

Conclusions: Collectively these data demonstrate Visiopharm is a viable means through which to use AI to assess epidermal AMBRA1 expression, but further work is required to develop a deep learning model to confirm the diagnostic performance of combined AMBLor. Ultimately the development of a deep learning approach to AMBLor assessment has the potential to improve its diagnostic accuracy, reduce subjectivity and histopathologist work-load.

Peripheral blood biomarkers in malignant melanoma

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Background: The prevalence of malignant melanoma increased significantly worldwide over the last 4 decades. The 5-year survival rate of metastatic melanoma barely reaches 50% despite the use of new treatments. There is an increasing need for easily accessible blood biomarkers for early detection and monitoring the disease. Different tumor markers have been tested as prognostic factors in melanoma; among them are S100, and lactate dehydrogenase (LDH). However, there is a growing body of literature on the relationship between plasma osteopontin (OPN) concentrations and melanoma progression.

Objectives: We aimed to compare serum S100B, serum LDH and plasma OPN levels and diagnostic value between melanoma patients with or without metastasis.

Methods: We used peripheral blood obtained from 130 metastatic and 163 tumor free. There was no significant difference in age/sex between the groups. Serum concentrations of S100B (sandwich immunoassay) and LDH (UV kinetic assay) were routinely measured during follow-up. OPN plasma levels were measured by ELISA. For categorical variables chi2 test was used. The Shapiro–Wilk test was performed to assess the normality of the population. If two groups were compared, we used Mann-Whitney test, as the Shapiro-Wilk test showed not normal distribution. Statistical calculations were performed using SPSS software.

Results: All biomarkers we tested were found to be significantly higher in patients with metastases compared to those without tumors. In our results, the mean value of OPN was significantly higher ($p < 0.001$) in patients with metastasis (88.55 ± 66.62) compared to those without metastasis (56.82 ± 28.76). The same result was obtained in case of S100B. It was 0.40 ± 1.02 in metastatic cases and 0.07 ± 0.24 in tumor free patients ($p < 0.001$). LDH also showed the same pattern. The mean value was 282.30 ± 171.60 in patients with metastatic tumor compared to those without metastasis 231.41 ± 59.69 at the time of blood sampling ($p = 0.003$).

Conclusions: Peripheral blood biomarker testing may provide a rapid, simple, easily accessible, easily reproducible means of early prediction of relapse and assessment of the efficacy of therapy. OPN appears to be a promising marker alongside LDH and S100B in the follow-up of melanoma patients, and the combined assessment of these markers increases diagnostic efficacy.

Receptor-interacting protein kinase-3 (RIP3) and mixed lineage kinase domain-like protein (MLKL) expression is increased in vessel wall of malignant melanoma

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Introduction and Objectives: Receptor-interacting protein kinase-3 (RIP3) is a well-known essential regulator of programmed necrosis, "Necroptosis". RIP3 mediated phosphorylation of mixed lineage kinase domain-like protein (MLKL) lead to membrane permeability is necessary for cell lysis in programmed necrosis.

Materials and methods: Recently, it is also reported that RIP3 promoted vascular permeability to allow extravasation of tumor cell. Therefore, we performed immunohistochemical stain to compare protein expression of RIP3 and MLKL in vascular endothelial cell of malignant melanoma and normal skin.

Results: Total four specimens of malignant melanoma skin and four age-, gender-matched normal skin were evaluated. For analysis of protein expression of RIP3 and MLKL, the image analysis was performed on a representative area of each specimen.

The protein expression level of RIP3 and MLKL in vascular endothelial cell of malignant melanoma (pigmented area per measured area) was increased compared with control.

Conclusions: In conclusion, we detected that increased expression of RIP3 and MLKL in vascular endothelial cells of malignant melanoma. Based on these results, we can suggest that increased expression of RIP3 and MLKL in vascular endothelial cell may promote vascular permeability and induce extravasation of tumor cell in malignant melanoma. Although it is preliminary data, we expect that RIP3 and MLKL play an important role in the metastasis of malignant melanoma.

Role of scavenger receptor CD36 in diet-induced obesity and metastatic melanoma

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Introduction and Objectives: Obesity impairs immune function and increases the risk of cancer. Recent findings highlight an impaired phenotype and functionality of natural killer (NK) cells under obese conditions. Upregulation of the extracellular lipid transporter CD36 on NK cells from obese individuals can increase metastatic tumour formation. In this study, we investigated whether a high-fat diet impairs NK cell phenotype and function in CD36 deficient (KO) animals. We also aimed to determine whether loss of CD36 confers protection against metastases.

Materials and methods: Adult CD36 KO mice (B6.129S1-Cd36^{tm1Mfe/J}) were fed on high fat diet (HFD, 45% kcal fat) for 2 months. Subsequently, lung metastasis was generated by intravenous inoculation of B16F10 melanoma cells. Controls were healthy sex/age-matched mice. After 14 days spleens were harvested and used for assessing the flow cytometry analyses of NK cells.

Results: High-fat diet did not increase the body weight, but impaired the phenotype and function of NK cells. Cytotoxic immune cells, NK cells and CD8⁺ T cells, were significantly decreased in HFD-mice and mice with pulmonary metastasis, while CD4⁺ cells and B cells showed a slight increase. Analysis of NK cell subsets indicated a significant decrease of mature subset CD27-CD11b⁺ and an increase of immature NK cell subset CD27-CD11b⁻. The expression of activation and maturation markers CD335, CD122, CD49b, CD11b, CD43, KLRG1 on NK cells was decreased in HFD-mice and mice with pulmonary metastasis. Also, decrease in NK cells functionality was detected in both groups compared to control group.

Conclusions: This study showed that loss of CD36 protects against diet-induced weight gain but results in impaired NK cell phenotype and function and failed to reduce tumour growth.

Acknowledgements: This work was partially supported by Core Program, implemented with the support NASR, projects nos. 23.16.02.02, 23.16.01.03 and 31PFE/2021.

Targeting G-quadruplexes of PBX1 by antisense oligonucleotide for melanoma therapy

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Introduction and Objectives: Accumulating evidence have suggested that the expression of Pre-B-cell leukemia homeobox transcription factor 1 (PBX1) is increased in melanoma cells and overexpression of PBX1 significantly promotes the melanoma cell growth¹⁻². However, the clinical impact of PBX1 on melanoma and the molecular mechanisms regulating PBX1 expression in melanoma are largely unknown.

Materials and Methods: We first shown that PBX1 is up-regulated in melanoma and its high expression predicts poor prognosis of patients with melanoma (Figs. 1a-f).

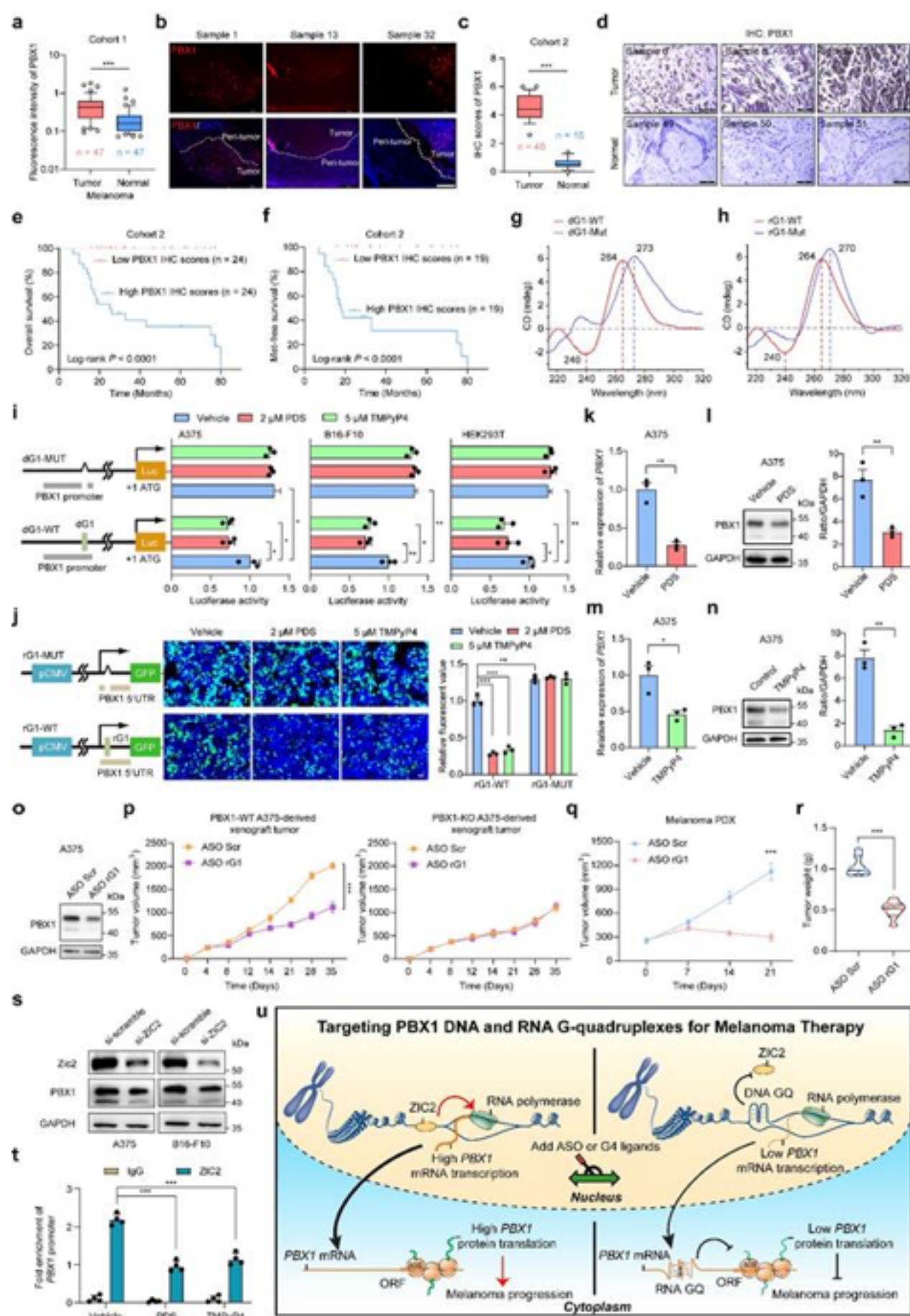
G-quadruplexes (G4s) are 4-stranded structures formed in guanine (G)-rich DNA or RNA strands and have been shown to involve in tumorigenesis by regulating the oncogene expression³⁻⁴. And we proved the presence of G4s motifs in the promoter and 5' UTR of PBX1. PBX1 G4s formation induced by G4 stabilizing compounds TMPyP4 and PDS significantly inhibited the melanoma growth and metastasis in vitro and in vivo (Figs. 1g-n) by downregulating the PBX1 expression.

Because of PDS and TMPyP4 cause side effects and cytotoxicity. Thus, we designed the antisense oligonucleotides (ASOs)⁵ specifically targeting rG1 complementary sequences in PBX1 5' UTR to induce PBX1 rG1 formation. Indeed, PBX1 rG1 formation induced by ASO significantly suppresses melanoma progression and the NF- κ B pathway in A375 cells, patient-derived xenograft-derived tumor cells (PDCs) and patient-derived xenograft (PDX) mouse models (Figs. 1o-r). Furthermore, we found that ASO treatment shows no significant effect on the growth of stable PBX1-knockout A375 cells both in vitro and in vivo (Figs. 1o, p), suggesting that ASO inhibits melanoma growth in a PBX1 dependent manner.

We next investigated the transcriptional factors involved in the regulation of dG1 on PBX1 transcription using PRO-MO, and found that the expression of ZIC2 positively correlate with the PBX1 expression in melanoma respectively. Mechanistically, PBX1 DNA G4 formation blocks ZIC2 occupancy in PBX1 promoter regions to inhibit the transcription of PBX1, while PBX1 RNA G4 inhibits the translation of PBX1 via steric blocking effects (Fig. 1s, t).

Results Our findings collectively revealed the clinical impact of PBX1 on melanoma and a novel regulatory mechanism for governing PBX1 expression and provided another therapeutic target that can combine with existing therapeutic strategy against melanoma or other cancers (Fig. 1u).

Supporting Document 1



Targeting G-quadruplexes of PBX1 by antisense oligonucleotide for melanoma therapy

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Introduction and Objectives: 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.

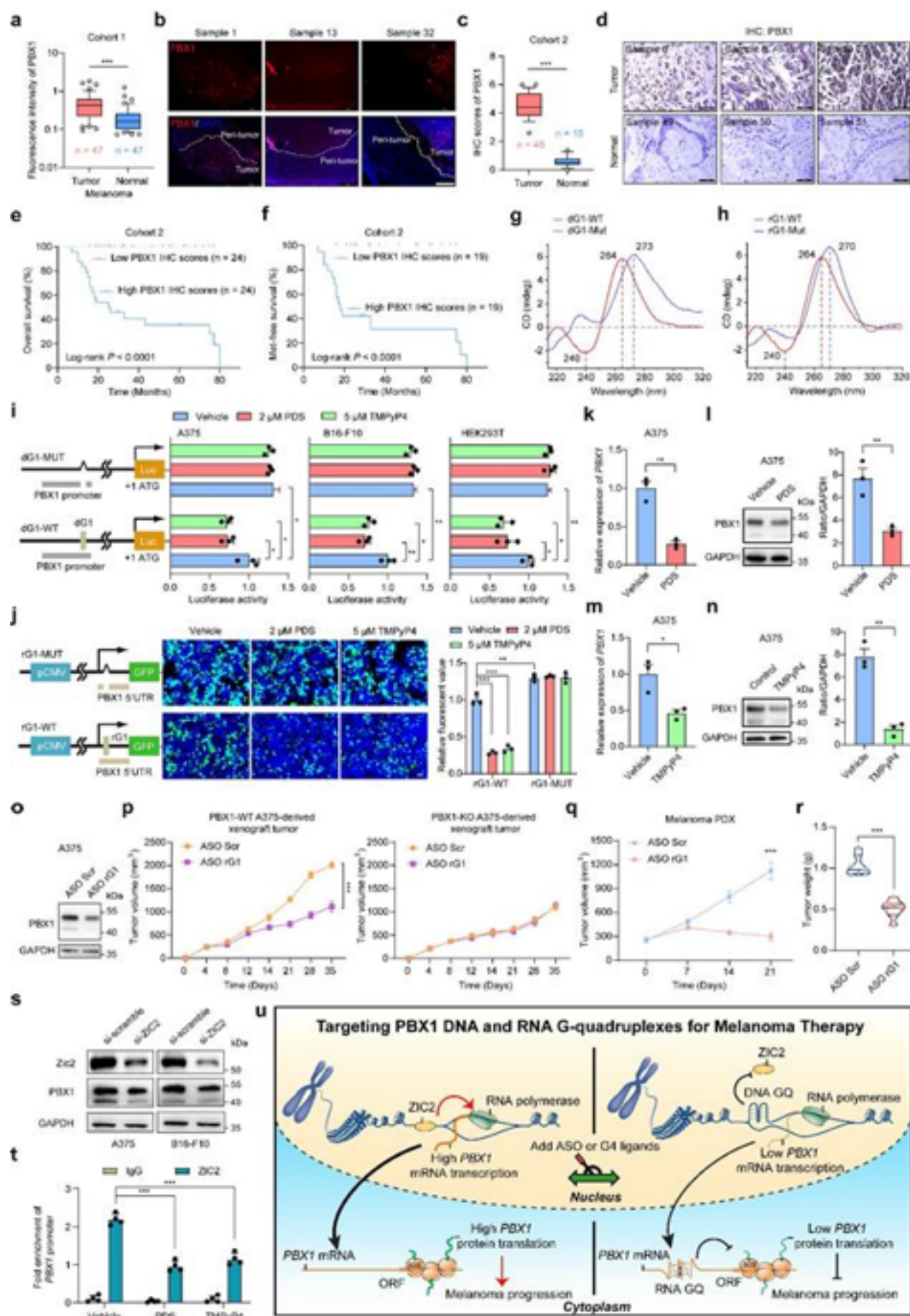
Materials and Methods: We investigated the expression of PBX1 in two melanoma cohorts by performing immunofluorescence (IF) and immunohistochemistry (IHC) assays. The PBX1 was expressed transgenically or knocked out in primary melanocytes, A375 or B16-F10 cell lines; proliferation, colony formation, 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 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. PBX1 G4s formation induced by G4 stabilizing compounds TMPyP4 and PDS significantly inhibited the melanoma growth and metastasis in vitro and in vivo by down-regulating the PBX1 expression. 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).

Conclusions: Our findings collectively 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.

Keywords: Melanoma; PBX1; G-quadruplexes; G4 ligands; ASO.

Supporting Document 1



Targeting tropomyosin receptor kinases induces DNA damage and apoptosis via NGFR-ROS signaling in cutaneous melanoma

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Introduction and Objectives: Targeted therapies with BRAF/MEK-inhibitors and immune checkpoint inhibitors are approved for stage III and IV melanoma¹⁻². Acquired and intrinsic resistance to therapies affects a significant subset of patients, who may benefit from the discovery of novel druggable targets³⁻⁵. Tropomyosin receptor kinases (Trks) are three transmembrane proteins mediating survival and differentiation signaling⁶. Trks belong to the neurotrophin receptor family, along with the nerve growth factor receptor (NGFR)⁷. While NGFR plays a role in melanoma initiation, progression and therapy resistance⁸⁻¹², the function of Trks remains controversial¹³.

We hypothesized that abrogation of Trk-mediated survival signaling with k252a, a pan-Trk kinase domain inhibitor, would result in melanoma cell apoptosis and diminished metastatic potential in vitro and in vivo.

Materials and Methods: Human primary melanoma cells were obtained from the URPP melanoma biobank Zurich or the American Type Culture Collection and cultured as indicated from the manufacturer. To investigate melanoma cell viability and apoptosis, the following methods were used: resazurin assay, propidium-iodide and annexin V/propidium-iodide staining and flow cytometry acquisition, calcein AM and ethidium-homodimer staining of three-dimension melanoma spheroids and image acquisition with confocal microscopy. For metastasis assessment, in vivo zebrafish xenograft models were generated.

Results: Trk inhibition with k252a resulted in significant reduction of melanoma cells viability, together with occurrence of G2-M cell cycle arrest and induction of DNA damage, as demonstrated by phosphorylation of H2AX (Figure 1a,c). K252a treatment induced a significantly higher melanoma cells mortality in two-dimensional cultures and in three-dimension melanoma spheroid models compared to the BRAF-inhibitor PLX-4032 (vemurafenib), regardless of BRAF-inhibitor sensitivity status (Figure 1b,d). Trk inhibition resulted in diminished cell proliferation in ex vivo melanoma patient cultures, and metastasis formation in vivo, in a zebrafish xenograft model (Figure 1e). We observed higher k252a induced apoptosis in NGFR^{high} melanoma cells (Figure 2a); furthermore, we demonstrated that Trk inhibition caused NGFR cleavage and activation of NGFR-mediated apoptotic pathway and mitochondrial reactive oxygen species overproduction, thereby providing a mechanistic explanation for k252a-induced killing effects (Figure 2b-i).

Conclusions: Trk inhibition and forced NGFR cleavage offer an interesting window of opportunity for advanced melanoma patients, warranting further studies.

A phase 3 trial comparing fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) to pembrolizumab in patients with completely resected high-risk melanoma

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Introduction and Objectives: Most patients (pts) with a newly diagnosed melanoma (Mel) have resectable disease and are potentially cured by surgery. However, regional nodal and/or distant relapses can occur after curative-intent resection. Postoperative adjuvant therapy with immune checkpoint inhibitors improves relapse-free survival (RFS) and distant metastasis-free survival (DMFS) of pts at high risk of Mel. Fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) are both high-affinity, fully human, IgG4 monoclonal antibodies (MAbs) that combined have shown high clinical activity in pts with advanced Mel in a phase 1 study. Additionally, combination of relatlimab (anti-LAG-3) and nivolumab (anti-PD-1) have shown superiority over nivolumab for PFS in advanced Mel. These observations provide a rationale for use of fianlimab and cemiplimab combination in high-risk adjuvant Mel.

Materials and Methods: Our study (NCT05608291) is a three-way, double-blind, phase 3 trial to compare fianlimab + cemiplimab to pembrolizumab in the adjuvant therapy (Rx) of high-risk, resected Mel. This trial will be conducted at 200 sites.

Pt eligibilities: (1) ≥ 12 years of age; (2) Stage IIc, III or IV (all M-stages) and histologically confirmed Mel, completely resected ≤ 12 weeks prior to randomization; (3) no prior systemic anti-cancer Rx or radiation Rx for Mel in the previous 5 years; (4) no evidence of metastatic disease on staging investigations; and (5) an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 (for adult pts), Karnofsky PS > 70 (pts > 16 years) or Lansky PS > 70 (pts < 16 years).

Study arms (all Rx Q3W IV): A. fianlimab (dose 1) + cemiplimab (350 mg); B. fianlimab (dose 2) + cemiplimab (350 mg); C. pembrolizumab (200 mg) + saline/dextrose placebo. The placebo controlled trial will enrol about 1530 pts, randomized 1:1:1 to Arms A:B:C, treated for up to 1 year. The trial will stratify by disease stage (IIIA vs IIC-IIIB-IIIC vs IIID-IV [M1a/b] vs IV [M1c/d]), and geography (North America vs Europe vs Rest of World).

The primary endpoint is investigator-assessed RFS. The secondary endpoints include efficacy (overall survival, DMFS, melanoma-specific survival), safety, pharmacokinetic, immunogenicity, and patient reported outcomes. The first analysis will be performed when 242 RFS events have been observed.

A phase 3 trial of fianlimab (anti-LAG-3) plus cemiplimab (anti-PD-1) versus pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma

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Introduction and Objectives: Fianlimab (anti-lymphocyte activation gene 3 [LAG-3]) and cemiplimab (anti-programmed cell death-1 [PD-1]) are both high-affinity, fully human, IgG4 monoclonal antibodies (Abs). Concurrent blockade of anti-LAG-3 and anti-PD-1 has shown enhanced efficacy (increase in progression free survival [PFS]) in advanced melanoma (Mel). We previously presented data from a phase 1 study showing a 63.8% objective response rate (ORR) across two separate cohorts of advanced PD-(L)1 naïve metastatic Mel patients (pts) treated with fianlimab plus cemiplimab with an acceptable risk-benefit profile.

Materials and Methods: This is a randomized, double-blind, phase 3 study to evaluate fianlimab plus cemiplimab compared to pembrolizumab in pts with previously untreated unresectable locally advanced or metastatic Mel (NCT05352672). This study will be conducted globally, at approximately 200 sites.

Key inclusion criteria are: (1) ≥12 years of age; (2) histologically confirmed unresectable Stage III and Stage IV (metastatic) Mel (3) no prior systemic therapy for advanced unresectable disease; (4) measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1; (5) valid LAG-3 results; (6) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 (for adult pts), Karnofsky PS ≥70 (pts ≥16 years) or Lansky PS ≥70 (pts <16 years); and (7) anticipated life expectancy of at least 3 months.

There are 4 arms to the study: (1) Arm A: fianlimab (dose 1) + cemiplimab (350 mg) every 3 weeks (Q3W), intravenously (IV); (2) Arm A1: fianlimab (dose 2) + cemiplimab (350 mg) Q3W, IV; (3) Arm B: pembrolizumab (200 mg Q3W, IV) + saline/dextrose placebo (placebo); (4) Arm C: cemiplimab (350 mg Q3W, IV) + placebo.

The trial is expected to enrol approximately 1590 pts. The primary endpoint is progression-free survival. The key secondary endpoints are overall survival and objective response rate. The additional secondary endpoints include disease control rate, duration of response, safety, pharmacokinetics of cemiplimab and fianlimab, and immunogenicity (incidence and titer of anti-drug Abs and neutralizing Abs). The study is currently open for enrolment.

Acral lentiginous melanoma shows a poorer response to immune checkpoint inhibition in the unresectable or metastatic setting – a EUMELAReg real world outcome study.

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Background: Melanoma and other skin cancers are prone to respond to immune checkpoint inhibition (ICI), due to a high tumor mutational burden (TMB), mainly caused by ultraviolet (UV) induced somatic mutations. The TMB of metastatic disease may therefore be related to the extent of mutagenic exposure the primary has been exposed to.

Acral lentiginous melanoma (ALM) is a clinico-pathological subtype of cutaneous melanoma, usually localised at the palms of the hand or the foot, fingers, toes, or the nail apparatus. The existing evidence is not finally settled as to whether these patients would benefit from new ICI immunotherapies.

Methods and patients: The EUMELAReg melanoma treatment registry (EMR) is a European initiative combining real world data on the treatment and outcome of melanoma patients all across Europe. We extracted cases with ALM and from these, we analysed cases with unresectable stage III or stage IV metastatic melanoma having been treated with systemic treatment.

First-line treatments were categorized for ICI-, BRAF V600 targeted, and other treatments and analysed for outcome parameters adjusted for prognostic factors. As a reference group, cases with superficial spreading or nodal subtype of cutaneous sites other than acral served as controls.

Results: A total of 229 cases with ALM and nonresectable or metastatic disease receiving first-line systemic treatment were identified in the registry. Among these, 179 patients received ICI, either anti-PD1 antibody or combined anti-CTLA4/anti-PD1 therapy. These were analysed in comparison to n = 1.295 cases with advanced disease from other subtypes.

The overall survival outcome comparison was adjusted for relevant prognostic covariates such as age, sex ECOG performance status, serum LDH levels, AJCC substage, number of metastatic sites, and treatment category. In a fully adjusted Cox regression model ALM patients had a significantly increased risk for death (HR 1.52; p=0.003) as compared to the reference group.

Conclusion: Our study confirms that ALM is a melanoma subtype that responds less well to ICI treatment than other cutaneous melanoma subtypes. Given the fact that treatment alternatives are sparse, in particular since BRAF V600 mutations are rare in ALM, new treatment approaches are urgently needed for patients with advanced ALM.

Adjuvant therapy with nivolumab versus placebo in patients with resected stage IIB/C melanoma (CheckMate 76K)

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Introduction and Objectives: Patients with resected stage IIB/C melanoma are at high risk of recurrence with outcomes similar to patients with resected stage IIIB disease. Adjuvant nivolumab (NIVO) has shown benefit in patients with resected stage III-IV melanoma. The phase 3 CheckMate 76K (CM76K; NCT04099251) trial assessed adjuvant NIVO vs placebo (PBO) in patients with completely resected stage IIB/C melanoma.

Materials and Methods: Patients aged ≥ 12 years were stratified by T category and randomized 2:1 to receive IV NIVO 480 mg or PBO Q4W for 12 months. The primary endpoint was recurrence-free survival (RFS); safety was a key secondary endpoint.

Results: Overall, 790 patients were randomized to NIVO (526) or PBO (264); 61% of all patients had stage IIB and 39%, stage IIC disease. Patients were followed for a minimum of 8 months (median 15.8 months NIVO; 15.9 months PBO); 66/526 (13%) vs 69/264 (26%) had a recurrence event. At this interim analysis, CM76K met the primary EP: NIVO significantly reduced the risk of recurrence vs PBO (stratified HR 0.42; 95% CI 0.30–0.59; stratified $P < 0.0001$); 12-month RFS rates for NIVO vs PBO were 89% (95% CI 86–92) vs 79% (74–84); substage rates were 93 vs 84% (IIB) and 84 vs 72% (IIC). RFS benefit was observed across predefined subgroups. For NIVO, 5% of all patients had distant recurrences and 2% regional; for PBO, it was 12% and 8%. Grade 3-4 treatment-related adverse events (TRAEs) for NIVO vs PBO were 10 vs 2%; any-grade TRAEs leading to discontinuation were 15 vs 3%. There was one TR death (0.2%) with NIVO (heart failure and acute kidney injury).

Conclusions: Adjuvant NIVO significantly improved RFS vs PBO and decreased the risk of recurrence or death by 58% in patients with resected stage IIB/C melanoma, with efficacy benefit across subgroups. The safety results were similar to the known anti-PD-1 monotherapy profile with no new safety signals. NIVO is an effective adjuvant treatment option with a clinically meaningful benefit in resected stage IIB/C melanoma. Encore of presentation at Society of Melanoma Research, September 2022.

CD200/CD200R protein expression in primary melanomas of patients who underwent treatment with immune checkpoint inhibitors: preliminary results

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Background: Expression of CD200 and its cognate ligand CD200R has been implicated in a variety of human cancer cells including melanoma cells. However, its roles in tumor growth and immunity are not clearly understood. In this pilot study, we aimed to correlate CD200/CD200R expression of primary tumors of advanced melanoma patients with the response to immune checkpoint inhibitors (ICI).

Methods: We analyzed immunohistochemically the expression of CD200/CD200R in tissue samples of 33 advanced melanoma patients in non-resectable stage III or IV and correlated our findings with the treatment response to initial immunotherapy using ICI (ipilimumab, nivolumab, pembrolizumab). Univariable and multivariable statistics were applied.

Results: Twenty-one (63.6%) of 33 patients showed partial or complete response to ICI. All primary melanomas showed relatively high CD200 and CD200R protein expression. However, there was no correlation between the CD200 and CD200R expression. Univariate analysis revealed that female gender and lower intra-tumoral CD200 expression were significantly associated with response to ICI. On logistic regression analysis, female gender and lower CD200 protein expression were confirmed as significant independent predictors for ICI treatment response.

Conclusions: Our preliminary data indicate that CD200 expression in primary melanoma has the potential to predict treatment response to ICI. Nevertheless, further studies also including other factors of the tumor microenvironment are needed.

Checkpoint inhibitor therapy induced depigmentation in a giant congenital melanocytic nevus: a case report

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Introduction: Congenital melanocytic nevus (CMN) is a commonly encountered benign skin lesion present at birth. Giant CMN (GCMN) are classified greater than ≥ 40 cm according to their projected size in adulthood. Melanomas are known to develop in CMNs and the larger the size of the CMN, the higher the risk of developing a melanoma. Melanomas arising in CMN appear as dermal or deep-seated melanoma. The most frequent genetic mutations in GCMNs are NRAS (up to 95%). Over the last decade, checkpoint inhibitor (CPI) therapy has emerged as an effective treatment for metastatic melanoma. By activating T-cell response against the tumor, a series of immune-related adverse events (irAE) can be triggered. The skin is the organ most frequently affected by irAEs, including vitiligo-like depigmentation (VLD).

Materials and Methods: Case report.

Results: A 26-year-old female patient with a huge GCMN (50% of the body surface area) was first diagnosed with cutaneous melanoma arising in the GCMN in 2011. The patient underwent a total excision of the melanoma with 1 cm excision margins. The mutation analysis revealed an NRAS mutation Q61K, no BRAF V600E mutation was detected. After four years, a second cutaneous melanoma was resected. In 2018, the patient developed a subcutaneous melanoma metastasis and a lymph node melanoma metastasis. After resection, the subcutaneous metastasis showed a NRAS (p.Gin61Lys) mutation. Adjuvant CPI therapy with nivolumab was started in 2019 with a total of 17 infusions. No further melanoma recurrences or new melanomas have developed since CPI therapy. In the follow up after discontinuation of CPI therapy, we detected progressively pronounced amelanotic areas consistent with VLD in regions without melanoma within the GCMN.

Conclusion: GCMN have a high risk to develop a melanoma and therefore a rigorous follow-up is required. This case demonstrates that CPI therapy can induce VLD in GCMN that persists and progresses years after CPI therapy is discontinued. A long term benefit might be possible.

Circulating inflammatory proteins associate with response to immune checkpoint inhibition therapy in patients with advanced melanoma

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Background: Inflammation can modulate tumour growth and progression, and influence clinical response to treatment. We investigated the potential of circulating inflammatory proteins for response stratification of immune checkpoint inhibitor (ICI) therapy for advanced melanoma.

Methods: Study subjects were 87 patients with unresectable stage III or IV cutaneous melanoma from the multiple centres across the United Kingdom (UK) and the Netherlands (NL) who received ipilimumab, nivolumab, or pembrolizumab, or a combination of ipilimumab and nivolumab. Serum samples were collected before and during ICI therapy at follow-up visits scheduled every third week over a 12-week period. We performed targeted quantification of 92 proteins involved in inflammation and tested for association of their pre-treatment and on-treatment levels, as well as longitudinal changes, with overall response rate, progression-free survival, and overall survival.

Results: We observed consistently higher pre-treatment levels of interleukin-6 (IL-6), hepatocyte growth factor (HGF), and monocyte chemotactic protein 2 (MCP-2), in non-responders compared to responders (meta-analysis $p=3.31 \times 10^{-4}$, 2.29×10^{-4} , and 1.02×10^{-3} , respectively). Patients' stratification according to the median value of IL-6, HGF, and MCP-2 highlighted a cumulative negative effect of pre-treatment levels of the three proteins on response ($p=1.13 \times 10^{-2}$), with overall response rate among patients presenting with combined elevated IL-6, HGF, and MCP-2 levels being three-fold lower (26.7%) compared to patients with none of the three proteins elevated (80.0%, $p=9.22 \times 10^{-3}$). Longitudinal data analysis showed that on-treatment changes in circulating inflammatory proteins are not correlated with response.

Conclusions: Our findings are in line with an increasing body of evidence that the pro-inflammatory cytokine IL-6 can influence response to ICI in advanced melanoma, and further support a role of circulating HGF and MCP-2 levels as prognostic biomarkers as suggested by previous smaller studies. Inflammatory proteins may serve as predictive biomarkers of ICI response and valuable targets for combination therapy.

Domatinostat-induced cutaneous toxicities in neoadjuvant treatment for stage III melanoma

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Introduction and Objectives: Patients with stage III melanoma and a low interferon-gamma (IFN- γ) signature expression in their tumor have demonstrated less favorable response rates upon neoadjuvant immune checkpoint inhibitor (ICI) therapy. Supplemental domatinostat (a class I histone deacetylase inhibitor) to neoadjuvant nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) was hypothesized to lead to an increased anti-tumor immune response due to its beneficial immune-modulating effects including IFN- γ signature expression increase. However, unexpected domatinostat-specific dermatologic adverse events (DAE) hampered domatinostat dose escalation. The objective of this study was to assess clinical and histologic patterns of domatinostat-induced cutaneous toxicity.

Materials and Methods: The DONIMI trial was a two-center investigator-initiated phase 1b trial testing IFN- γ signature-driven neoadjuvant combinations of domatinostat with nivolumab \pm ipilimumab in adult (≥ 18 years) patients with resectable stage III melanoma. Experienced dermatologists and pathologists reviewed laboratory testing, clinical pictures, and skin biopsies of treatment-related DAEs.

Results: Eleven out of 40 patients developed DAEs consisting of prodromal systemic symptoms followed by a generalized maculopapular rash that typically covered $>30\%$ of the body surface area (grade 3 CTCAEv5.0). Systemic symptoms included fever, malaise, headache, oral mucosal and abdominal complaints. Two patients had raised liver enzymes. There were no signs of eosinophilia or atypical lymphocytes in peripheral blood. Symptoms typically had an onset of 10-12 days after treatment initiation and were managed by systemic corticosteroids and permanent cessation of domatinostat. One patient developed a type-I allergic urticarial rash. Histopathological assessment revealed a vacuolar interface dermatitis with apoptotic keratinocytes with a superficial perivascular lymphocytic infiltrate without eosinophils, in some cases accompanied by a small vessel vasculitis.

Conclusions: New ICI treatment strategies with supplemental drugs, targeting other immunosuppressive pathways such as domatinostat, may lead to unexpected dermatologic toxicities with thus far unknown mechanisms and different clinical presentations than ICI-associated dermatitis or classic drug reaction with eosinophilia and systematic symptoms (DRESS).

Long-term follow-up and subgroup analyses of metastatic melanoma patients treated with IDO/PD-L1 targeting peptide vaccine and nivolumab

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Background: In combination with nivolumab, the IDO/PD-L1 peptide vaccine is a promising approach for treating patients with advanced melanoma. We previously published the initial phase I/II trial results on anti-PD-1 therapy naïve patients with metastatic melanoma treated with the IDO/PD-L1 vaccine and nivolumab [1]. We now report the long-term follow-up data and a sub-group evaluation of patients with unfavorable baseline characteristics.

Methods: The trial was an investigator-initiated phase I/II study (ClinicalTrials.gov: NCT03047928). Thirty patients were included, and all patients were treated with a maximum of 15 IDO/PD-L1-targeting peptide vaccines [2] (6x q2w followed by 9x q4w). Nivolumab (3 mg/kg) was administered every second week (q2w) for a maximum of two years. Long-term clinical efficacy, toxicity, and survival data were evaluated. Responses were assessed according to RECIST 1.1.

Results: At data cut-off, January 5th, 2023, a complete response rate (CRR) of 50% was reached while the overall response rate (ORR) was 80%. The median progression-free survival (mPFS) was 25.5 months with a minimum follow-up time of 29.8 months. The median overall survival (mOS) was not reached. A subgroup analysis revealed that patients with unfavorable baseline characteristics, including M1c, elevated LDH levels, and negative PD-L1, obtained favorable and durable responses. The immune-related adverse events were still comparable to patients receiving anti-PD1 monotherapy. No additional toxicity was observed in patients with unfavorable baseline characteristics.

Conclusion: These follow-up data confirmed long-lasting activity for anti-PD-1 therapy naïve patients with metastatic melanoma treated with the IDO/PD-L1 vaccine and nivolumab with unprecedented CRR and ORR rates of 50% and 80% respectively. Importantly, patient subgroups with unfavorable prognostic baseline characteristics obtained remarkable response rates as well.

1 Initial results are reported in Nature Medicine, December 2021

2 IO Biotech (www.iobiotech.com) has licensed the patent of the vaccine IO102/IO103 T-win®

Obesity and immune-checkpoint inhibitors in advanced melanoma: a meta-analysis of survival outcomes from clinical studies

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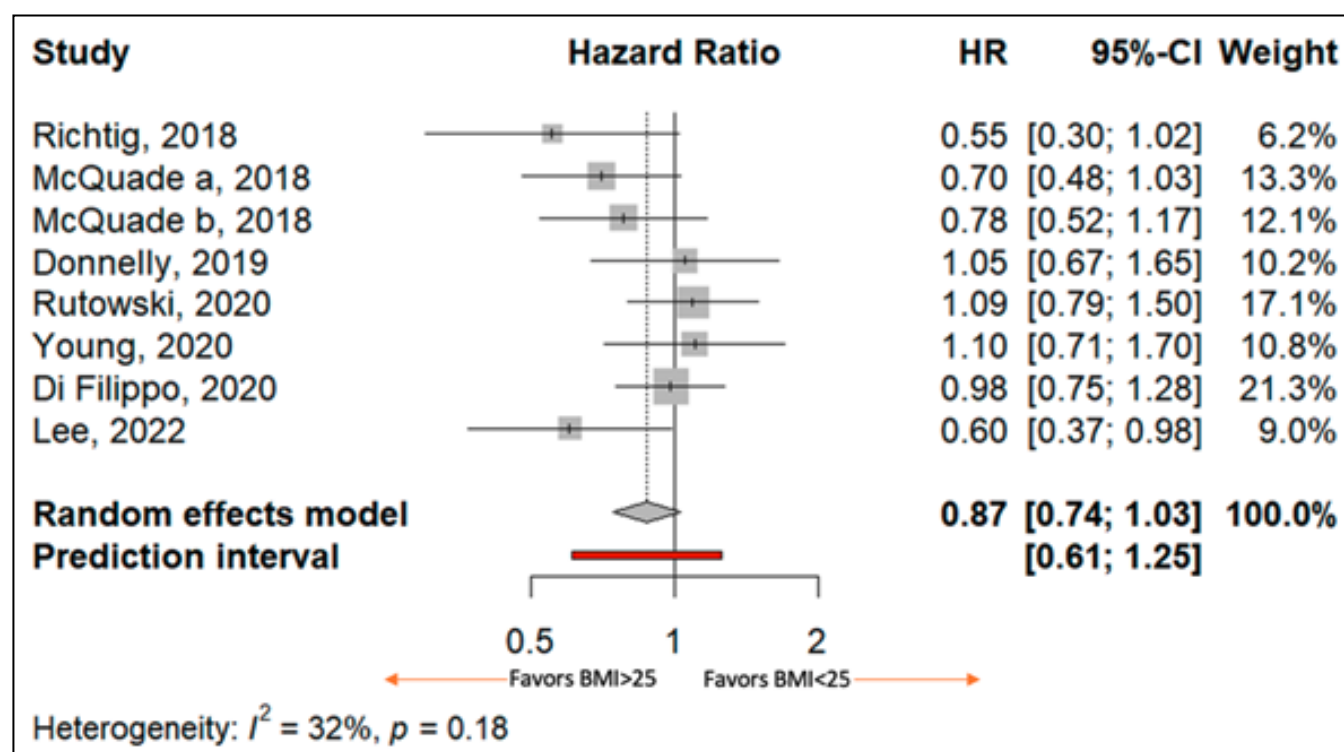
Introduction: Obesity is an inflammatory condition that has been associated with different types of cancer. However, its role in melanoma incidence, progression, and response to immune-checkpoint-inhibitors (ICI) is still controversial. On the one hand, increased levels of lipids and adipokines can promote tumor proliferation, on the other, immunotherapy seems to be more effective in obese animal models, presumably due to an increase in CD8+ and subsequent decrease in PD-1+ T-cells in the tumor microenvironment. In humans, several studies have investigated the role of BMI (body mass index) and other adiposity-related parameters as prognostic markers of survival in advanced melanoma patients treated with ICI.

Materials and Methods: The aim of this research is to systematically review the scientific literature on studies evaluating the relationship between overweight/obesity and survival outcomes in patients with advanced melanoma treated with ICI and to perform a meta-analysis on those sharing common characteristics. A literature review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As for overall survival (OS) and progression-free survival (PFS), the main analysis was conducted for studies using BMI<25 as the reference category, and BMI>25 or BMI 25–30 as the exposed category. A sensitivity analysis using the “leave-one-out” method was performed. Heterogeneity among studies was measured through the I² statistic.

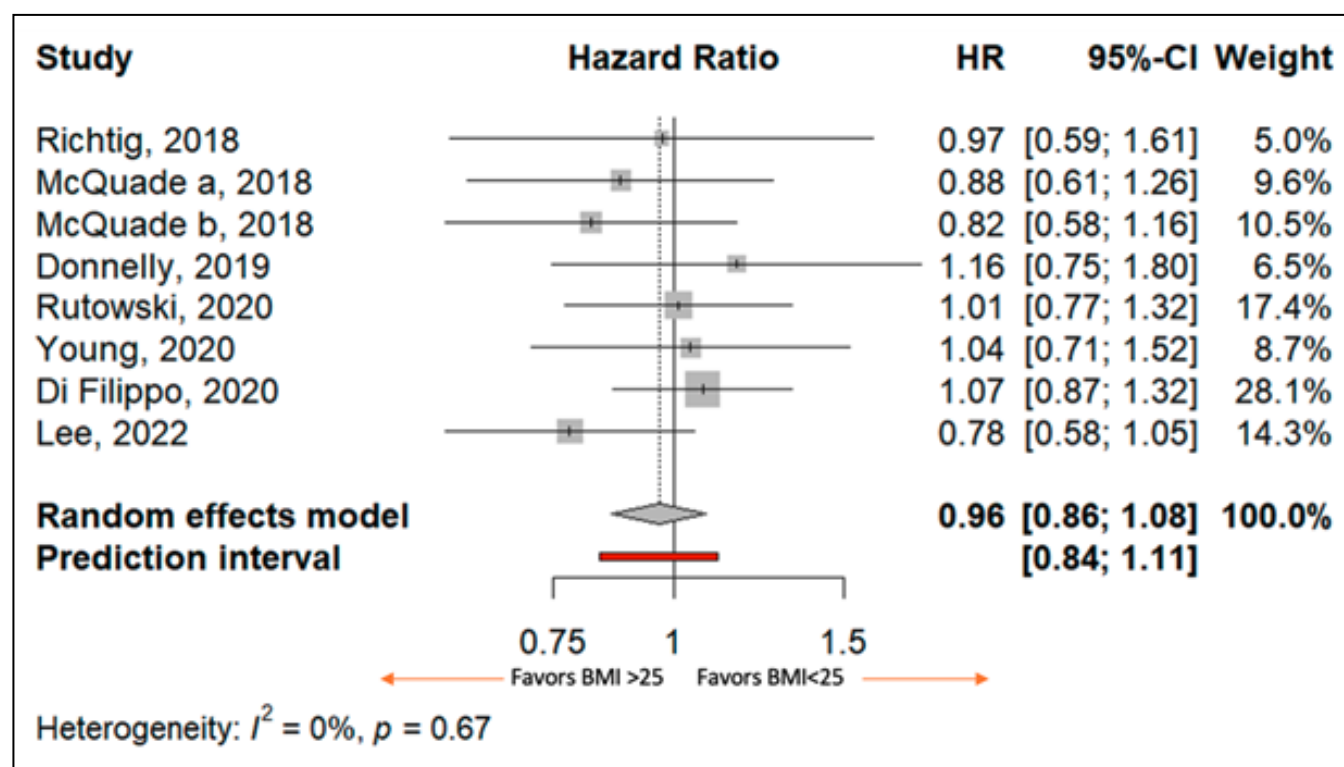
Results: A total of 1070 records were initially identified through a literature search, 556 of which were duplicates. After screening for eligibility and inclusion criteria, 18 were ultimately included. Eleven studies out of eighteen (61.1%) found a potential protective role of the evaluated BMI-related parameter with regard to the study endpoint. Conversely, seven studies (38.9%) did not find any significant association. In the meta-analysis of the association between overweight (defined as BMI>25 or BMI 25–30), OS, and PFS, 7 studies were included, yielding a summary Hazard Ratio of 0.87 (95% CI: 0.74 – 1.039) and 0.96 (95% CI: 0.86 – 1.08), respectively (Figures 1-2).

Conclusions: Despite few suggestive preliminary findings, there is currently no solid evidence to consider BMI as a valid predictor of melanoma patients' survival outcomes in terms of PFS and OS.

Supporting Document 1



Supporting Document 2



Phase 1 study of fianlimab, a human lymphocyte activation gene-3 monoclonal antibody, in combination with cemiplimab in advanced melanoma: Expansion cohort analysis

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Introduction and objectives: Concurrent blockade of human lymphocyte activation gene-3 (LAG-3) may enhance efficacy of anti-programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) therapies. We present updated safety and efficacy data from a Phase 1 study in patients with advanced melanoma treated with anti-LAG-3 (fianlimab) 1600 mg + anti-PD-1 (cemiplimab) 350 mg intravenously every 3 weeks for 12 months.

Materials and methods: We included patients with advanced melanoma who were anti-PD-1/PD-L1-naïve (expansion cohorts [ECs] 6 and 15; enrolled sequentially) or anti-PD-1/PD-L1-experienced within 3 months of screening (EC7). Results: As of the July 1, 2022, data cutoff, 40 patients in each of EC6 + EC15 and 15 patients in EC7 received fianlimab + cemiplimab. For EC6 + EC15 and EC7, respectively, median age was 69.0 and 59.0 years, 60.0% and 46.7% were male, and 90.0% and 60.0% were white.

Median treatment duration was 30.9 weeks (EC6 + EC15) and 9.0 weeks (EC7). Grade ≥ 3 treatment-emergent adverse events (TEAEs) occurred in 40.0% (EC6 + EC15) and 46.7% (EC7) of patients. Serious TEAEs occurred in 28.8% (EC6 + EC15) and 33.3% (EC7) of patients. The investigator-assessed objective response rate was 63.8% (seven complete responses; 44 partial responses) in EC6 + EC15 and 13.3% in EC7. Kaplan-Meier estimation of median progression-free survival was 24.0 months (95% confidence interval [CI]: 9.9–not evaluable) in EC6 + EC15 and 1.5 months (95% CI: 1.3–7.7) in EC7. Median duration of response has not been reached in these cohorts.

Conclusions: Fianlimab + cemiplimab demonstrated clinically meaningful efficacy among patients with anti-PD-1/PD-L1-naïve advanced melanoma across sequential ECs with a similar safety profile to cemiplimab monotherapy.

Phase 1 study of fianlimab, a human lymphocyte activation gene-3 monoclonal antibody, in combination with cemiplimab in advanced melanoma: Subgroup analysis

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Introduction and objectives: Concurrent blockade of lymphocyte activation gene-3 (LAG-3) may enhance efficacy of anti-programmed cell death-1 (PD-1) therapies. We previously presented Phase 1 safety and efficacy data in patients with advanced melanoma treated with anti-LAG-3 (fianlimab) in combination with anti-PD-1 (cemiplimab) demonstrating high clinical activity among patients with anti-PD-1/PD-ligand 1 (PD-L1) naive (expansion cohort [EC] 6 and 15) advanced melanoma. Among 80 patients in EC6+15, the objective response rate (ORR) was 63.8%, disease control rate (DCR) was 80.0%, and median duration of response (mDOR) was not reached (NR).

Factors associated with poorer prognosis and reduced response to immunotherapy in patients with advanced melanoma include advanced disease stage, elevated lactate dehydrogenase (LDH) levels, and metastasis sites, including liver or other visceral organs (M1c).

Materials and methods: Patients with advanced melanoma received fianlimab 1600 mg and cemiplimab 350 mg intravenously every 3 weeks for 12 months. In this subgroup analysis we evaluated fianlimab and cemiplimab in patients with poor prognostic features. ORR, DCR and mDOR are reported for patients in EC6+15 with liver metastases at baseline, LDH > upper limit of normal (ULN) at baseline, LDH>ULN at baseline and M1c stage.

Results: As of 1 July 2022 (data cutoff), 80 patients in EC6+15 (40 patients each) were treated with fianlimab and cemiplimab. In EC6+15 combined, at baseline, 19 patients (23.8%) had liver metastases, 28 patients (35.0%) had LDH>ULN, and 13 patients (16.3%) had LDH>ULN at baseline and any M1c.

In patients with liver metastases at baseline, ORR in EC6+15 combined was 47.4%, DCR was 63.2%, and mDOR was 9.0 months (95% CI: 2.8–not evaluable [NE]). In patients with LDH>ULN at baseline, ORR for EC6+15 was 57.1%, DCR was 71.4%, and mDOR was NR (95% CI: 7.3–NE). In patients with LDH>ULN at baseline and any M1c, ORR for EC6+15 was 53.8%, DCR was 69.2%, and mDOR was NR (95% CI: 5.7–NE).

Conclusions: Despite small numbers in subgroups, the efficacy analysis from EC6+15 combined demonstrated high activity of fianlimab in combination with cemiplimab in patients with advanced melanoma and poor prognostic features at baseline.

Pilot study of the Lung Clearance Index as screening parameter of pulmonary impairment in patients under PD-1-inhibitor therapy

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Introduction and Objectives: Immune checkpoint blockade (ICB) has been a breakthrough in the treatment of malignant tumors, but it may also lead to severe adverse event. Reportedly, pneumonitis occurs in 2–4% of patients, of which 1–2% have grade 3 events. 0.2% of the pneumonitis are fatal [1]. Very early detection of the disease may lead to better outcomes. In this study we tried to establish an early detection system using Multiple Breath Washout technique with the Lung Clearance Index (LCI), a marker of ventilation mismatch known to indicate early pulmonary impairment.

Materials and Methods: Patients suffering from melanoma or metastatic cutaneous squamous cell carcinoma (cSCC), treated with PD1-inhibition either in the adjuvant or metastatic setting were recruited. Controls were age- and sex-matched. Patients with known pulmonary disease and regular smokers were excluded.

Methods: ATS/ERS standard spirometry, LCI and diffusion capacity (DLCO) were measured during 2022 using ND-DMed/EasyOnePro/Labâ.

Statistics were done with SPSS 25â. For group differences t-tests were used, binomial tests in the pairwise comparison.

Results: 19 patients age (mean±SD) 66.8±14.3 years receiving PD-1-inhibition and 19 controls age 67.2 ± 13.1 years were included. 17 (89%) were suffering from melanoma and 2 (11%) from cSCC; 7 (37%) patients received adjuvant therapy. Patients were treated from 2-12 months (mean 3 months) at time of testing.

LCI in the PD-1-treatment group was 8.41±1.15, 0.32 higher compared to 8.09±1.11 in the control group, but the difference was not significant (p=0.40). Further analysis revealed that the FEF 25-75% in the PD-1-treated patients was significantly reduced (p=0.045) compared with the control group. None of the patients complained about any lung associated symptoms.

Discussion/Conclusions: Patients undergoing PD-1 therapy show a slightly impaired lung function compared to the control group which may be caused by subclinical inflammation. Whether this will resolve or exacerbate during treatment will need to be addressed in further clinical studies. Furthermore, we showed that performing LCI is feasible and may be easily integrated in the clinical daily routine and could contribute to early detection of (auto)-inflammation in the lungs.

Randomized phase 3 study (STARBOARD) evaluating encorafenib (enco) + binimetinib (bini) + pembrolizumab (pembro) for first-line treatment of unresectable locally advanced or metastatic BRAF V600-mutant melanoma

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Background: BRAF V600 mutations are frequently found in metastatic melanoma. This mutation constitutively activates the MAPK pathway, which leads to melanoma progression. Patients with BRAF V600-mutant metastatic melanoma typically receive BRAF inhibitors (BRAFi) + MEK inhibitors (MEKi), such as enco + bini, or immune checkpoint inhibitors (CPIs; eg, pembro). However, these have limitations. BRAFi and MEKi may increase BRAF V600-mutant tumor sensitivity to CPIs. Previous studies reported improved progression-free survival (PFS) in patients with advanced BRAF V600-mutant melanoma receiving BRAFi + MEKi + CPI compared with targeted therapy alone. This phase 3 trial will evaluate the efficacy and safety of enco + bini + pembro vs placebo + pembro for unresectable locally advanced or metastatic BRAF V600-mutant melanoma. A safety lead-in (SLI) was built in to determine the recommended phase 3 dose (RP3D) prior to starting phase 3.

Trial design: STARBOARD (NCT04657991) is a randomized, double-blind, placebo-controlled, phase 3 study evaluating approximately 600 patients with BRAF V600 advanced melanoma. Patients will be stratified by prior systemic adjuvant treatment (CPI, BRAFi/MEKi, or none) and by disease stage (per AJCC 8th edition; IIIB, IIIC, IIID, IV M1a[0], and IV M1b[0] vs IV M1a[1], IV M1b[1], IV M1c[0], IV M1c[1], IV M1d[0], and IV M1d[1]). Patients must have measurable disease (per RECIST 1.1); ECOG performance status of 0 or 1; and adequate bone marrow, hepatic, and renal function. Patients must not have received prior systemic therapy for unresectable or metastatic melanoma; adjuvant treatment with BRAFi/MEKi, anti-PD-1, or anti-CTLA-4 is permitted. Patients cannot have symptomatic brain metastases. Study treatments and end points are shown in Table 1. RP3D was established in May 2022; phase 3 enrollment began in June 2022.

Supporting Document 1

	Phase 3
Treatment (21-day cycle)	Recommended phase 3 dose from SLI: encorafenib plus binimetinib and pembrolizumab Control: placebo plus pembrolizumab alone
Primary	PFS (Recommended phase 3 dose vs control; by BICR)
Secondary	Key: OS (Recommended phase 3 dose vs control) Other: PFS by investigator assessment, objective response rate, duration of response, disease control rate, and time to response, all by BICR and investigator assessment, PFS2, quality of life, safety, pharmacokinetics

BICR, blinded independent central review; OS, overall survival.

Real-world effectiveness of pembrolizumab in advanced melanoma: analysis of an Uruguayan National database.

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Br Federic Loureiro², Br Paula Motta², Br Lucca Pandolfo², Br. Ribeiro Marco²,
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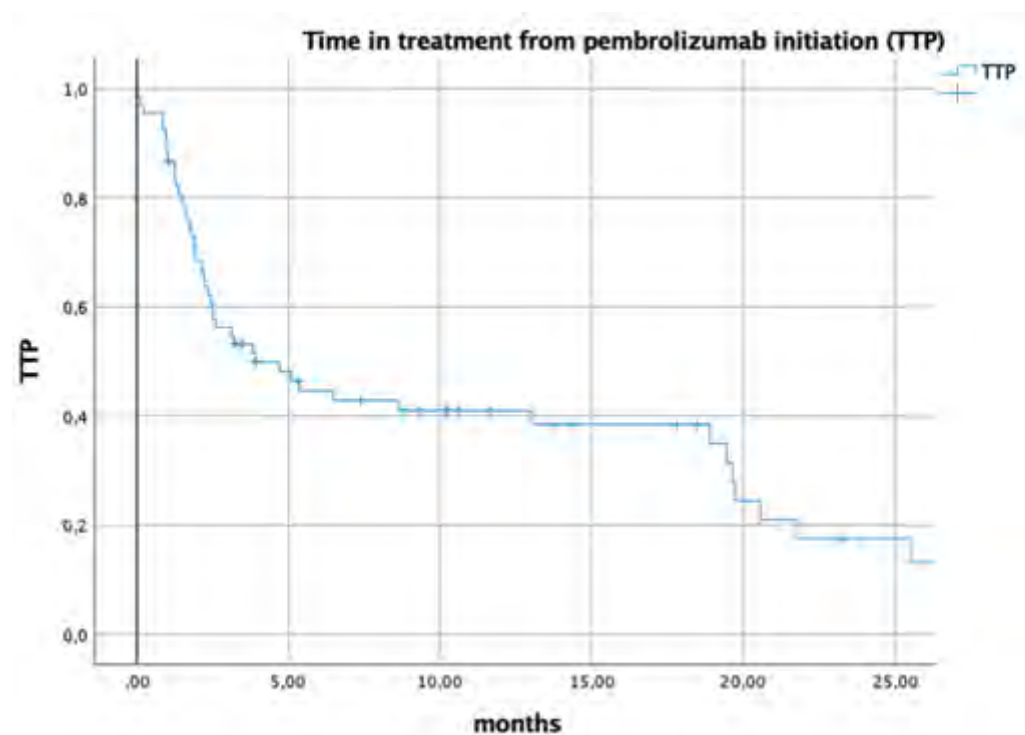
Introduction: Immunotherapies such as the anti-PD-1 pembrolizumab and nivolumab are the cornerstone of systemic therapy for advanced melanoma. However, many patients are treated outside of clinical trials (CT), and the results of observational studies provide essential information for understanding the effectiveness of therapies outside this situation. CT results may not be generalizable to real-life clinical practice (RWCP) because of close monitoring of the trial environment and strict eligibility criteria that exclude many patients, such as those with poor performance status or active/untreated brain metastases. Here we examined RWCP pembrolizumab use in advanced melanoma patients in Uruguay, a Latin-American country.

Methods: This was an observational, descriptive study based on the analysis of an anonymized database of Uruguayan patients with melanoma who received pembrolizumab treatment from 03/2020 to 03/2022, provided by the “Fondo Nacional de Recursos.” Statistical analysis was performed using SPSS Statistics 25 version. Overall survival (OS) and time on treatment from pembrolizumab initiation (TTP) were analyzed using the Kaplan–Meier method. For the OS, only those treatments which the authorization of at least one drug dosage upon request were included. The median follow-up for the survival analysis was 16,5 months.

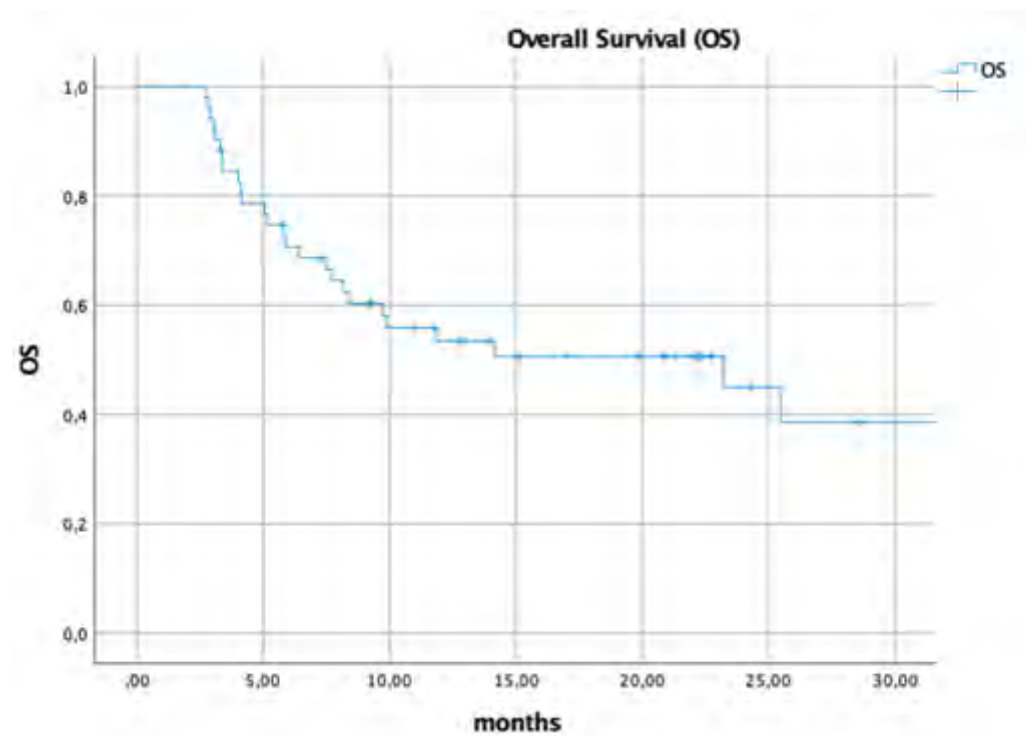
Results: Pembrolizumab was administered to 71 patients as first line of palliative treatment. Median age at pembrolizumab initiation was 64,1 years (range 28–87); most patients were male (64%), 26,8% had elevated lactate dehydrogenase (LDH) level, and 38% had ECOG >1. Overall, 11% had brain metastases. Median OS was 23,2 months (95% CI 2,99–43,4); 1-year and 2-year survival rates were 70,6% and 47%, respectively; and median TTP was 3.9 months (95% CI 1,3–6,8). Significantly better OS ($p = 0,017$) was evident for normal (vs. elevated) LDH levels.

Conclusions: These findings support effectiveness of pembrolizumab in the real-world clinical setting in a Latin-Americans patient population with advanced melanoma, including patients who would not be eligible for clinical trials.

Supporting Document 1



Supporting Document 2



Real-world outcomes in patients with resected stage III-IV melanoma treated with adjuvant nivolumab: interim results from the ADJUMEL study in France

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Introduction: 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 analysis of the AdjuMel study (NCT04550247) reported the baseline characteristics for 352 patients treated in real-world with adjuvant nivolumab in France². The aim of the present analysis is to describe real-world safety and preliminary effectiveness for resected stage III-IV patients receiving adjuvant nivolumab in France.

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 and over a 5-year follow-up. 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 M12 visit.

Results: 343 patients were included in this interim analysis. Their median follow-up was 11.6 months (range 2.10-14.32). Median age was 65 years (range, 27-95), 57.7% of patients were male, and 36.7% had a BRAF mutation. At treatment initiation, 86.8% of patients were stage III (among them: 19.9% stage IIIA, 29.4% IIIB, 50.7% IIIC- IIID), and 13.2% were stage IV. Complete lymph node dissection (CLND) before nivolumab treatment had been performed in 44.9% of patients. At 12 months, 44% of patients were still on treatment. Based on Kaplan-Meier method, median time to treatment discontinuation was 7.4 months (range, 0.00-12.42). The estimated 1 year-RFS rate was 64.6% (95% CI 58.8-69.8). 49.9% of patients had at least one treatment related adverse event (TRAE), and 9.7% had at least one TRAE grade 3-4. No treatment-related deaths were reported.

Conclusions: This real-world cohort of 343 patients provides valuable insight into the characteristics of the current population receiving NIVO in the adjuvant setting in France. The safety data reported is consistent with the known safety profile of NIVO monotherapy. Given the short median of follow-up of this analysis, longer term follow-up is needed to confirm the effectiveness results.

Response to anti-PD-1 treatment in acral melanoma

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Introduction: With the introduction of immune checkpoint inhibitors (ICIs), the survival of melanoma patients immensely improved particularly in cutaneous form (CM), which is the most common one. Acral melanomas (AM) have a low incidence in the Caucasian population and differ from other CM due to their specific genetic profile and lower tumour mutation burden (TMB). There are indications of poorer prognosis in patients with AM treated with ICIs compared to other CM, possibly due to low TMB and reduced number of tumour-infiltrating lymphocytes.

Which may be possible due to low TMB and reduced frequency number of tumour-infiltrating lymphocytes

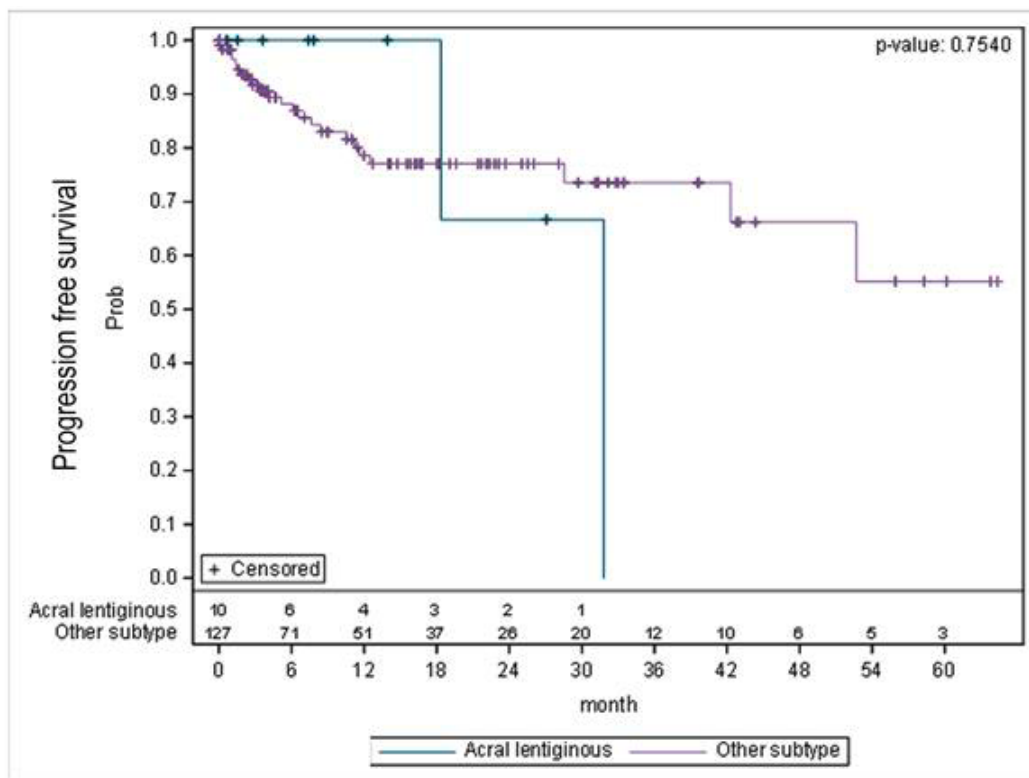
We assessed the response to anti-PD-1 monotherapy among AM patients, compared to other CM in the real clinical setting.

Materials and Methods: We conducted a retrospective analysis among previously untreated unresectable and metastatic melanoma patients treated with anti-PD-1 monotherapy in University Clinical Center Nis, Military Medical Academy Belgrade and Clinical Center Kragujevac from February 2017 to February 2023. Data were extracted from Central South Eastern European Registry (CSEEREG) a part of the European Melanoma Registry (EuMelaReg). The efficacy of anti-PD-1 was compared between AM and other CM through progression-free survival (PFS) and overall survival (OS), with subgroup analysis.

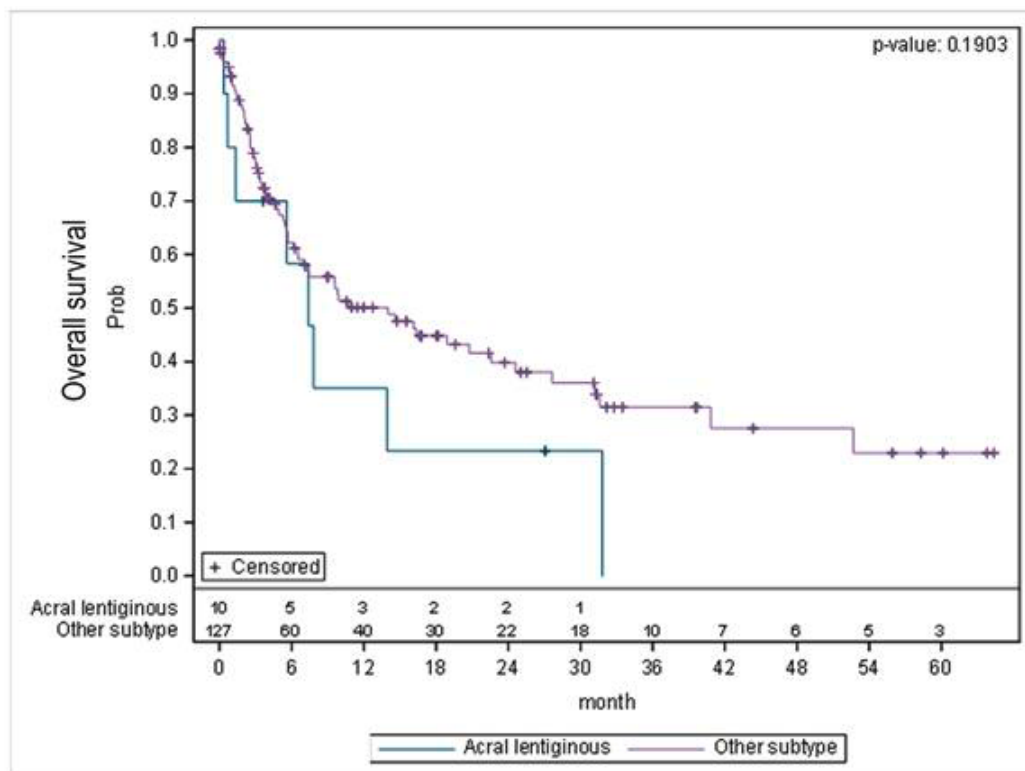
Results: Altogether 137 patients (10 AM and 127 CM) with advanced CM were included. The Median PFS was shorter in AM patients treated with anti-PD-1 but without statistical significance compared to other CM (14.01 vs 7.40; $p=0.19$). A similar trend was observed in OS, but still without statistical significance (31.8 vs NR; $p=0.75$). Women were predominant in AM group compared to other CM (60% vs 37.8%), with all of the AM patients being BRAF wild type (100% vs 70.9%). No difference in age, Breslow thickness, ulceration, clinical stage or LDH levels was observed at baseline.

Conclusion: Even though statistical significance was not achieved in terms of PFS and OS, probably due to a small number of patients, a clear trend is observed in terms of poorer response to anti-PD-1 monotherapy among AM patients compared to other CM patients.

Supporting Document 1



Supporting Document 2



Response to anti-PD-1 treatment in cutaneous head and neck melanoma

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Introduction: Based on the primary anatomical site, cutaneous melanomas are divided into four subgroups: head and neck (HandN), upper limbs (UL), trunk (T) and lower limbs (LL). Before the introduction of novel agents HandN melanomas were often considered to have poorer prognoses than other anatomical sites. They tend to develop due to chronic ultraviolet (UV) exposure, with a predominance in the elderly. Ultraviolet exposure potentially leads to a higher tumour mutation burden (TMB), which is being established as a predictive biomarker for anti-PD-1 treatment. Ultraviolet signature present in the primary site transcends to the metastatic site, therefore the primary anatomical site may have an important role even in advanced melanoma.

We assessed the response to anti-PD-1 monotherapy among HandN melanomas, compared to other CM in the real clinical setting.

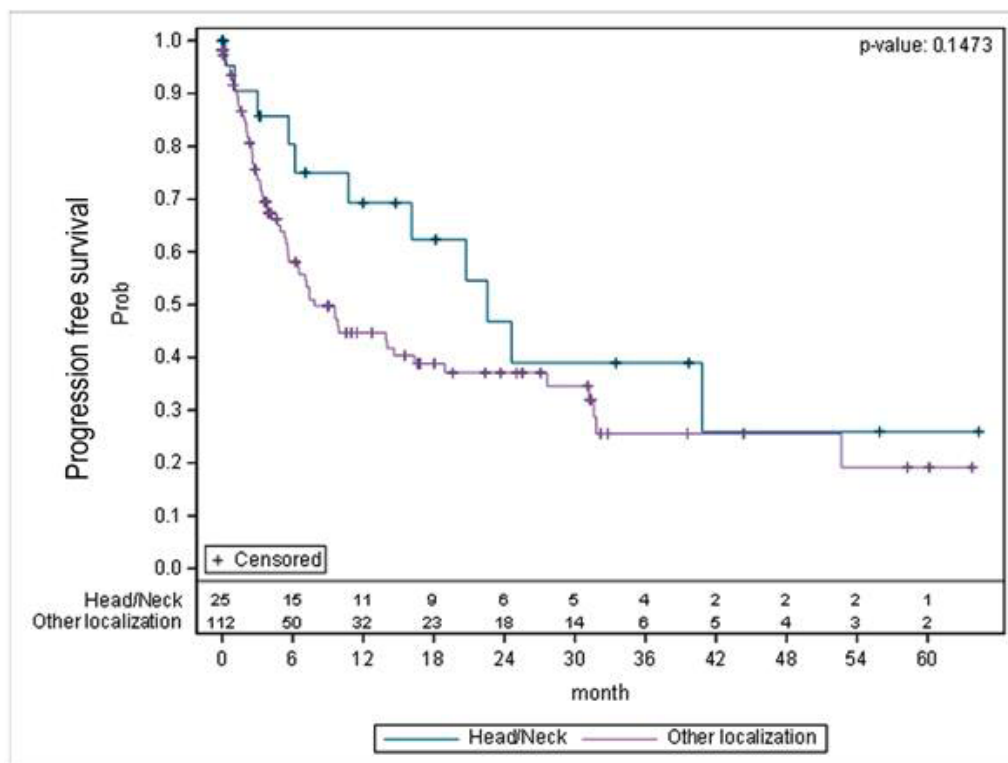
Materials and Methods: We conducted a retrospective analysis among previously untreated advanced melanoma patients treated with anti-PD-1 monotherapy at University Clinical Center Nis, Military Medical Academy Belgrade and University Clinical Center Kragujevac from February 2017 to February 2023. Data were extracted from Central South Eastern European Registry (CSEEREG) a part of the European Melanoma Registry (EuMelaReg). The efficacy of anti-PD-1 was compared between HandN melanomas and other anatomical sites through progression-free survival (PFS), with subgroup analysis.

Results: Altogether 137 patients (HandN 25; UL 26; T 55; LL31) were included. The Median PFS was longer in HandN melanoma patients, but without statistical significance compared to other anatomical sites (22.07 vs 7.83; $p=0.14$). Compared to each site individually, statistical significance was seen compared to UL (22.07 vs 3.85; $p=0.043$) and numerical compared to T (22.07 vs 9.61; $p=0.16$) and LL (22.07 vs 7.83; $p=0.435$).

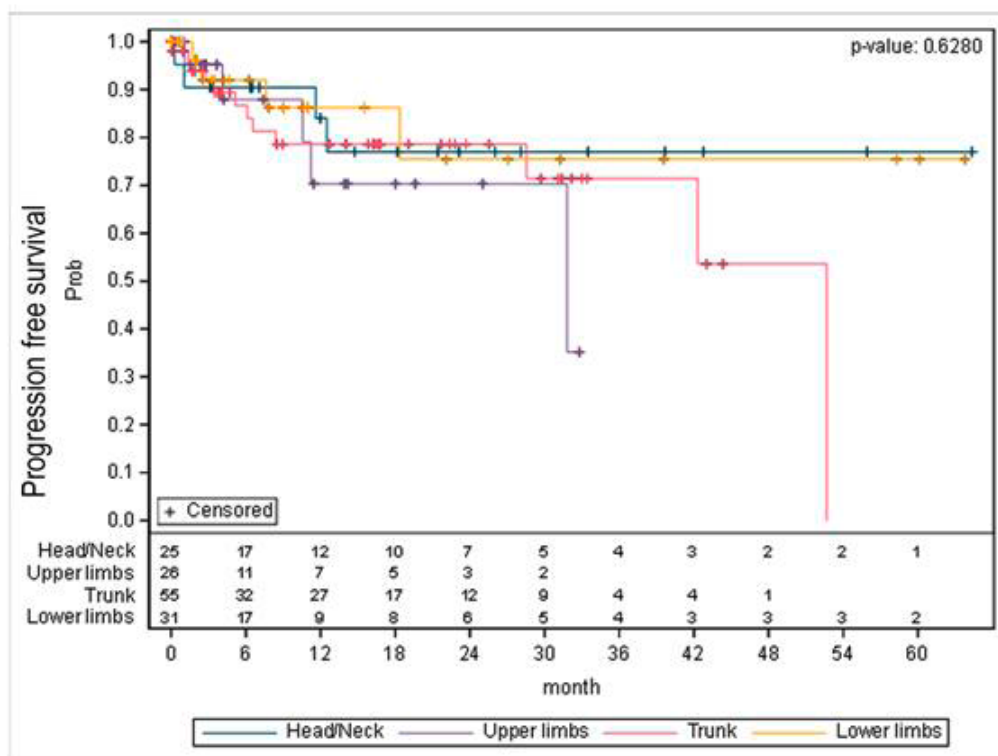
HandN melanoma patients were older, but without statistical significance (median age 71 vs 65.5 years; $p=0.18$). No difference in sex, Breslow thickness, ulceration status, clinical stage or levels of LDH was observed at baseline.

Conclusion: The introduction of novel agents improved outcomes in melanoma patients, but there are still plenty of uncertainties in delineating responders from non-responders in everyday clinical practice. Anti-PD-1 treatment altered the anatomic site-specific clinical behaviour, potentially shifting HandN melanomas into anti-PD-1 treatment favourable anatomical site.

Supporting Document 1



Supporting Document 2



The effectiveness of immunotherapy combined with radiotherapy in the treatment of head and neck mucosal melanoma: a case report

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Mucosal melanoma (MM) is a rare condition with a poor prognosis. Head and neck MM are most common. Although wide surgical excision is the treatment of choice, anatomic location, size of tumor and involved structures can limit its role. Therefore radiation and systemic therapy seem to be a vital option in unresectable cases.

Case report: A 70-year-old patient presented with a giant inoperable mucosal melanoma of the nasal cavity. The bleeding, deforming viscerocranium tumor penetrated to the oral cavity which resulted in breathing difficulties and partial dysphagia. There was also limited distant spread.

The immunotherapy with an anti-PD1 antibody (pembrolizumab, 200 mg/3-weekly) was started. Due to the remarkable growth of the primary tumor, the radiotherapy was added: 20 Gy in 5 fractions over five days using 3D-conformal technique. The immediate tumor regression occurred within 2 weeks. The non-operative treatment resulted in excellent oncological, functional and cosmetic outcome, with acceptable toxicity. The regression, however, was not observed among distant metastases and after four cycles of anti-PD1 antibody, the therapy was switched to anti-CTLA4 antibody (ipilimumab 3 mg/kg/ 3-weekly for four doses). This approach resulted in good disease control for over a year. 13 months from the initial radiotherapy, the primary tumor progressed. Regarding the good response to the radiotherapy, the re-irradiation of 20Gy in 5 fraction was performed with great response lasting 6 months.

Results: Combining radiotherapy with immunotherapy provides an opportunity to increase immunostimulatory potential of radiation which can increase tumor antigens visibility and promote priming of T cells. Moreover it can also exert immunosuppressive action on tumor microenvironment. If it is feasible to provide both local and systemic control, the treatment benefit for the patients is very critical.

Utilization of two alternative pembrolizumab dosing schedules for patients with melanoma in a German skin cancer registry

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Introduction and Objectives: Pembrolizumab 400 mg every 6 weeks (Q6W) received European regulatory approval across all adult indications for pembrolizumab monotherapy in April-2019. This retrospective study aimed to describe patient characteristics and pembrolizumab utilization patterns after Q6W approval according to frequency of administration (Q3W or Q6W).

Materials and Methods: Drawing on the deidentified German ADOReg skin cancer registry, we studied patients aged ≥ 18 years with stage III or IV melanoma initiating first-line pembrolizumab systemic monotherapy from 4-April-2019 to 31-May-2021 ("index period") as either (i) therapy for unresectable melanoma (advanced cohort) or (ii) adjuvant therapy after complete resection of stage III cutaneous melanoma (adjuvant cohort), excluding those in clinical trials or receiving concomitant therapy. Patient characteristics associated with Q6W initiation were identified using univariable logistic regression, and we also examined the proportions of patients switching from Q3W to the Q6W dosing schedule (Q3W-to-Q6W). The Kaplan-Meier method was used to estimate real-world time on treatment (rwToT) with pembrolizumab. Follow-up period was through 31-May-2022, with start of COVID pandemic defined as 1-March-2020.

Results: Of 110 patients in the advanced cohort and 236 patients in the adjuvant cohort, 24% and 26%, respectively, initiated first-line pembrolizumab Q6W (Table). Median observed follow-up was 14.5 and 17.4 months in advanced and adjuvant cohorts, respectively. In the advanced cohort, patients had significantly greater odds of initiating pembrolizumab Q6W during the COVID-19 pandemic compared with the pre-pandemic period (OR, 4.20; 95% CI 1.45-12.18). In the adjuvant cohort, those attending non-university clinics (vs. university clinics) had lower odds of initiating pembrolizumab Q6W (OR, 0.48; 95% CI 0.27-0.88). All other ORs crossed 1. The pembrolizumab rwToT is depicted in the Figure. Among patients who initiated pembrolizumab Q3W, 16/84 (19%) in the advanced cohort switched to Q6W, while 43/174 (25%) in the adjuvant cohort switched to Q6W. The proportions who switched Q3W-to-Q6W were numerically higher in both cohorts during the pandemic (56%/74%, advanced/adjuvant) than pre-pandemic (44%/26%).

Conclusions: Pembrolizumab administration during the COVID-19 pandemic was associated with choice of Q6W dosing at initiation and more frequent switch from Q3W to Q6W, highlighting the flexibility provided by the extended dosing schedule.

Supporting Document 1

Table. Patient characteristics by cohort and dosing schedule at initiation of first-line pembrolizumab monotherapy.

Data are n (%) unless otherwise noted.

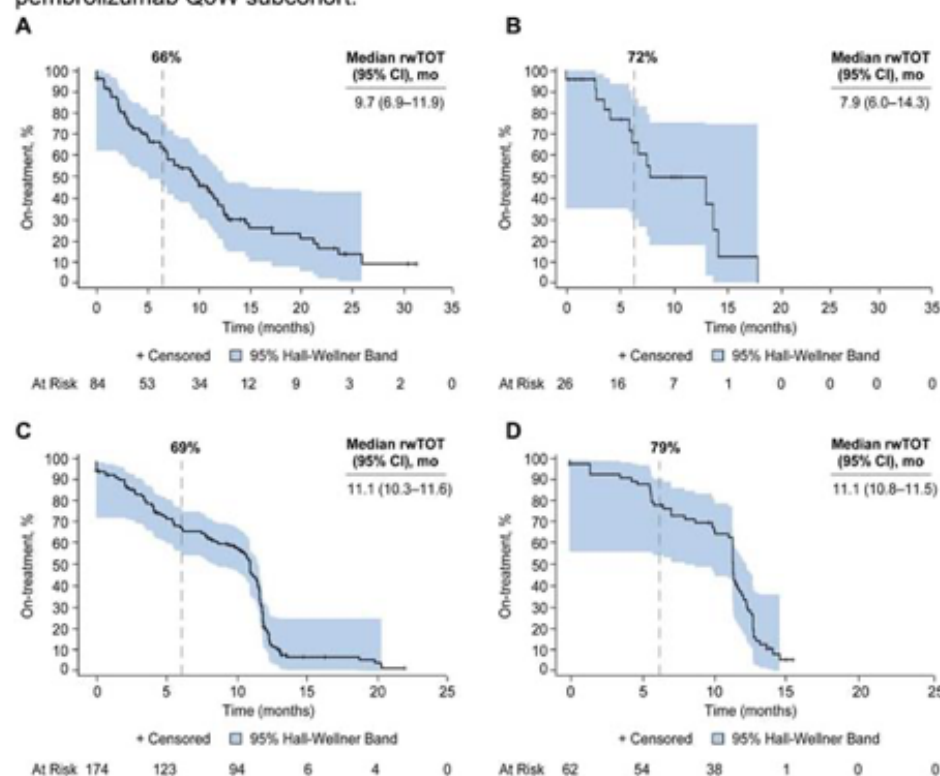
Characteristic	Advanced cohort			Adjuvant cohort		
	All N = 110	Q3W n = 84	Q6W n = 26	All N = 236	Q3W n = 174	Q6W n = 62
Male sex	65 (59)	52 (62)	13 (50)	135 (57)	99 (57)	36 (58)
Age, mean (SD)	70 (15)	70 (15)	71 (17)	62 (14)	61 (15)	65 (13)
Clinic type ^a						
University	61 (55)	46 (55)	15 (58)	115 (49)	76 (44)	39 (63)
Other	49 (45)	38 (45)	11 (42)	118 (51)	95 (56)	23 (37)
Initiated during COVID	63 (57)	42 (50)	21 (81)	140 (59)	97 (56)	43 (69)
Melanoma stage						
Stage III	50 (45)	35 (42)	15 (58)	236 (100)	174 (100)	62 (100)
Stage IV	60 (55)	49 (58)	11 (42)	0	0	0
ECOG PS ^a						
0–1	79 (95)	62 (95)	17 (94)	194 (99)	141 (99)	53 (100)
2–3	4 (5)	3 (5)	1 (6)	2 (1)	2 (1)	0
<i>BRAF</i> mutant ^a	24 (25)	18 (25)	6 (26)	52 (28)	38 (28)	14 (29)

^aPercentages for clinic type, ECOG PS, and *BRAF* mutation status were calculated for known values, excluding missing values.

ECOG PS, Eastern Cooperative Oncology Group performance status.

Supporting Document 2

Figure. Kaplan-Meier estimates of real-world time on treatment (rwToT) for all patients in the (A) advanced melanoma Q3W subcohort, (B) advanced melanoma Q6W subcohort, (C) adjuvant pembrolizumab Q3W subcohort, and (D) adjuvant pembrolizumab Q6W subcohort.



Characterization of the Melanoma Tumor Immune Microenvironment by Flow Cytometry

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Introduction and Objectives: Melanoma is one of the most aggressive human tumours that arises from the uncontrolled proliferation of melanocytes. Like many other solid tumours, malignant melanoma is highly heterogeneous and substantially resistant to unselective treatments. Despite many important advances, development of resistance remains a significant obstacle to melanoma curability and can be modulated by several factors, both intrinsic and extrinsic to the cancer cells. One such important factor is certainly the tumour microenvironment (TME), an intricate and complex network of cells, molecules, and paracrine factors that are tightly interconnected with melanoma cells, thereby influencing their initiation, progression, and sensitivity/resistance to therapeutic interventions. We aimed to characterize the macrophage and the lymphocytic T population that infiltrate the TME of BRAF inhibitor sensitive and resistant melanoma.

Material and Methods: Syngeneic mouse models employing 5555 basal and 5555 Vemurafenib (Vem) resistant melanoma cells were performed injecting around 1x10⁶ cells into the flanks of C57BL/6 mice. Once the tumour was established, mice were sacrificed and the tumour was removed to obtain a single-cell suspension to perform flow cytometry analysis.

Results: When we analyse the macrophage population, we observe an increase of Tumor Associated Macrophages (TAMs) CD206+ and Arg+ (M2-type) in the resistant mouse tumors in comparison with basal mouse tumors. In addition, the resistant syngeneic mouse tumors present a decrease of TAMs that are MHCII+ (M1-type). The analysis of the lymphocyte population reveals that tumors from the resistant model had more CD4+ and FoxP3 lymphocytes, which indicates an increase of Treg population.

Conclusions: The increase in M2-type TAMs and Treg indicates that there is more pro-tumor activity in the resistant model. These thereby hindering protective immunosurveillance of neoplasia and hampering effective immunosuppressive responses, thus promoting tumor development and progression. All of this data indicates that the study and description of the immune system that surround or infiltrate neoplasms during tumor progression and resistance acquisition is particularly interesting. Modulation of tumor immune microenvironment may become a new tool to be combined with current antineoplastic therapies.

Balloon Cell Malignant Melanoma: A case report of a rare entity

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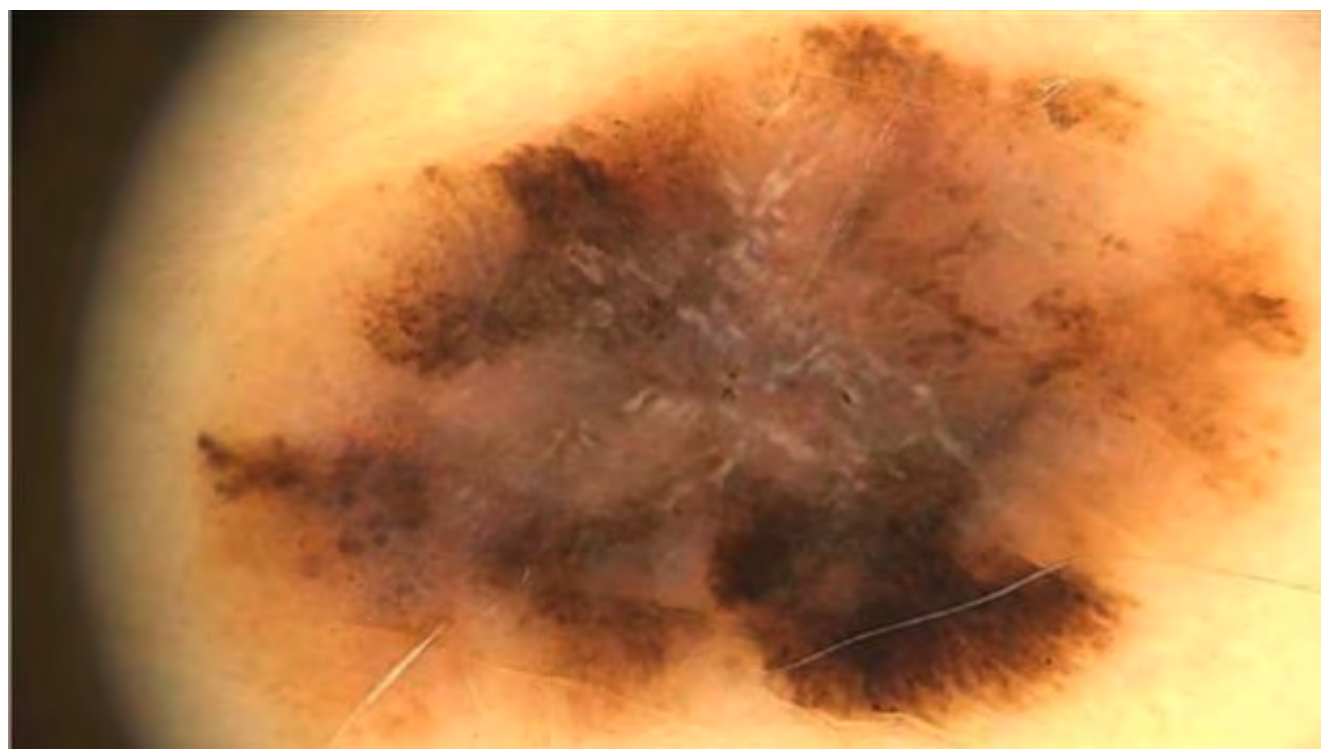
Introduction and Objectives: Cutaneous malignant melanoma accounts for 1.7% of global cancer diagnoses, with its incidence rising in recent years. Balloon cell melanoma (BCM) is the rarest histological variant of malignant melanoma, with only 0.15% of melanoma diagnoses characterized as BCM. Since first reported in 1970, less than 120 cases have been described in the literature. Histologically, the lesion is characterized by the aggregation of large, round, or polygonal balloon cells, with nuclear pleomorphism, atypia and lack of melanocyte maturation.

Materials and Methods: We present a case of a 36-year-old Caucasian woman with a novel atypical lesion on the right anterior thigh. The clinical evaluation revealed an atypical, asymmetric, irregular, pigmented lesion with a diameter of 8mm displaying a multi-colour component and a scarring blue-grey veil and milky-red areas on dermoscopy.

Results: Following excision, a biopsy of the lesion revealed dermal nodular aggregates of large vesicular balloon melanoma cells separated by delicate fibrous septae and islands of tumour cells abutting the dermo-epidermal junction. Immunohistochemical staining was also performed for further characterization. The pathological staging of the melanoma was pT1a, constituting a primary tumour of <0.8mm in thickness without ulceration. Further management continued as per protocols for its pathological stage.

Conclusions: The lack of distinguishing clinical features poses a diagnostic challenge. To our knowledge, this is the first case of balloon cell melanoma described in Cyprus. This report aims to acknowledge this rare entity and its unique histopathologic findings, which will aid in expanding our knowledge regarding its pathophysiologic mechanism and further optimizing its management.

Supporting Document 1



Clinical Features and Outcomes of Paediatric Spitz-type Lesions

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Introduction and Objectives: A limited number of studies explore clinical features and outcomes of Spitz-type lesions. As such, there are no definitive management guidelines for Spitz-type lesions; recommendations in the UK favour a “safe” approach, with a low threshold for excision. We aim to contribute to the literature describing Spitz-type lesions in children to better clarify clinical features and outcomes.

Materials and Methods: We conducted a retrospective cohort study in Addenbrooke's Hospital, Cambridge, UK, reviewing all patients with age ≤ 18 years who had histologically confirmed Spitz-type lesions from November 2014-September 2020. Information collected included patient demographics, lesion details, follow-up, outcomes, and recurrence.

Results: 91 children (male:female 42:49, mean age at diagnosis: 9.4 years, SD: 4.6 years) were identified, consisting of 64 (70.3%) Classic Spitz or Spitzoid naevi, 26 (28.6%) Atypical Spitz Tumours (AST), and one (1.1%) Spitzoid malignant melanoma based on histological features. Assessing clinical features of Spitz-type lesions where documented, we found 22.0% (20/91) showed amelanosis, 44.0% (40/91) had a raised bump, 12.1% (11/91) displayed bleeding, 25% (20/80) had non-uniform colour, 55.1% (43/78) were evolving in size, and 35.9% (28/78) were evolving in colour. All patients underwent minimal margin excision biopsies, and five wide local excisions were performed; two due to presence or high suspicion of melanoma, and three due to incomplete excision. We found two patients with multiple Spitz-type lesions, one in the same site, and one in distant sites. 59 patients (64.8%) were discharged without requiring follow-up, and the other 32 had a mean follow-up time of 13.3 months. We have found no incidences of local recurrence after confirmed excision, no distant metastases, and no mortality in all patients to date.

Conclusions: Outcomes for paediatric Spitz-type lesions continue to be exceptionally good, remaining a low-risk lesion which is more likely to be benign in children than in adults. Our findings extend the existing literature in a British cohort and support international calls for reconsideration any aggressive management policies regarding wide excision for paediatric patients with clinically banal Spitz-type lesions.

Clinical Review of Mucosal Melanoma: The 11-Year Experience of a Referral Center

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Background: Mucosal melanoma is a rare neoplasm. Late diagnosis is caused by occult anatomic sites and scarcity of symptoms. Novel biological therapies have now become available. Demographic, therapeutical, and survival records on mucosal melanoma are scarce.

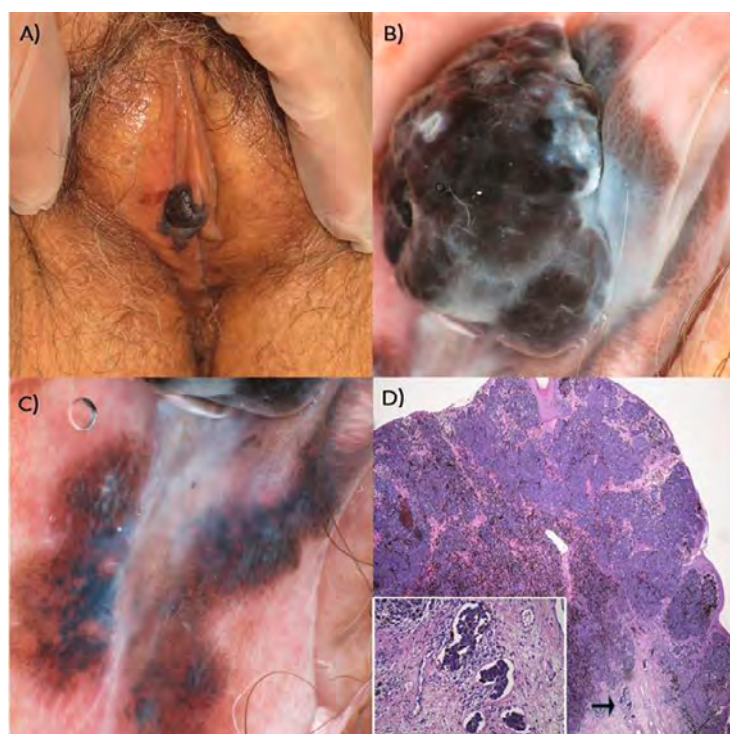
Objectives: To provide an 11-year retrospective clinical review of real-world data on mucosal melanomas managed in a tertiary referral center in Italy.

Methods: We included patients with histopathological mucosal melanoma diagnosis from January 2011 to December 2021. Data were collected until the last known follow-up or death. Survival analysis was performed.

Results: Among 33 patients, we found 9 sinonasal, 13 anorectal, and 11 urogenital mucosal melanomas (median age 82, females 66.7%). Eighteen cases (54.5%) presented with metastasis ($p < 0.05$). In the urogenital subgroup, only 4 patients (36.4%) showed metastasis, all in regional lymph nodes. Sinonasal mucosal melanomas were surgically managed with a debulking procedure (44.4%); every case of anorectal and urogenital melanomas underwent radical surgery (30.8% and 45.5%). Fifteen patients were treated with biological therapy ($p < 0.05$). Radiation therapy was used in all mucosal melanomas of the sinonasal region ($p < 0.05$). Overall survival was longer for urogenital melanomas (26 months). Univariate analysis showed an increased hazard ratio for death in patients with metastasis. A negative prognostic value of metastatic status was reported by the multivariate model, while administration of first-line immunotherapy demonstrated a protective role.

Conclusions: At diagnosis, the absence of metastatic disease is the most relevant factor that influences the survival of mucosal melanomas. Moreover, the use of immunotherapy might prolong the survival of patients with metastatic mucosal melanoma.

Supporting Document 1



Clinical, dermoscopic and histopathological features of acral melanoma – description of seven cases

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Introduction and Objectives: Acral melanoma (AM) is a rare subtype of melanoma, most commonly presenting on plantar surfaces of hands and feet. Due to its specific location, the diagnostics of AM may be late.

Materials and Methods: We present a case series study of patients treated in the Maria Skłodowska-Curie National Research Institute of Oncology (Gliwice, Poland – 4/7) and Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University of Gdańsk (Gdańsk, Poland – 3/7). We analyzed the cases of acral melanoma based on their clinical, dermoscopic and histopathological presentation. Dermoscopic features were described according to the International Society of Dermoscopy standardization of terminology [1].

Results: Patients were aged 66-87 (57% males). All of the AM presented on the feet, including 4 (57%) on the heel. Only one case was diagnosed at stage 0 (melanoma in situ). Breslow thickness of invasive melanomas varied from 2.1 to 10 and Clark level from III to V.

More than half of the AM manifested as a tumor. Under dermoscopic examination, the most common pattern was structureless zones (100%), usually brown or black (71%), with asymmetry in colour (100%) and distribution (86%). Positive sticky fiber sign occurred in 5 (71%) cases.

Conclusions: Dermoscopic patterns of acral melanoma may pose a diagnostic challenge due to its atypical presentation. Opposite to published data, we can find not only typical parallel ridge pattern but also structureless zones and asymmetry in colour and distribution. The differences may result from advanced stages of presented AM.

References: Kittler H. et al. Standardization of terminology in dermoscopy/dermatoscopy: Results of the third consensus conference of the International Society of Dermoscopy. *J Am Acad Dermatol.* 2016 Jun;74(6):1093-106.

Controlled randomized multi center clinical study to assess the efficacy of an emollient PLUS balm containing an *Aquaphilus dolomiae* extract (ADE-G1) associated with educational program versus real life in xerotic cancer patients.

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Introduction: Severe xerosis is a common and often neglected skin adverse event of anticancer therapies. Improving the evidence of the efficacy of topical emollient on this frequent issue is of interest to improve patients' quality of life.

Objectives: To evaluate the effectiveness of an emollient PLUS balm containing ADE-G1 associated to an educational program (treated group) for the management of moderate to severe drug induced xerosis in adult cancer volunteers.

Methods: This comparative multi-center study involved xerotic patients treated with systemic anticancer drugs, randomized in two parallel groups (ClinicalTrials.gov Identifier: NCT04181177): -treated group applied twice daily the study product and was educated; -controlled group was proposed best supportive care at physicians' discretion, then the study product and education if insufficient improvement at 4 weeks (cross-over). The investigator and patients assessed at baseline, at 1 month for both groups: -global body xerosis severity (NCI-CTCAE 5.0 scale), a target xerosis area; - subjective signs, impact of patient's skin condition on their quality of life; - overall tolerance; -instrumental evaluation by corneometer and Dsquam quantification. Statistical inter-group analysis was conducted on principal and secondary criteria.

Results: 29 adults (mean age 63 yo.) were enrolled: 15 in treated group; 14 in control group. Between baseline-the end of treatment phase (treated group) the inter-group analysis showed a significant improvement of both global body xerosis severity (at least 1 grade up to the absence of xerosis) ($P=0.047$) and target area ($P=0.008$). DLQI score improved at the end of follow-up (-57% in treated group, NS). Hydration index and Dsquam quantification also improved significantly ($P=0.029$; $P=0.023$ respectively). The study product was very well tolerated and accepted by subjects.

Conclusion: This randomized controlled clinical study support using the emollient PLUS balm containing ADE-G1 for xerotic cancer patients, associated to educational program, showing a significant benefit versus real life control group.

Delays in time from biopsy to wide local excision of Stage I and Stage II melanoma: a single centre retrospective audit

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Introduction and Objectives: Timely treatment of cutaneous melanoma can improve patient outcomes. A recent study showed that Stage I and II melanomas had worse melanoma specific mortality (MSM) and overall mortality (OM) if time between diagnostic biopsy and therapeutic excision was >3 months¹. We assessed time from biopsy to wide local excision (WLE) and/or sentinel lymph node biopsy (SLNB) for all Stage I and II melanomas in our centre over a 5-year period (2018-2022).

Materials and Methods: This was a retrospective longitudinal audit of all stage I and II melanomas diagnosed in our centre between January 2018 and January 2022. Patients were identified using a departmental database. Cases without completed WLE at time of data collection were excluded. Time between histological diagnosis to WLE +/- SLNB was recorded.

Results: 192 cases of stage I and II melanoma were identified, 113 women, 79 men. Mean age at diagnosis was 62.4 years (SD 17). 161(84%) had Stage I. 31(16%) had Stage II. 18 (10%) had WLE <1 month after diagnosis. 133 (69%) had WLE performed 1-3 months after diagnosis. 41 (21%) had WLE excision performed >3 months after diagnosis. Of stage I melanomas, 130 (81%) had WLE within 3 months of diagnosis. 20 (65%) stage II had WLE within 3 months of diagnosis. 2 (6%) stage II had WLE after 6 months. Most patients had WLE by plastic surgery in an external centre (135/192, 70%). 25 (19%) of these had WLE >3 months after diagnosis. Of the 57 (30%) who had surgery within our department, 16 (28%) had WLE >3 months after diagnosis.

Conclusions: The majority of patients with stage I (81%) and II (65%) melanoma had WLE completed within 3 months of biopsy. Patients with stage II melanoma experienced longer delays to surgical treatment, perhaps reflecting the need for concurrent SLNB or more complex surgery. Additional delays in the study time-period may be reflective of the pandemic. Nonetheless the proportion of our patients waiting longer than 3 months for WLE is concerning. This has been addressed with the local multi-disciplinary team and will be re-audited. This study was retrospective and was not powered to assess melanoma specific mortality.

Image analysis of cutaneous melanoma histology: a systematic review and meta-analysis

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Introduction and Objectives: The current subjective histopathological assessment of cutaneous melanoma is challenging. The application of image analysis algorithms to histological images may facilitate improvements in workflow and patient management. To date, several individual algorithms applied to melanoma histological images have been reported, but before any such tool could be integrated into clinical workflow, the accuracy of the technology should be carefully evaluated and summarised. Therefore, the objective of this review was to evaluate the accuracy of existing image analysis algorithms applied to histological images of cutaneous melanoma.

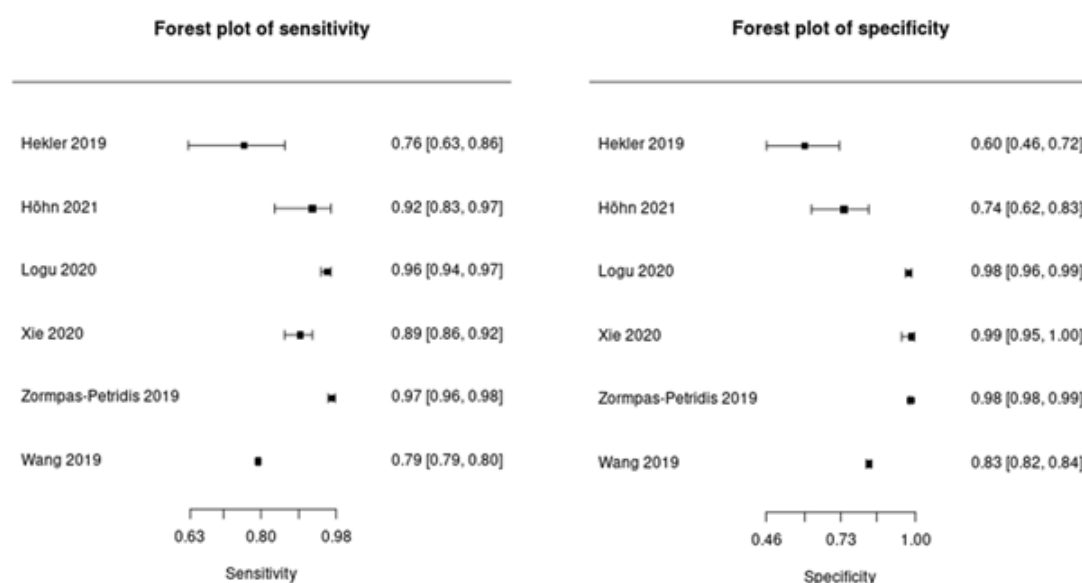
Materials and Methods: Database searching of PubMed and Embase from inception to 11th March 2022 was conducted alongside citation checking and examining reports from organisations. All studies reporting accuracy of any image analysis applied to histological images of cutaneous melanoma, were included. The reference standard was any histological assessment of haematoxylin and eosin-stained slides and/or immunohistochemical staining. Citations were independently deduplicated and screened by two authors with disagreements resolved through discussion.

The data was extracted concerning study demographics; type of image analysis; type of reference standard; conditions included and test statistics to construct 2x2 tables, in accordance with our protocol and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Diagnostic Test Accuracy (PRISMA-DTA) Statement. A bivariate random-effects meta-analysis was used to estimate summary sensitivities and specificities with 95% confidence intervals (CI). Assessment of methodological quality was conducted using a tailored version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. The primary outcome was the pooled sensitivity and specificity of image analysis applied to cutaneous melanoma histological images.

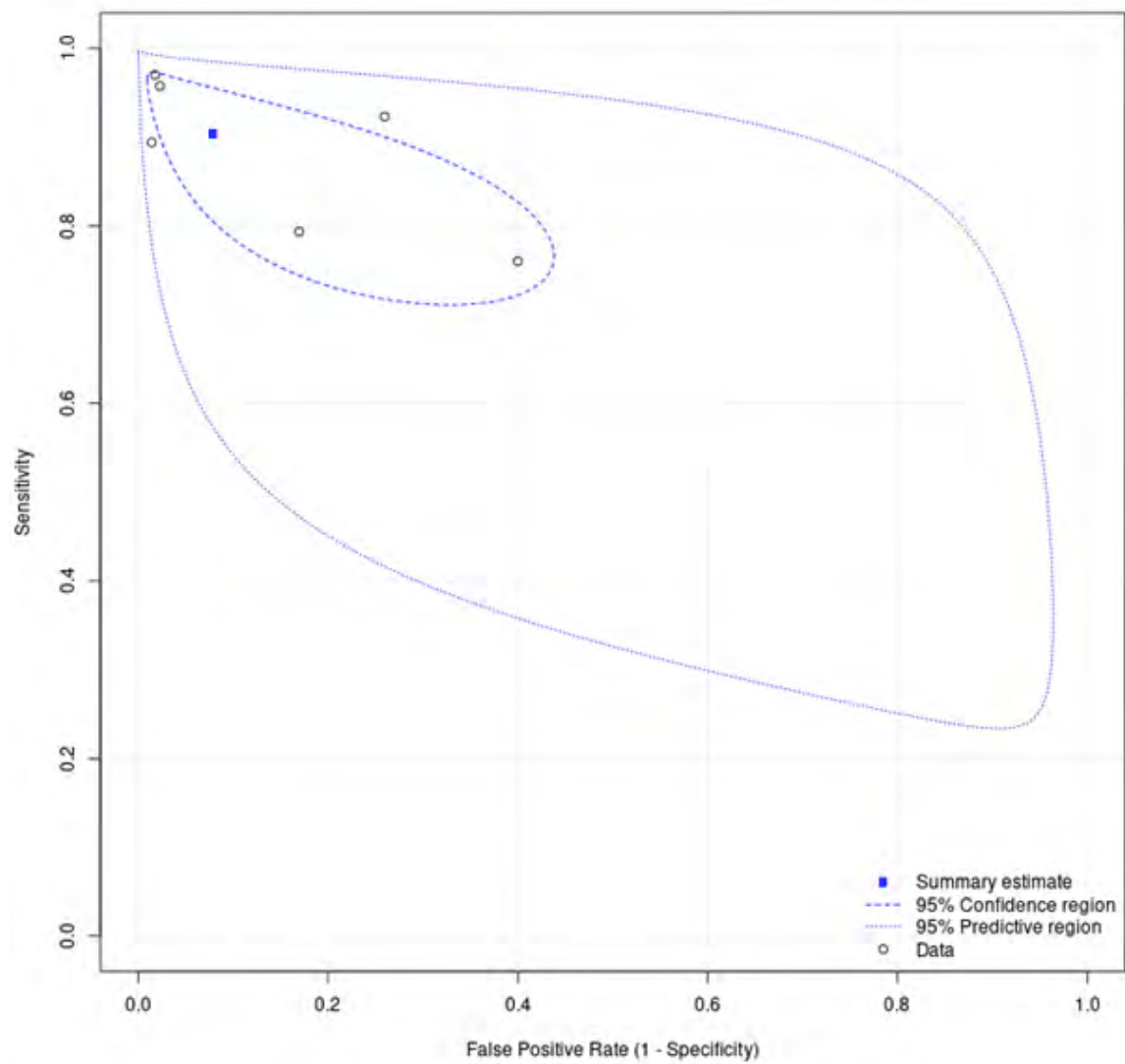
Results: Sixteen studies were included in the systematic review, representing 4,888 specimens. Six studies were included in the meta-analysis. The mean sensitivity and specificity of automated image analysis algorithms applied to melanoma histological images was 90% (CI 82%, 95%) and 92% (CI 79%, 97%), respectively.

Conclusions: Based on limited and heterogeneous data, image analysis appears to offer high accuracy when applied to histological images of cutaneous melanoma. Future work should address the clinical application of such models and evaluate their use as a screening tool or for prognostic/ predictive biomarker generation.

Supporting Document 1



Supporting Document 2



Imatinib mesylate in combination with pembrolizumab in patients with advanced KIT-mutant melanoma following progression on standard therapy: a phase I/II trial (IMPAKT trial)

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Purpose: To date, several clinical trials have been conducted to target KIT gene alterations in melanoma. Imatinib mesylate, a small-molecule inhibitor of the KIT tyrosine kinase, provides a rapid but not durable clinical response in KIT-mutant melanoma. Meanwhile, recent basic and clinical evidence have revealed another aspect of KIT-targeted therapy, namely the enhancement of antitumor activity of immune checkpoint inhibitors. Herein, we designed clinical trial of co-administrating imatinib mesylate and pembrolizumab (anti-PD-1 antibody) to evaluate its safety and efficacy.

Patients and Methods: This is an open-label, single-arm, phase I/II clinical trial involving Japanese patients with metastatic KIT-mutant melanoma that are refractory to standard therapy including anti-PD-1 therapy. Phase I study is a dose-escalation study comprising two dose levels of imatinib mesylate (200mg/day and 400mg/day, respectively) with fixed dose of pembrolizumab (200 mg every 3 weeks) to evaluate safety and tolerability and determine recommended phase II dose. The primary endpoint of the Phase II study is the objective response rate after 4 cycles (3 weeks/cycle) of pembrolizumab and imatinib mesylate at the dose determined in Phase I, based on RECIST version 1.1. A Simon's minimax two-stage design is employed to test the null hypothesis of a 5% response rate vs 30% alternative, which will be rejected when a lower confidence limit of two-sided 90% confidence interval of true response rate is over than threshold response rate. The secondary endpoints include progression free survival, overall survival, best overall response and incidence of adverse events. Totally, a target size of 22 patients will be expected.

Conclusions: The study is now ongoing. If this study shows efficacy and acceptable safety profile, it will contribute to the development of novel treatment option for patients with KIT-mutant melanoma that are refractory to standard therapy.

Improved sensitivity in BRAFV600E detection in combined tissue and extracellular vesicles-based liquid biopsy in melanoma

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Introduction and Objectives: Liquid biopsy approaches can complement or substitute regular biopsies. Our group has shown that detection of BRAFV600E mutation in EV-associated nucleic acids (EV-NAs) isolated from lymphatic drainage of melanoma patients has prognostic significance (1). In this work, we compared the prognostic capacity of BRAF status in melanoma patients using an EV-NA-based liquid biopsy test in plasma and a clinically standard tissue biopsy test.

Materials and Methods: Plasma was collected from a cohort of 22 melanoma patients in their visit to the dermatologist (stages II-IV) at a median time of 2 months after tissue biopsy. Samples were collected and processed in less than 2 hours. BRAF status in tissue samples was determined using Cobas assay. Plasma samples were analyzed using a combined cfDNA and EV-associated nucleic acid isolation approach followed by an allele-specific quantitative PCR for BRAFV600E mutation.

Results: 10 patients carried BRAFV600E mutation when analyzed by tissue biopsy and 8 patients were positive for the mutation according to plasma analysis. The mutant allele frequency oscillated between 0.01-3.43% in plasma samples. No total overlap was observed between both types of analysis. Patients identified as BRAF mutant carriers by tissue biopsy and/or liquid biopsy displayed a significantly worse 2-years overall survival compared with non-carriers (log rank test, $p=0.0184$). Whereas the information about BRAF status provided by a single analysis alone was not able to discriminate high risk patients (log rank test, $p=0.3366$ and $p=0.0611$, respectively) (4).

Conclusions: Our results indicate that evaluation of BRAF mutation both in tissue and plasma rises the detection rate of mutant BRAF in comparison to individual approaches, patients with BRAFV600E mutation present a high risk of progression within the first two years. We propose BRAF status should be considered as an additional clinical factor for adjuvant therapy in melanoma patients. Our data encourage the analysis of BRAF status by tissue and liquid biopsy in all metastatic melanoma patients in the first visit to the dermatologist. Similar analysis in larger cohorts would demonstrate the utility of this screening to identify patients at risk of progression.

International consensus: Using dermocosmetics to reduce risks of oncology-treatment related skin toxicities

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Introduction and Objectives: Skin toxicities – one of the most frequent adverse events associated with cancer therapies. Further, new side effects emerge as new oncology drugs are approved (e.g., targeted therapies, immunotherapies) which are associated with a negative impact on quality of life, oncologic treatment dose reductions, and/or treatment discontinuation. Cancer treatment-related skin toxicities result mostly from alterations in skin barrier function, inflammation, immune responses, and phototoxicity. Maintenance of skin barrier function and photoprotection may facilitate prevention and management of adverse events to optimize treatment outcomes.

Methods: A multidisciplinary group of healthcare professionals, in partnership with the Association Francophone des Soins Oncologiques de Support (AFSOS) and Multinational Association of Supportive Care in Cancer (MASCC), held a consensus meeting to discuss the role of dermocosmetics in preventing and managing cancer treatment-related skin toxicities.

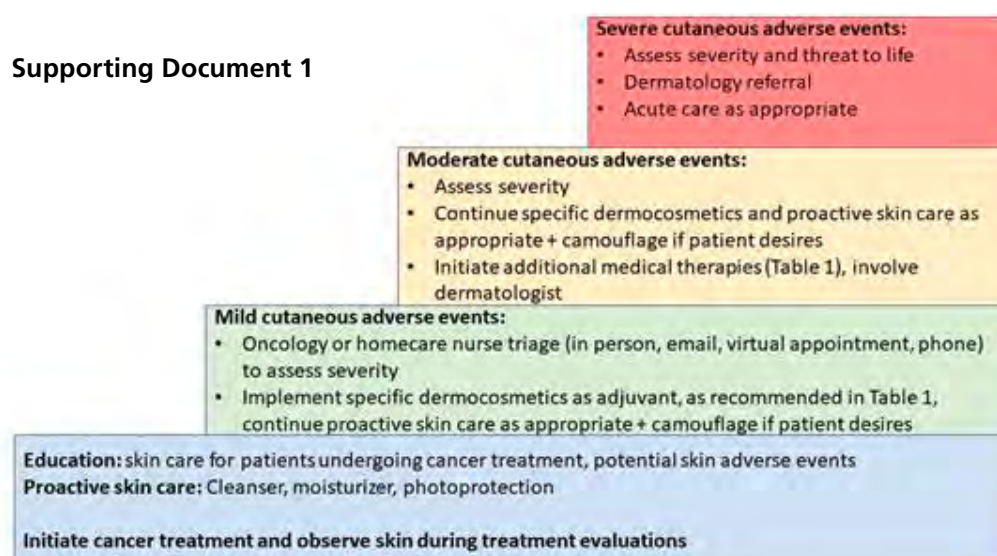
Results: Dermocosmetics (or cosmeceuticals) are non-prescription products that give both therapeutic and cosmetic benefits. Through these actions, such as support of epidermal skin barrier and cutaneous microbiome, dermocosmetics may improve patient outcomes and reduce interruptions of cancer treatments. Skin toxicity management strategies should start with implementation of preventative skin care regimens at the beginning of cancer therapy including broad spectrum photoprotection, skin hydration, and non-basic/neutral cleansers with pH close to 5. Specific recommendations can be made based on type of cancer therapy and expected skin toxicity:

- Urea, particularly in the case of some oncology treatments leading to hand foot syndrome, is important due to its exfoliating and hydrating actions. Urea should be avoided with irritated skin.
- Consider a stepped care approach to managing skin toxicities (Figure 1).

Conclusions: Based on clinical experience and review of literature, the group created recommendations for the management of specific skin toxicities. Increasing data provide support for the beneficial impact of dermocosmetics in management of cancer treatment-related skin toxicities.

Funding Source: The international consensus publication was made possible by an unrestricted educational grant provided by La-Roche Posay International

Supporting Document 1



Lentigo maligna: still a tumor of the elderly?

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Introduction and Objectives: Lentigo maligna (LM) is a melanocytic tumour commonly found on chronically sun-exposed areas.¹ The majority of LMs are in situ but there is a percentage of them that invades the dermis and is defined lentigo maligna melanoma (LMM). LM has a longer period of intraepidermal growth and has historically been recognized as a tumor of the elderly, being clinically a large macule.¹ However, before becoming a large macule and thus clinically worrisome, this tumor should be smaller and arise in a younger subset of patients. However, with the exception of few case reports, there is paucity of data regarding clinical and dermoscopic features of LM in young patients. Our aim was to describe dermoscopic features of LM located on the face of patients aged 50 or less.

Materials and Methods: A total of 85 cases of histologically confirmed facial LM / LMM were retrospectively selected among 8 different dermatology clinics from 6 different countries. Inclusion criteria was histopathologically proven LM-LMM in patients younger or equal to 50 year-old. Clinical and dermoscopic features were analyzed.

Results: A total of 85 cases were enrolled. Briefly the vast majority (93%) of facial LM were in situ and the mean size of the lesions was 10.33 mm. Cheeks (46%) were the most common site of localization. The most represented dermoscopic features were: asymmetrically pigmented follicular openings (81%) and gray color (72%). Interestingly, showed that the age of the patient was associated with the size of the LM and with the number of dermoscopic criteria per lesion: the fewer the age, the smaller the lesion and the lower dermoscopic criteria.

Conclusions: Our study shows that LM in young tends to be smaller in size and generally shows few suggestive dermoscopic features, therefore it may be a challenging diagnosis. We conclude that dermatologists must be aware that lentigo maligna is not just a tumor of the elderly and every pigmented lesion on the face, even in young patients, must be carefully analyzed before using any laser or cosmetic treatments.

LONG-TERM OUTCOMES OF ISOLATED PERFUSION WITH HYPERTHERMIA IN PATIENTS WITH LIMB MELANOMA OF THE EXTREMITIES

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Isolated regional limb perfusion is considered as one of the effective treatment options in patients with local recurrences of melanoma or transit metastases of tumor located distal to the axilla and inguinal region. The aim of this study was to evaluate the long-term outcomes of the treatment of melanoma of the extremities by isolated regional perfusion.

Methods: All patients underwent isolated regional perfusion with hyperthermia using melphalan at doses of 10 mg/l for the lower limb and 13 mg/l for the upper limb. The primary endpoint was 5-year overall survival (OS). Survival analyses were performed using Kaplan-Meier model. Secondary endpoints included recurrence-free survival, objective response rate (ORR; RECIST 1.1) and the frequency of limb amputation.

Results: 72 patients (12 men and 60 women) with melanoma of the extremities were eligible for analysis. The median age was 56.7 (25 to 78) years. 66.7% of patients previously underwent surgery and adjuvant chemotherapy. The 1-year OS was 91.7%, the 5-year OS in patients who underwent isolated regional perfusion was 55.6%. The complete response rate was 13.9%, partial response – 72.2%. Recurrence of transit metastases within 5 years occurred in 52 (72.2%) patients. Amputation was performed in 11.1% of cases.

Conclusion: In this analysis of patients with local recurrences of melanoma, high response rate and long-term survival with isolated regional perfusion with hyperthermia using melphalan were seen. This is an effective and safe method of treatment with a low rate of amputations and metastasis occurrence.

Melanoma awareness in a high-risk population in Switzerland

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Dr Stephanie Huber¹, Dr Michael Kunz¹, Prof Alexander A. Navarini^{1,2}, Dr Lara Valeska Maul^{1,2}

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Introduction and Objectives: The global incidence of melanoma has risen rapidly over the last decades in Caucasian populations with Switzerland having one of the highest rates in Europe. Ultraviolet (UV) radiation is one of the main risk factors for melanoma. Our aim was to investigate the UV protection behavior and melanoma awareness in a high-risk cohort for melanoma.

Materials and Methods: In this prospective monocentric study, we assessed general melanoma awareness and UV protection habits in at-risk patients for melanoma (≥ 100 nevi, ≥ 5 dysplastic nevi, known CDKN2A mutation and/or positive family history) and melanoma patients using questionnaires.

Results: Between 01/2021 and 03/2022, a total of 269 patients (mean age 54 ± 14 years, 52% male, 53.5% at-risk, 46.5% melanoma patients) were included. We observed a trend of using higher sun protection factor (SPF) among melanoma vs. at-risk patients (Figure 1; SPF 50+: 48% [$n = 60$] vs. 26% [$n = 37$]). The UV protection in terms of sunscreen use with an SPF ≥ 30 was significantly higher among subjects with college or university degrees compared to patients with lower levels of education ($p = 0.0007$). Interestingly, we found an opposite observation for annual sun exposure as patients with a higher education level spent significantly more time in the sun ($p = 0.041$). Neither a positive family history for melanoma nor gender, Fitzpatrick skin type, melanoma subtype or stage nor the anatomic location of the melanoma on the body influenced sun protection behavior regarding the SPF used and the amount of sun exposure per year. Study participation led to an improved sun protective behavior as 51% reported using sunscreen more frequently after inclusion.

Conclusions: UV protection remains a crucial factor in melanoma prevention. We suggest to further raise melanoma awareness through public skin cancer prevention campaigns with particular focus on individuals with low education levels.

Supporting Document 1

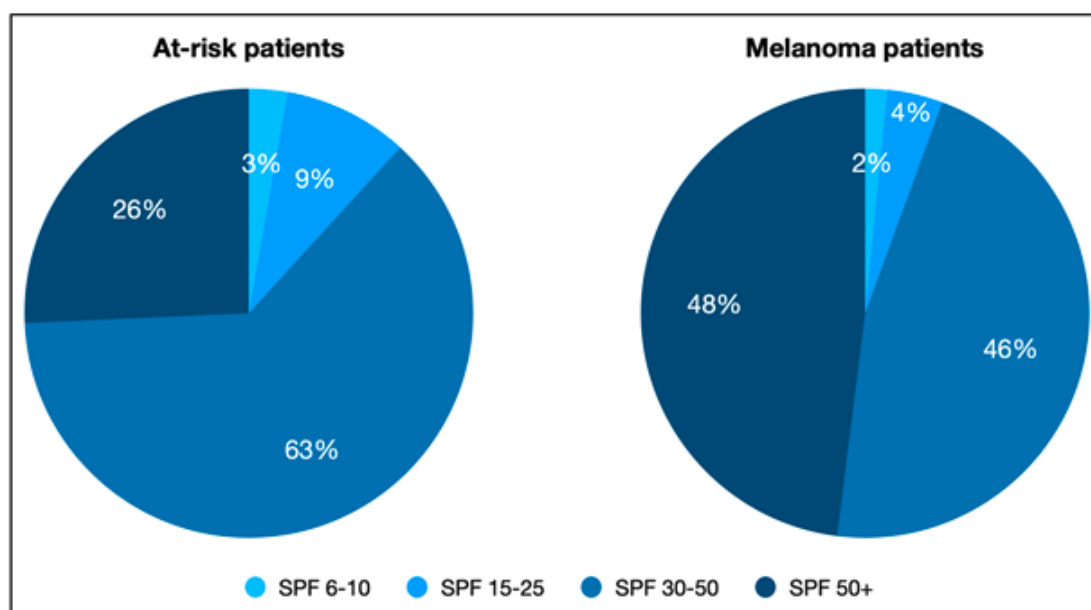


Figure 1: SPF use of at-risk patients vs. melanoma patients. Significant trend for melanoma patients to use higher SPF than at-risk patients (SPF 50+: 48% [$n = 60$] vs. 26% [$n = 37$], $\chi^2 = 15.33$, $df = 3$, $p = 0.0016$). SPF is color-coded.

Melanoma cells in Optical Super High Magnification Dermoscopy

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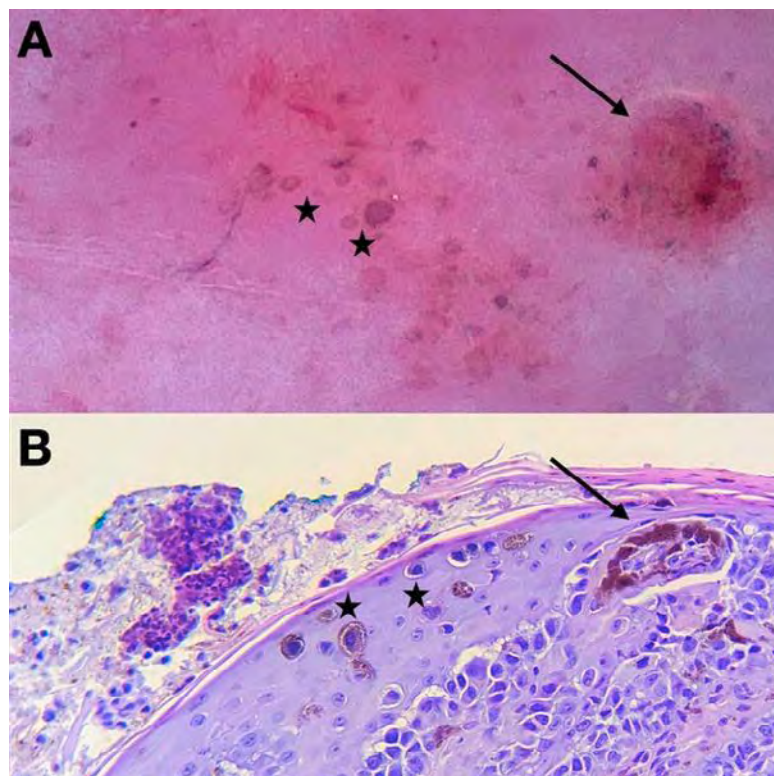
Introduction and Objectives: Melanoma is one of the conditions with the worst prognosis in a dermatologist's practice. Early diagnosis is not only a great challenge but also the chance of a complete cure for the patient. Optical super-high magnification dermoscopy (OSHMD) is an easily accessible variant of dermoscopy which, thanks to up to 400x magnification, allows a very accurate analysis of skin lesions. The aim of the study is to describe the concordance between OSHMD and histopathological image in a patient with melanoma.

Materials and Methods: A 38-year-old woman presented with a few-month history of an 8-mm tumor on her back. Standard dermoscopy (20x magnification) and OSHMD (400x magnification) were performed with Medicam 1000 (FotoFinder Systems GmbH) camera.

Results: Dermoscopy revealed ulceration in the center of the lesion with looped vessels at the periphery and dark brown dots unevenly distributed throughout the whole lesion. OSHMD enabled visualization of the structures invisible in standard dermoscopy and revealed the presence of scattered irregular round cells of different sizes (indicated with asterisks) and a nest of melanocytes (marked with an arrow) (A). Such an image clearly reflects the pagetoid spread of melanoma cells visible in the histopathological examination performed after the excision of the lesion (B).

Conclusions: An excellent correlation of the images convinces us that OSHMD allows the visualisation of single melanocytes. Furthermore, as melanoma develops in the epidermis, and dermoscopy ranges to the dermo-epidermal junction, OSHMD may be a useful tool in the diagnostic process of early melanoma.

Supporting Document 1



New solutions for personalized monitoring of melanoma patients using circulating tumor-derived DNA

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Introduction and Objectives: Currently, melanoma patients are monitored by clinical assessment, imaging (e.g. PET-CT), and sometimes blood biomarkers (e.g. S100). Numerous studies support the role of circulating tumor-derived DNA (ctDNA) as a sensitive biomarker; however, standardized interpretation of ctDNA has yet to be established.

Materials and Methods: We developed two liquid biopsy monitoring tools based on ctDNA assessment: PM (Personalized Monitoring, a portfolio of digital PCR assays), and LBM (Liquid Biopsy Melanoma, a targeted sequencing assay). Both tools use tailored software packages to automatically analyze, interpret, and report data. The software has been trained on healthy subject data to eliminate bias and enable more robust results.

PM allows detection and quantification of the most common SNVs in melanoma: BRAF, NRAS, GNA11, GNAQ and SF3B1. LBM captures melanoma-relevant target regions in 67 genes and HLA-types and can identify novel (resistance) markers at the time of disease progression, sparing invasive tumor sampling. All findings are annotated with a curated knowledge database of approved and off-label therapies and ongoing clinical trials.

Results: We have analyzed ctDNA in 30 patients with metastatic cutaneous and uveal melanoma. We evaluated the results in comparison to PET-CT and blood biomarkers like S100 and LDH. Patients with detectable ctDNA at a random timepoint have progressed more frequently in PET-CT than those without detectable ctDNA.

In 10 patients with uveal melanoma, we have performed both PM and LBM. We detected ctDNA in all patients and observed high correlation between the digital PCR based PM and targeted NGS analysis based LBM. Furthermore, using LBM we could identify novel mutations in the samples collected at the time of disease progression, compared to baseline.

Conclusions: ctDNA detection with PM or LBM can be used as a prognostic tool for patients with metastatic melanoma. PM and LBM are tools for both broad and specific longitudinal monitoring of melanoma patients. While PM is a radically simplified and sensitive solution to rapidly quantify ctDNA, LBM delivers a comprehensive genetic snapshot of the tumor's molecular profile in the blood.

Repeatability of deep-learning based risk scores of 2D and 3D convolutional neural networks for dermoscopic melanoma detection: A prospective real-world study in Switzerland

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Introduction and Objectives: Deep-learning convolutional neural networks (CNN) have shown promising advances in dermoscopic melanoma recognition by outperforming even experienced dermatologists under artificial conditions. While CNN robustness has previously been tested using artificial image transformations, the effects of real-world alteration caused by repeated camera positioning remain unknown.

Materials and Methods: In our standardized real-world prospective study at the Department of Dermatology of the University Hospital Basel, we investigated the repeatability of computer-guided risk scores of two commercially available 2D/3D CNNs for melanoma recognition between January and July 2022. Five consecutively captured dermoscopic images of 117 lesions among 66 patients were classified with either 2D or 3D CNN malignancy risk assessment with a study-defined cut-off score of >0.5 for 2D CNN and >5.0 for 3D CNN. Lesions were divided into four intrasystem groups (n=18), depending on their initial risk scores and clinical/histological dignity assessment (1st score malignant, clinically malignant; 1st and 2nd scores malignant, histologically benign; 1st score malignant, clinically benign; 1st score benign, clinically benign).

Results: In intersystem comparison, 3D CNN showed significantly superior measurement repeatability for clinically benign lesions with an initial malignant risk score (mean variation coefficient: 3D: 49.5(±34.3)%; 2D: 71.4(±22.5)%; p=0.03), while 2D CNN outperformed for clinically benign lesions with benign scoring (mean variation coefficient: 3D: 49.7(±22.7)%; 2D: 23.8(±29.3)%; p=0.002). In both systems, lowest measurement repeatability was observed for lesions with an initial malignant risk score and a benign expert consensus assessment. In this scenario, highest CNN dignity assessment sensitivity was achieved by mean calculation of the first three risk scores (sensitivity of 3D: 94%; 2D: 89%).

Conclusions: Our data indicate that potential user-induced image changes in real-world repeated measurements can relevantly influence CNN classification. For clinical application, we propose to use the mean calculation of three initial CNN risk scores. However, we suggest further optimization of CNN robustness in dermoscopic melanoma recognition through cross-validation with repetitive-imaging sets prior to clinical implementation for daily routine.

Supporting Document 1

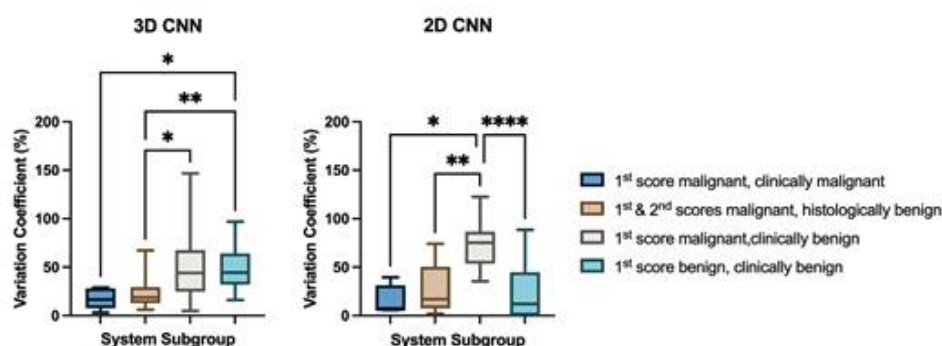


Figure 1. 2D/3D CNN intrasystem analysis of variation coefficients of five sequentially captured dermoscopic images of melanocytic lesions in four subgroup scenarios. Min to max graphically displayed with line at the median. Statistical analysis: Kruskal-wallis test with Dunn's multiple comparisons; *P < 0.05; **P < 0.01; ***P < 0.001, ****P < 0.0001.

Supporting Document 2

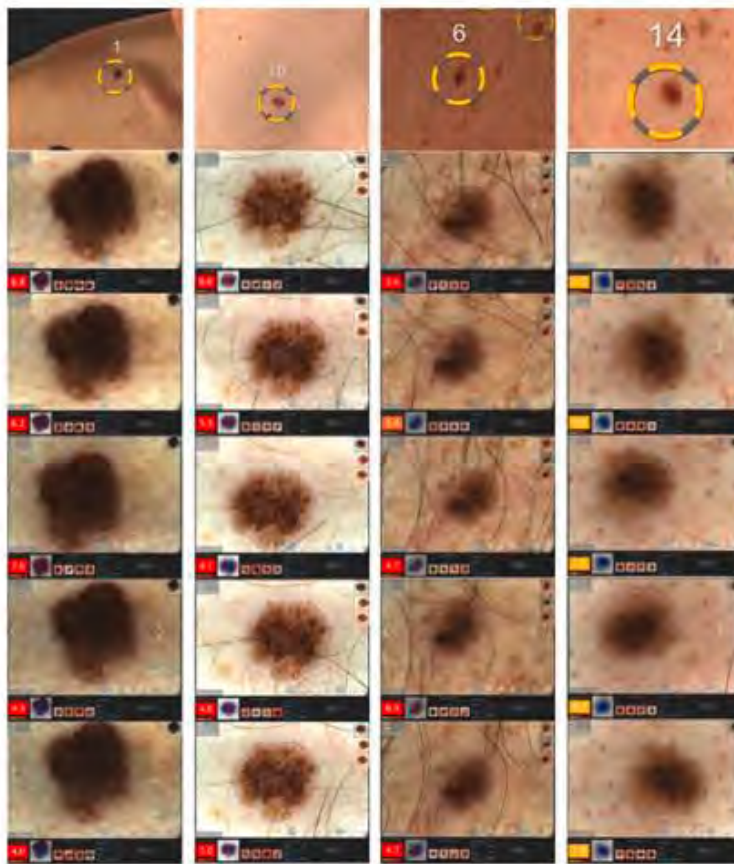


Figure 2. 3D CNN measure repeatability image examples. Macroscopic images are shown at the top with repeated dermoscopic images below. The blue border lines indicate the image area used for CNN risk score calculation. **Lesion 1:** 3 initial malignant risk scores, last 2 scores benign. Clinically malignant (physician's risk score=5). Histology: Melanoma in situ. **Lesion 10:** Total of 3 malignant risk scores, 2 benign. Clinically benign. Histology: Melanocytic naevus. **Lesion 6:** 2 malignant risk scores, 3 benign. Clinically benign. Expert consensus: Benign. **Lesion 14:** All risk scores benign. Clinically benign. Expert consensus: Benign.

Safety, efficacy, and biomarker assessment of RP1 in combination with nivolumab in patients with advanced skin cancers

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Introduction and Objectives: RP1 is an oncolytic immunotherapy that expresses human GM-CSF and the fusogenic protein GALV-GP-R-. The objective of this study is to evaluate the safety and efficacy of RP1 combined with nivolumab (nivo), with relevant biomarker assessments, in a range of tumor types. Data reported here relate to study patients with melanoma and anti-PD-1-naïve non-melanoma skin cancers (NMSC).

Materials and Methods: RP1 is administered via intratumoral injection every 2 weeks, first alone at a concentration of 10^6 PFU/mL and then starting with the second dose at 10^7 PFU/mL in combination with nivo. Up to 8 total doses of RP1 and 2 years of nivo are given, with the option to re-initiate RP1 if clinically warranted.

Results: The ORR (CR+PR) was 62.5% in anti-PD-1-naïve cutaneous melanoma (n=8), 37.5% for anti-PD-1-resistant or anti-PD-1+anti-CTLA-4-failed cutaneous melanoma (n=16), and 100.0% and 20.0% for anti-PD-1-naïve (n=1) and anti-PD-1-resistant (n=5) mucosal melanoma, respectively. For anti-PD-1-naïve NMSC, ORR was 64.7% in cutaneous squamous cell carcinoma (n=17; 47.1% CR); 25.0% in basal cell carcinoma (n=4); 75.0% in Merkel cell carcinoma (n=4); and 66.6% in angiosarcoma (n=6). Though not yet mature, median DOR was 13.27 months (current range 3.67–16.93 months) for melanoma and 7.32 months (current range 1.88–23.11 months) for anti-PD-1-naïve NMSC. Any-grade TEAEs (>25%) in all cohorts combined were chills (29.8%), pyrexia (29.8%), fatigue (28.6%), and pruritus (25.0%). Grade ≥ 3 TEAEs (>5%) were disease progression and fatigue. No deaths related to RP1 were observed, with 1 death related to nivo (myocarditis). Immunohistochemistry demonstrated increases in CD8 T cell density, PD-L1 expression, and CD8/foxp3+ cell ratio.

Conclusions: RP1+nivo induced deep and durable antitumor activity in patients with advanced skin cancers, including anti-PD-1 and anti-PD-1/anti-CTLA-4-failed melanoma. The combination was generally well tolerated, consistent with prior data. Enrollment into a registration-directed cohort of patients with anti-PD-1-failed cutaneous melanoma (n=125) and a cohort with anti-PD-1-failed NMSC (n=30) is ongoing.

Sarcoma mimicking melanoma

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Soft tissue sarcoma and melanoma sometimes present common histologic, molecular, and immunohistochemical features. This study aims to review case reports and case series in the literature in which the initial diagnosis of melanoma is revised to diagnosis of sarcoma. The purpose is to describe the clinical, histologic, immunohistochemical and molecular features to be referred to during the diagnostic process.

Stage IIA cutaneous melanoma: regional ultrasound and CT scan are really useful to detect relapses? A Multicenter Retrospective Observational Study

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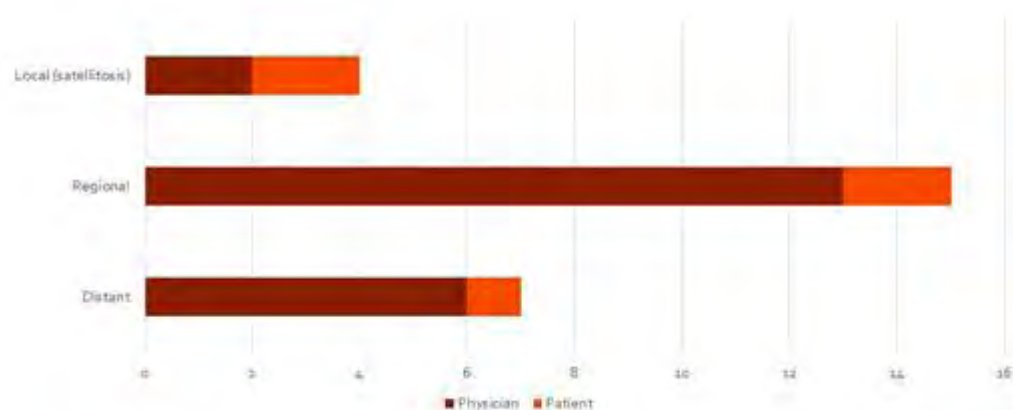
Introduction and Objectives: Stage 2A of cutaneous melanoma is characterized by a Breslow thickness between 1,1 and 2,0 mm with ulceration or between 2,1 and 4,0 mm without ulceration.¹ The scientific evidence relating to the role of radiological investigations in the staging and follow-up of this stage of the disease is still scarce. For this reason, there are procedural differences between the SiDeMaST guidelines and the international ones.² The aim of this study is to investigate the role of imaging procedures in the follow-up of stage IIA melanoma asymptomatic patients.

Materials and Methods: Data were extracted at the two dermatological clinics of Naples and Modena/Reggio Emilia. Age at diagnosis, sex, and follow up (FUP) period have been exported. Among these cohort of patients, patients who relapsed will be further investigated, recording modality of detection (by patients or by doctors), and if detected by doctor in which way (clinical examination, ultrasound, CT scan). In addition, false positive data was collected.

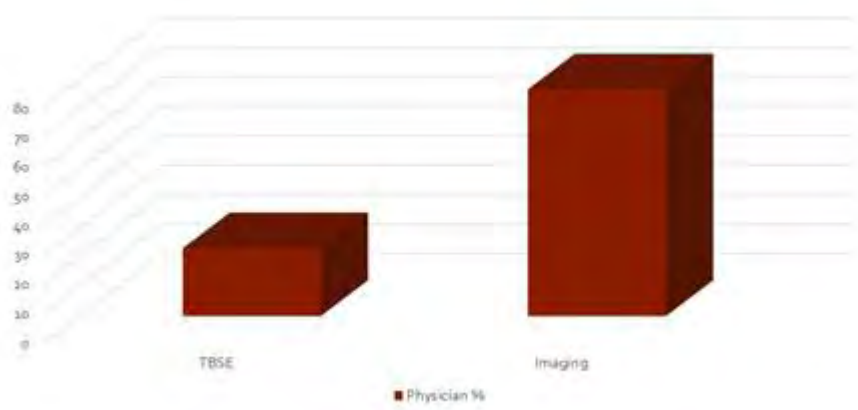
Results: In total, data from 213 patients were collected, of which 187 did not relapse and 26 relapsed for a recurrence rate of 12.2%. The mean follow-up time was 3 years, the mean time to recurrence was 17 months. 80% of recurrences were identified by the doctor and 20% by the patient. Among those identified by the doctor, 76% were identified by radiological examinations. 60% of lymph node recurrences were detected by ultrasound, 85% of distant metastases were detected by CT. The false positive rate was 7% ($p < 0.05$). The main limitation of our study is represented by the fact that it was not possible to demonstrate a survival benefit thanks to radiological investigations. Prospective studies are needed, particularly comparing, in stage IIA patients, those followed with clinical examination and radiographic surveillance and those without.

Conclusions: However, the possibility of offering new effective therapies, such as target therapy and immunotherapy in relapsed patients, should be an important push to reconsider the role of radiological investigations in the follow-up of stage 2A patients.

Supporting Document 1



Supporting Document 2



Sun exposure and associated risks: Insight from an international survey with a focus on the Organ Transplant Recipient population

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Introduction: This survey investigates knowledge and behaviors regarding sun exposure among population who have been treated with immunosuppressive anti-graft rejection drugs because of an organ transplantation.

Methods: The survey (N= 17,001) was conducted online in 17 countries (5 continents) from 28 September-18 October 2021. Automated selection from the Ipsos Panel ensured samples of 1,000 individuals in each country fit the quotas method based on gender, age, employment status, and regions. Data covered demographics, phototype, exposure habits and practices, knowledge and understanding of risks. The current abstract focuses on individuals treated with immunosuppressive anti-graft rejection drugs because of an organ transplantation.

Results: This subpopulation represents 3% of the general population (n=434), it comprised 65% men, average age was 39.7 years (SD:14.6) and 57% were of phototype 1-2. 85% were aware of sun-related skin-health issues, a similar awareness among general population (88%). 79% knew that sun protection is useful when the weather is overcast, a better knowledge compared to the general population (61%). Furthermore, 75% understood the difference between UVA and UVB vs 30% in the general population. But, 69% indicated it was safe to expose themselves without protection when already tanned, a larger misconception compared to the general population (23%).

Only 46% systematically/often use all protections measures during exposure; still a higher practice versus the general population (12%). And, 63% said they protected from the sun all year round, a better habit compared to the general population (23%). However, among the 93% who declared using sunscreen, 85% applied sunscreen only once or twice a day, a worse practice versus the general population (74%). And when already tanned 37% decreased frequency of application and/or used lower protection (44% among general population). 89% regretted not having previously used better protection, a stronger regret versus the general population (57%).

Conclusions: Although individuals who have been treated with immunosuppressive anti-graft rejection drugs because of an organ transplantation had better knowledge and behavioral attitudes compared to the general population, they do not sufficiently perceive the importance of photoprotection in a prevention objective. This leads to discuss the implementation of new information tools with more impact.

Sun exposure and associated risks: Insight from an international survey with a focus on the population with past medical history of skin cancers

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Introduction: This survey investigates knowledge and behaviors regarding sun exposure among population who have been treated for skin cancer (melanoma/non melanoma) or pre-cancerous lesions in 17 countries.

Methods: The survey (N= 17,001) was conducted online in 17 countries (5 continents) from 28 September-18 October 2021. Automated selection from the Ipsos Panel ensured samples of 1,000 individuals in each country fit the quotas method based on gender, age, employment status, and country regions. Data covered demographics, phototype, exposure habits and practices, knowledge and understanding of risks. The current focus was defined as individuals with a history of melanoma/non melanoma skin cancer, pre-cancerous lesions.

Results: This sub population represents 8% of the general population (n=1372), it comprised 54% men, average age was 49.9 years (SD:17.6) and 58% were of phototype 1-2. 90% were aware of sun-related skin-health issues (vs 88% in the general population). 79% did know that sun protection is useful when the weather is overcast, a better knowledge versus the general population (61%). However, 34% indicated it was safe to expose themselves without protection when already tanned, a larger misconception versus the general population (23%). 54% did not understand the difference between UVA and UVB vs 70% in the general population.

Only 28% systematically/often use all protections measures during exposure; still a higher practice compared to the general population (12%). However, 42% said they protected from the sun all year round, a better habit compared to the general population (23%). During sun exposure, among the 91% who declared using sunscreen, 74% applied sunscreen only once or twice a day, a similar practice among general population (74%). And when already tanned 38% decreased frequency of application and/or used lower protection (44% among general population). 82% regretted not having previously used better protection, a stronger regret compared to the general population (57%).

Conclusions: Although individuals who have been treated for skin cancer or pre-cancerous lesions had better knowledge and behavioral attitudes compared to the general population, they do not sufficiently perceive the importance of photoprotection in a prevention objective. This leads to discuss the implementation of new information tools with more impact.

The 31-gene expression profile outperforms AJCC and CP-GEP in stratifying risk of recurrence in patients with stage I cutaneous melanoma

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Background: American Joint Committee on Cancer (AJCC) staging stratifies patients with cutaneous melanoma (CM) according to risk of dying based on pathological tumor characteristics and the presence of locoregional/distant metastasis at diagnosis. Stage I CM is considered low risk for recurrence and melanoma-specific death; however, due to the large number of patients diagnosed as stage I, they account for the largest number of melanoma deaths. Thus, additional methods that better identify which patients are truly low risk versus who may benefit from increased clinical surveillance are needed. The 31-gene expression profile (31-GEP) test is validated to stratify patients into low (Class 1A), intermediate (Class 1B/2A), or high (Class 2B) risk of recurrence, metastasis, and death.

Methods: We analyzed survival data for patients with stage I CM who were 31-GEP tested and enrolled in previous prospective and retrospective studies (combined cohort, n=1261), and stage I patient data provided by Surveillance, Epidemiology, and End Results (SEER) registries (diagnosis=2013-2018) that were linked to data for patients clinically tested with the 31-GEP (SEER cohort, n=5651 after exclusions). AJCC and CP-GEP, another GEP-based prognostic test, data were from previously published reports.

Results: Patients with low-risk 31-GEP results had significantly higher 5-year recurrence-free survival (RFS) rates than those with intermediate- or high-risk 31-GEP results (97.3% vs. 88.6% vs. 77.3%, $p<0.001$)—better stratification than seen in AJCC stage IA versus stage IB patients (93.3% for IA vs. 87.6% for IB, p -value not reported) or another GEP-based test, CP-GEP (low-risk: 92.9% vs. high-risk: 86.0%, $p=0.184$). The 31-GEP stratified 5-year melanoma-specific survival (MSS) in both the combined cohort and the SEER cohort (Class 1A=99.7% and 98.0% vs. Class 1B/2A=97.6% and 97.5% vs. Class 2B=88.8% and 92.3%, $p<0.001$) better than AJCC (IA=98.5% vs. IB=96.1%, p -value not reported). CP-GEP did not report MSS.

Conclusions: In stage I CM patients, the 31-GEP provided more prognostic stratification of 5-year RFS and MSS than AJCC staging alone, while the CP-GEP test did not provide more stratification. Incorporating the 31-GEP into clinical practice can help guide risk-aligned care in a low-risk population by identifying high-risk patients who may be missed using AJCC staging alone.

The Value of Adjuvant Radiotherapy in the Treatment of Melanoma: a retrospective multi-center analysis

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Introduction and Objectives: Post-surgical adjuvant radiotherapy (RT) may improve regional tumor control in melanoma. However, its effect on overall survival is limited. The approval of “modern” systemic therapies has fundamentally changed the adjuvant treatment landscape, also impacting on the role of adjuvant RT. We aimed to characterize the population of melanoma patients still undergoing adjuvant RT in times when PD1-antibodies and BRAF/MEK-inhibitors are considered standard-of-care in adjuvant therapy.

Methods: Melanoma databases in five centers in Austria and Switzerland were queried for patients who received adjuvant RT between 2017 and 2021. Patient and tumor characteristics, details of RT regimens and recurrence-free survival were analyzed.

Results: A total of 71 patients who received adjuvant RT were identified (31 % female, 69% male) with a mean age of 64 years (27–83). Median follow-up was 27 months (2–58).

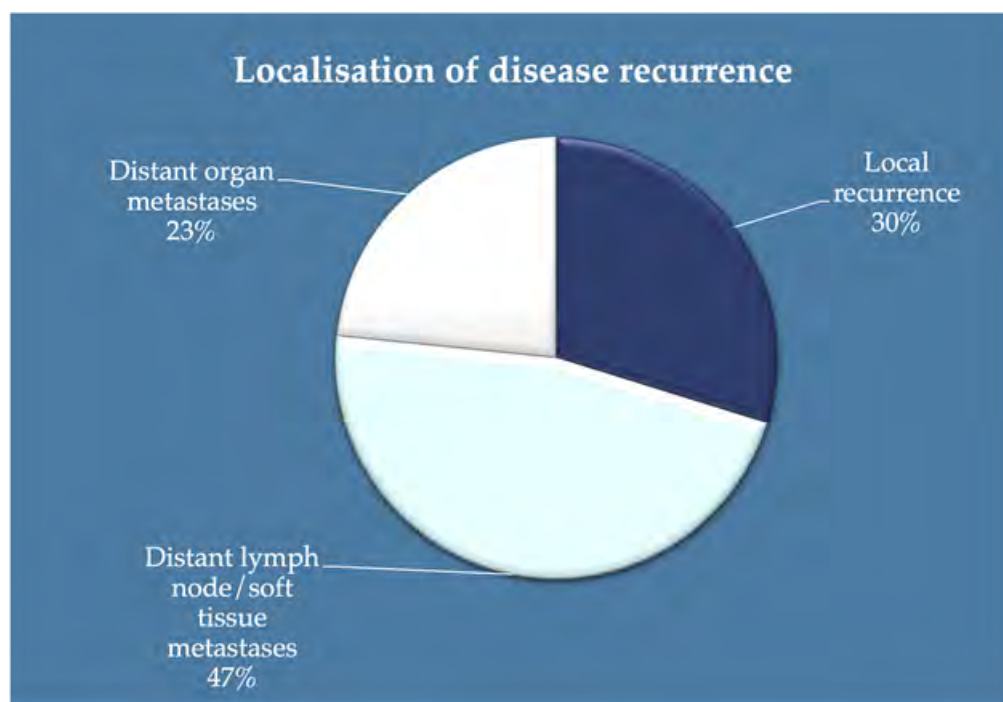
In 49% of patients, a trans-capsular lymph node metastasis had been present, in 27% three or more lymph nodes were affected and 14% of patients were irradiated due to lymphogenic recurrence.

99% also received adjuvant systemic therapy (63% nivolumab, 11% pembrolizumab, 23% BRAF/MEK-inhibitors and 1% ipilimumab). Adjuvant RT was performed prior to systemic therapy in 48% patients. With a median interval of 14.5 days, most of these patients received systemic adjuvant therapy shortly after adjuvant RT. 31% and 18% of patients received RT concurrent with or after completion of systemic therapy, respectively.

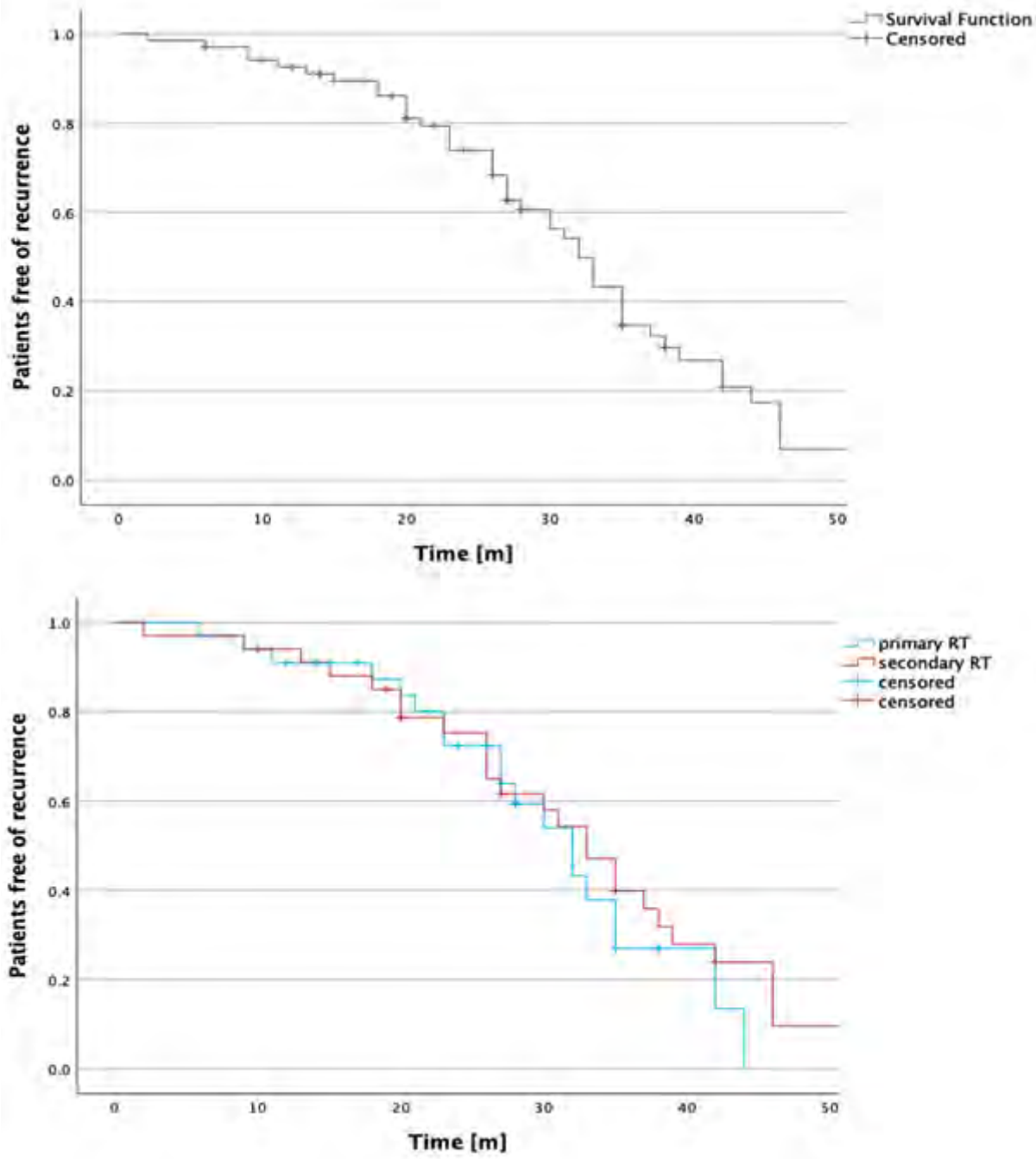
66% of patients developed disease recurrence after adjuvant treatment, most often affecting distant lymph nodes or soft tissue (figure 1). Recurrence-free survival was 91%, 71%, and 33%, at 1, 2, and 3 years after initiation of adjuvant RT, respectively (figure 2).

Conclusion: Although still recommended in certain guidelines, adjuvant RT is infrequently conducted in the era of immuno- and targeted therapy. In most cases, radiotherapy is utilized as an upfront strategy adjunct to subsequent systemic treatment. Considering the marked effect of systemic adjuvant therapies on recurrence-free survival and no trend towards improved landmark RFS rates in the present data compared to the literature, it remains unclear whether combining RT and systemic therapy can improve RFS outcomes through enhanced local disease control and potential abscopal effects.

Supporting Document 1



Supporting Document 2



Use of circulating extracellular vesicles and ctDNA from lymphatic fluid exudate as surrogate markers of minimal residual disease in melanoma patients

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Introduction and Objectives: Five-year relapse free survival in stage III melanoma after surgery and adjuvant immunotherapy is 55%. There are no definitive tools for accurately predict the individual patient risk. Liquid biopsies in cancer patients have the potential to implement more precise prognosis tools. Although plasma has been the main source for liquid biopsy analysis, other fluids are of special interest in early stages of disease. Lymphatic fluid exudate obtained after lymphadenectomy in melanoma patients is not commonly analyzed, but as it is in close contact with the metastatic nodes, we hypothesized that its analysis could be highly sensitive. In addition to circulating free DNA (cfDNA), the use of circulating extracellular vesicles (EVs) is emerging as an additional source for liquid biopsy.

Materials and Methods: Molecular analysis through targeted Next Generation Sequencing (NGS) is performed in cfDNA and EVs obtained from plasma and seroma of patients with stage III melanoma undergoing lymphadenectomy. cfDNA and EVs are purified using a differential ultracentrifugation protocol or filtration kits (Qiagen), and after DNA extraction NGS is performed.

Results: Nine patients have been enrolled at March 2023. All patients have undergone lymphadenectomy. Melanoma stage was IIIC in 7 (77%) cases and IIIB in 2 (22%) cases. NGS analysis of tumor tissue revealed BRAF mutation in 5 cases (BRAV600E in 3, BRAV600R and BRAV600 K in 1 case, respectively), NRAS mutation in one case and FAT1 mutation in one additional patient. After a median follow up of 10 months, one (11%) patient had regional recurrence, while this case was the only one positive for molecular disease detection (BRAV600R mutation) in seroma. Eight patients negative for molecular detection in seroma continue disease free at the data cut off analysis. No molecular alterations in plasma samples have been detected.

Conclusions: Our data support that presence of tumor mutations in seroma-derived EVs or cfDNA obtained post-lymphadenectomy could be predictive of a higher risk of relapse. Study recruitment will continue until 20 patients have been included and have been followed until melanoma relapse or for a minimum of 24 months.

Vitamin D receptor expression in cutaneous melanoma tissue: prognostic properties and influencing factors

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Background: A reduction of the VDr expression is proposed as a negative prognostic marker since reduced expression is observed in cutaneous melanoma (CM) in comparison to normal skin and melanocytic nevi (1).

Aims: To investigate a correlation of 25-hydroxy vitamin D, demographic/clinical parameters of CM patients and genetic variants of VDr with VDr expression in primary CM tissue. To investigate the correlation of CM VDr expression with pathology parameters of the primary tumor.

Methods: Plural clinical parameters and baseline 25OHD levels were assessed in a prospectively recruited cohort of 407 CM patients. VDr expression in CM tissue was determined in both the nucleus and in the cytoplasm semi-quantitatively using histochemistry. 13 single nucleotide polymorphisms of the VDr were genotyped by using TaqMan allelic discrimination assay. In a univariate analysis, VDr expression was correlated with clinical/demographic parameters, 25OHD levels, VDr SNPs as well as pathology parameters of primary CM tissue. In a multivariate analysis, VDr expression was correlated with clinical parameters.

Results: Cytoplasmic VDr expression in CM tissue was increased in patients with actinic keratosis (pcytoplasmic%: 0.03, pH-score: 0.02) and in patients who stated to have a high sun exposure during their life (pcytoplasmic%: 0.005 and pH-score: 0.002), in contrast to reduced VDr cytoplasmic expression in female patients (pH-score: 0.04), patients taking VD supplements (pH-score: 0.02), and patients presenting with idiopathic guttate hypomelanosis (pcytoplasmic%: 0.01 and pH-score: 0.03). Decreased nuclear VDr expression, was significantly linked to patients with blond/light brown hair and a fair skin color (pnuclear: 0.03). In multivariable analysis only high total sun exposure remained significant (pH-score: 0.01).

When exploring SNP genotypes, we detected an association of rs2228570 or Fok1 (p-value_{cytoplasmic}: 0.001 and p-value_{H-score}: 0.02) with cytoplasmic VDr expression. Pathological parameters of CM tissue were associated with VDr expression in both the nucleus and the cytoplasm, with higher mitotic rate (p-value: 0.002) and perineural invasion (p-value: 0.04) being significantly associated with low nuclear VDr expression.

Conclusions: Clinical/demographic parameters and genetic variants of the VDr have an influence on the VDr expression in CM tissue. This study also indicates a prognostic property of VDr expression in CM outcome.

One war and two battles of melanoma patients in Ukraine in 2022

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Treatment of melanoma patients in Ukraine is far from excellent and associated with several limitations: insufficient equipment for sentinel lymph node biopsy, lack of reimbursement for targeted and immunotherapy, a small number of clinical trials.

Due to Russian invasion of the Ukrainian territory medical care for melanoma patients during 2022 had the following features:

1. Since February 24, 2022, access to medical care for cancer patients has become less available due to difficulties with getting to clinics, interruptions in mobile communications and the Internet, and the lack of necessary medicines.
2. In the first days of the war, many doctors shared their personal phone numbers through social networks so that patients could consult online regarding the treatment of postoperative wounds, complications of systemic therapy, and receive psychological support.
3. Guidelines for oncological patients were revised depending on the proximity to the combat zone.
4. In the first months of the war, oncological centers in Western Ukraine were overloaded with patients, including those with melanoma. Although all cancer centers tried to resume oncological care for patients as quickly as possible.
5. An active search for clinics in Western Ukraine and Europe was carried out to find the best treatment possible for people residing close to the combat zone.
6. With the help of patient organizations and using social networks, the needs for targeted and immunotherapy were collected for patients who remained in Ukraine, and 3 pharmaceutical companies MSD, Novartis and Roche provided most of these patients with modern treatment.
7. Since May 2022, the team of the Ukrainian Ministry of Health has created a program for the medical evacuation of cancer patients to European countries that have accepted and continue to accept our patients for treatment.

A significant number of patients with melanoma fled, and unfortunately continue to flee the war to European countries, and all of them received modern treatment, including targeted therapy and immunotherapy. During 2022, Ukrainian patients and doctors received incredible support from all over the world, which allowed us to fight 2 battles and express gratitude to everyone who had helped us.

A national database study of sentinel lymph node biopsy performance for skin cancer in Japan: comparison with breast cancer and evaluation of factors influencing the performance

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Introduction and Objectives: Sentinel lymph node biopsy (SLNB) is an established procedure that can detect occult nodal metastases. In Japan, health insurance covers SLNB for breast cancer and various skin cancers, including melanoma, squamous cell carcinoma (SCC), and Merkel cell carcinoma (MCC). However, the actual SLNB performance remains unknown. This study aimed to evaluate the performance rate of SLNB in each type of cancer and identify the factors associated with the performance.

Materials and Methods: This study was a retrospective review of the SLNB performance rate in patients with breast cancer or skin cancers, utilizing a database that linked the Hospital-Based Cancer Registries and the Diagnosis Procedure Combination survey. Patients with metastatic tumors and tumors in situ were excluded from the analysis. Demographic information, tumor characteristics, and treatment characteristics were analyzed by univariate and multivariable logistic regression analyses. Statistical analyses were performed in Stata version 17 (Statacorp LLC).

Results: A total of 613 hospitals participated, and 71,652 patients between 2018 and 2019 were included. SLNB was performed in 86.4% (57,904/67,036) of patients with breast cancer, 44.7% (694/1,552) with melanoma, 3.1% (89/2,849) with SCC, and 13.5% (29/215) with MCC, respectively. Multivariate analysis showed that SLNB was performed significantly less frequently in patients with skin cancer than in patients with breast cancer (Table 1. odds ratio (OR)= 0.03, 95% CI: 0.03-0.04). In addition, SLNB was performed significantly less frequently in patients with SCC or MCC than in patients with melanoma (Table 2. SCC; OR = 0.04, 95% CI: 0.03-0.05. MCC; OR = 0.19, 95% CI: 0.13-0.29.). Factors associated with low SLNB performance included age >75 years, female sex, head and neck primary tumor site, and hospital with <500 beds.

Conclusions: We investigated the SLNB performance of breast and skin cancer and highlighted the lower SLNB performance rate for skin cancer compared with breast cancer for the first time. SLNB is underutilized even in patients recommended for it by the guidelines, likely due to patient or tumor conditions. Moreover, our study confirmed the necessity of consultation with high-volume cancer centers as smaller hospitals had lower SLNB rates.

Supporting Document 1

Table 1

Factors associated with compliance with performance of sentinel lymph node biopsy in eligible patients: comparison between breast cancer and skin cancer

		Frequency of Performing SLNB in Eligible Patients				
		No/Total No(%)	Univariate Analysis OR (95% CI)	P	Multivariate Analysis OR (95% CI)	P
Cancer type	Breast Cancer	57904 / 67036 (86.4)	1 [Reference]		1 [Reference]	
	Skin Cancer	812 / 4616 (17.6)	0.03 (0.03-0.04)	<0.001	0.05 (0.04-0.05)	<0.001
Age at diagnosis (y)	>75	9903 / 16286 (60.8)	1 [Reference]		1 [Reference]	
	65-75	16531 / 19209 (86.1)	3.98 (3.78-4.19)	<0.001	3.08 (2.91-3.27)	<0.001
	<65	32282 / 36157 (89.3)	5.37 (5.13-5.62)	<0.001	3.56 (3.39-3.75)	<0.001
Sex	Male	754 / 2808 (26.9)	1 [Reference]		1 [Reference]	
	Female	57962 / 68844 (84.2)	14.51 (13.32-15.81)	<0.001	1.13 (0.99-1.29)	0.076
Incidence years	2018	26342 / 34583 (82.0)	1 [Reference]		1 [Reference]	
	2019	30374 / 37089 (81.9)	1.00 (0.96-1.04)	0.96	0.99 (0.95-1.04)	0.737
Hospital beds	<500	23276 / 28846 (81.3)	1 [Reference]		1 [Reference]	
	500-750	22588 / 27718 (81.5)	1.02 (0.97-1.06)	0.468	1.16 (1.10-1.21)	<0.001
	>750	12852 / 15288 (84.1)	1.22 (1.15-1.28)	<0.001	1.66 (1.56-1.77)	<0.001

Abbreviations: SLNB, sentinel lymph node biopsy. OR, odds ratio. CI, confidence interval.
 SCC, squamous cell carcinoma. MCC, Merkel cell carcinoma.
 The bold values indicate statistical significance ($p < 0.05$).

Supporting Document 2

Table 2

Factors associated with compliance with performance of sentinel lymph node biopsy in eligible patients with skin cancer

		Frequency of Performing SLNB in Eligible Patients				
		No/Total No(%)	Univariate Analysis OR (95% CI)	P	Multivariate Analysis OR (95% CI)	P
Cancer type	Melanoma	694 / 1552 (44.7)	1 [Reference]		1 [Reference]	
	SCC	89 / 2849 (3.1)	0.04 (0.03-0.05)	<0.001	0.06 (0.05-0.08)	<0.001
	MCC	29 / 215 (13.5)	0.19 (0.13-0.29)	<0.001	0.42 (0.27-0.68)	<0.001
Age at diagnosis (y)	>75	283 / 3006 (9.4)	1 [Reference]		1 [Reference]	
	65-75	281 / 908 (31.0)	4.31 (3.58-5.20)	<0.001	2.47 (1.97-3.08)	<0.001
	<65	248 / 702 (35.3)	5.26 (4.31-6.40)	<0.001	2.19 (1.73-2.78)	<0.001
Sex	Male	432 / 2381 (18.1)	1 [Reference]		1 [Reference]	
	Female	380 / 2235 (17.0)	0.92 (0.79-1.08)	0.309	0.69 (0.57-0.84)	<0.001
Incidence years	2018	1197 / 2381 (50.3)	1 [Reference]		1 [Reference]	
	2019	1118 / 2235 (50.2)	1.07 (0.92-1.24)	0.044	0.99 (0.82-1.19)	0.902
Tumor site	Trunk	130 / 651 (20.0)	1 [Reference]		1 [Reference]	
	Head and neck	134 / 2162 (6.2)	0.26 (0.20-0.34)	<0.001	0.51 (0.38-0.70)	<0.001
	Upper extremity	136 / 607 (22.4)	1.16 (0.88-1.52)	0.291	0.97 (0.70-1.34)	0.841
	Lower extremity	412 / 1192 (34.6)	2.12 (1.69-2.65)	<0.001	1.67 (1.27-2.20)	<0.001
Hospital beds	<500	102 / 1211 (8.4)	1 [Reference]		1 [Reference]	
	500-750	291 / 1930 (15.1)	1.93 (1.52-2.45)	<0.001	1.67 (1.27-2.20)	<0.001
	>750	419 / 1475 (28.4)	4.31 (3.42-5.44)	<0.001	3.11 (2.37-4.08)	<0.001

Abbreviations: SLNB, sentinel lymph node biopsy. OR, odds ratio. CI, confidence interval.
 SCC, squamous cell carcinoma. MCC, Merkel cell carcinoma.
 The bold values indicate statistical significance ($p < 0.05$).

A new nose at 96 – successful surgical treatment of lentigo maligna in a nonagenarian is possible within a primary care setting

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Introduction and Objectives: Lentigo maligna melanoma, otherwise known as Hutchinson melanotic freckle, is a subtype of melanoma that is commonly found on the chronically sun damaged skin of elderly individuals, particularly on the head and neck.

The mean age of peak incidence of this type of melanoma occurs in the seventh and eighth decades of life, significantly later than other melanoma subtypes, and tends to affect a greater proportion of females compared to males.

Whilst, the gold standard of treatment remains surgical excision with a 5-10mm margin, with increasing age comes the decreasing likelihood of being classed as a safe surgical candidate. The risks of general anaesthesia and the extent of the patient's comorbidities have often outweighed the potential benefits of cure beyond the eighth decade of life, with many clinicians now seeking alternative off-label options such as the use of topical imiquimod.

However, given that the incidence and mortality of untreated melanoma are rising in recent years, and to date no randomised control trials comparing surgical vs non-surgical management for lentigo maligna exist, it is important to publish on outcomes in patients undergoing surgery as the current recommendation in treatment, particularly in the extremes of age.

The author presents a case of a 96-year-old female who successfully underwent curative surgical treatment of her nasal lentigo maligna under local anaesthetic in the primary care setting. At one year follow up, her nose is looking great and she remains cancer-free and in good health.

Supporting Document 1



Supporting Document 2



Efficacy of topical diphencyprone immunotherapy for in-transit and other cutaneous metastases of melanoma: A systematic review and meta-analysis

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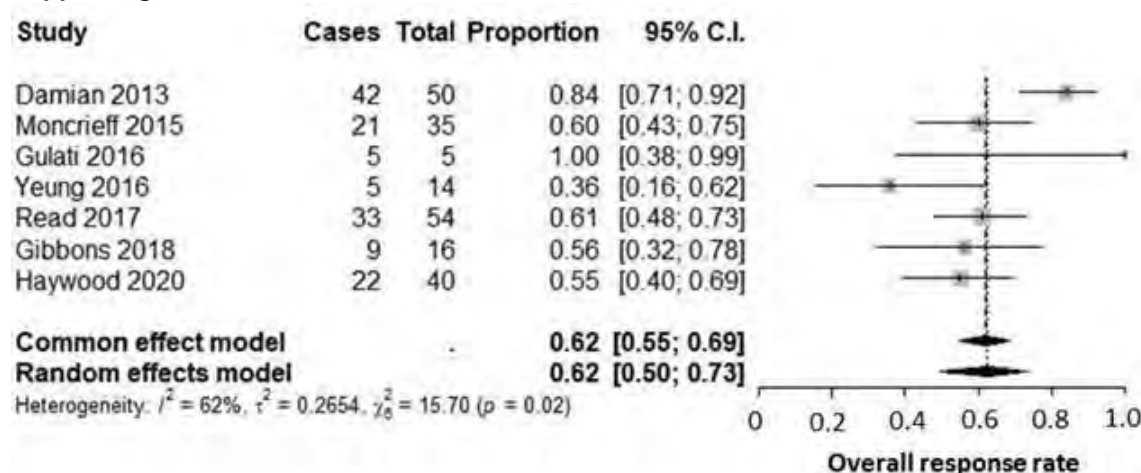
Introduction and Objectives: Approximately 5-10% of patients with high-risk melanoma develop in-transit cutaneous metastases (ITMs) between the primary tumour and draining nodal basins due to intralymphatic seeding. Topical diphencyprone (DCP), a contact allergen used to treat alopecia areata, has demonstrated efficacy in treating ITMs – however evidence is limited to small cohort studies and single arm trials. We sought to conduct a meta-analysis of efficacy outcomes for DCP in treating ITMs and other cutaneous melanoma metastases to highlight its therapeutic potential.

Methods: Two reviewers screened PubMed, EMBASE, Medline, the Cochrane Central Register of Controlled Trials and Web of Science databases using a combination of 'diphencyprone' and 'melanoma' MeSH terms. Information regarding study design, patient cohort, and efficacy outcomes including complete response (CR) and overall response rate (ORR) were extracted. Quality of data was assessed using the NIH Study Quality Assessment Tool. A meta-analysis of proportions was conducted with the Meta package in R (version 4.2), using a random-effects model and the inverse variants method.

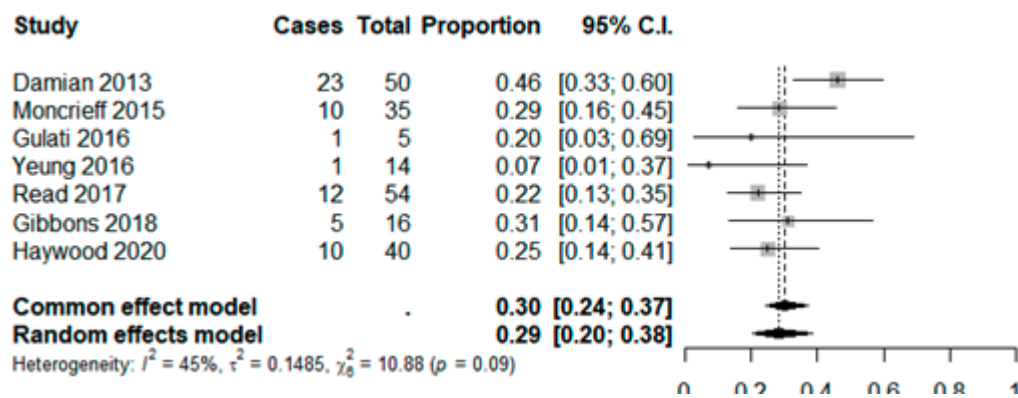
Results: After removal of duplicates, 128 articles were screened. A final 7 studies were retained after screening of abstracts and full-texts, as per exclusion criteria. These report outcomes of DCP in 214 patients with ITMs. 3 studies were rated 'good', 3 as 'fair' and 1 as 'poor' in quality. Pooled ORR was 62% (95%CI 50-73%, Figure 1) while pooled CR rate was 29% (95%CI 20-38%, Figure 2). Heterogeneity as measured by the I² statistic was high for ORR (62%) and moderate for CR (45%). There was insufficient subgroup data to conduct meta-regression analysis or to pool duration of responses/progression-free survival of DCP therapy.

Conclusions: While evidence for topical DCP in treating ITMs is limited, the high pooled ORR suggest it may have value in treating patients who may not be eligible for or cannot tolerate surgery or systemic immunotherapy, particularly given its low cost and ease of self-administration. Further studies are required to determine which patients are more likely to benefit from DCP immunotherapy, its efficacy in comparison to other locoregional treatments (e.g. T-VEC), and associated survival outcomes such as progression-free and overall survival.

Supporting Document 1



Supporting Document 2



How to determine accurate surgical margins for the malignant melanoma?: discrepancy between clinical surgical margin and pathological permanent margin

Dr Se Yeon Lee², MD PhD Egle Ramelyte¹, Dr Sung Kwon², How to determine accurate surgical margins for the malignant melanoma? : discrepancy between clinical surgical margin and pathological permanent margin Sang Hwa Kim², Hak Chang², How to determine accurate surgical margins for the malignant melanoma?: discrepancy between clinical surgical margin and pathological permanent margin Byung Jun Kim²

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Introduction and Objectives: Recommended surgical margin for the malignant melanoma is based on the depth of the primary lesion. However, its clinical discrepancy with pathologic margins has not been addressed previous studies. This study aimed to evaluate the discrepancy and discussed the method for optimal margin controls.

Materials and Methods: This single-center, retrospective study included 157 cases which got the surgical treatments for the malignant melanoma, with sufficient medical records for surgical and pathologic margins. The delta margins, which were defined as average surgical margins minus average pathologic margins, between the melanoma in situ (MIS) and the invasive melanoma (IM) groups were analyzed. Additionally, delta margin ratio was defined as delta margins over surgical margins. Not only between MIS and IM, but difference according to the growth phase were also analyzed.

Results: Except 18 cases which were marginal lesions such as atypical melanocytic proliferation and etc., 104 cases were IM and 35 cases were MIS. The absolute value of delta margin ratio was larger in MIS (16.99 ± 35.24 %) rather than IM (4.61 ± 37.75 %) but was not statistically significant ($p=0.283$). Also, delta margin ratio depending on growth phase (10.87 ± 46.50 % for radial type and 8.56 ± 33.33 % for vertical type) were not statistically significant, either ($p=0.869$).

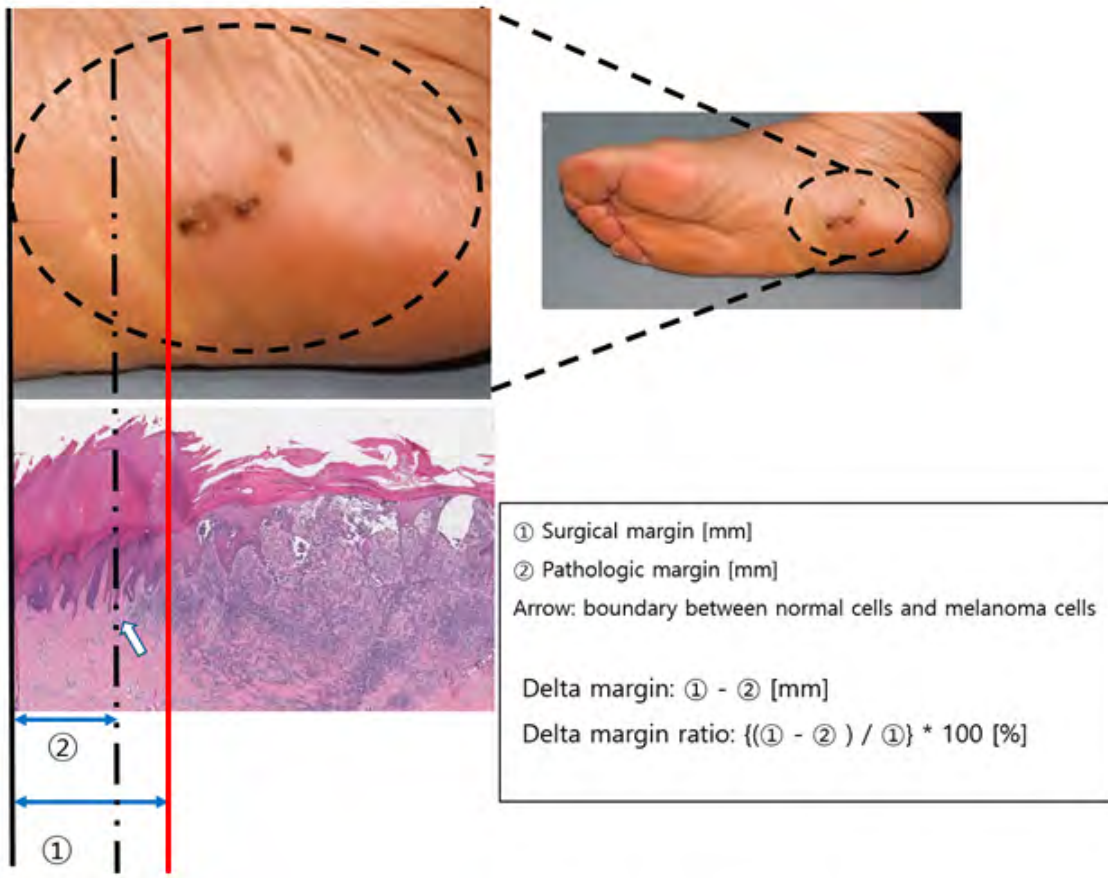
Conclusions: MIS exhibited tendency toward a larger discrepancy between surgical and pathologic margins compared with that of IM. Therefore, in order to obtain a safe resection margin, surgeons should consider meticulous surgical technique such as staged excision or Mohs surgery, especially for MIS.

Supporting Document 1

		Total (n=139)	Results of pre-operational biopsy		p-value ¹⁾
			MIS (n=35)	IM (n=104)	
n (%)		139	35 (25.18)	104 (74.82)	
Age					0.700*
Mean \pm SD		65.16 \pm 11.42	65.57 \pm 9.17	65.02 \pm 12.12	
Median(Min,Max)		65.00(32.00,92.00)	66.00(42.00,83.00)	65.00(32.00,92.00)	
Sex, n (%)	Male	64(46.04)	11(31.43)	53(50.96)	0.045†
	Female	75(53.96)	24(68.57)	51(49.04)	
Delta margin(%), Mean \pm SD		7.72 \pm 37.40	16.99 \pm 35.24	4.61 \pm 37.75	0.283**

* Independent t-test, † Chi-square test, ** Wilcoxon rank sum test

Supporting Document 2



Is wider excision indicated for all completely excised primary melanomas?

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Aims: The purpose of wide local excision (WLE) in melanoma is primarily to reduce local recurrence by removing subclinical disease which may affect clinical outcome. However, the frequency of residual disease in these specimens is generally small.

We undertook a retrospective analysis of the histology results of WLE specimens after complete primary excision biopsy over a 5-year period.

Method: The clinicopathological data of 1647 patients were reviewed using our melanoma database. Incomplete or close primary excision (<1mm margin), acral melanoma and inadequate data were excluded. Presence or absence of residual disease (RD) was correlated with various factors including Breslow thickness (BT), ulceration, lymphovascular spread (LVS), satellites and pT stage.

Results: 724 WLE specimens from 724 patients were available for analysis. RD (9 in situ; 4 invasive; 4 satellites) was present in 17 specimens (2%). 16 of these were from melanomas thicker than 1 mm (4.8%). Indeed, 99.7% of melanomas up to 1 mm were clear. RD seems to be associated positively with BT, ulceration, pT stage and specimen width (p 0.001), mitosis (p 0.004), and LVS (p 0.02).

Conclusion: Our data appear to show that most thin melanomas when first adequately excised do not reveal any residual disease on further excision and would support the practice of 1 cm margin primary excision to achieve both peripheral and deep clear margins. This would avoid the need for further surgery in a group which forms the majority of melanoma patients with both patient and cost benefits.

Perioperative examination of inflammatory markers in relation to sentinel lymph node biopsy in patients with melanoma; a pilot study

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Abstract: Introduction and Objectives: Sentinel lymph node biopsy (SLNB) is essential in staging melanoma and for properly selecting patients for adjuvant immunotherapy (1). However, subsequent inflammation due to surgical injury and wound healing is theorized to potentially aid malignant progression, by improving conditions for remaining tumor cells, and may therefore effect prognosis (2-6). We want to test if an association between SLNB and a systemic inflammatory response can be made. A systemic inflammatory response will be measured by neutrophil-to-lymphocyte ratio (NLR), an indicator for systemic inflammation and established prognostic factor in several malignancies (7-9). Supplementary markers for inflammation will also be assessed.

Materials and Methods: We conducted a prospective uncontrolled longitudinal pilot study. In total, 20 patients diagnosed with melanoma and undergoing SLNB were included. Perioperative blood samples were collected prior to SLNB, 2 hours and 6 hours postoperatively. Blood samples were assessed for inflammatory cells (Neutrophil granulocytes, lymphocytes, eosinophil granulocytes, basophil granulocytes and Metamyelo.+Myelo+Promyelocytes) with particular interest in NLR, supplementary pro-inflammatory cytokines (IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF- α and IFN- γ) and additional acute phase reactants (CRP and LDH).

Results: NLR increases significantly from 1.94 (95% CI:1.5:2.3) preoperatively to 9.5 (95% CI:7.5:11.6) 2 hours postoperatively (mean diff. 7.6 95% CI:-9.68:- 5.54) ($p<0.0001$). NLR increases further 6 hours postoperatively to 16.04 (95% CI:9.89:22.19) (mean diff. 6.47 95% CI:-11.49:-1.46) ($p=0.0151$). Remaining granulocytes decreases postoperatively. No perioperative changes in acute phase reactants are found. Among supplementary pro-inflammatory cytokines, mean IL-6 increases from baseline to 2 hours postoperatively ($p<0.0001$), along with mean IL-10 ($p<0.0001$). While TNF- α ($p=0.0064$) ($p=0.0026$) and IFN- γ ($p=0.0003$) ($p=0.0125$) decreases both at 2 and 6 hours postoperatively respectively. Remaining pro-inflammatory cytokines show nonsignificant changes.

Conclusion: SLNB induces a moderate postoperative systemic inflammatory response measured by NLR. This finding emphasizes the need for further investigation on perioperative inflammatory response, as inflammation may impact micrometastasis. In prospect, research on perioperative inflammation and prognosis may represent a target for optimizing treatment.

Quality of Life after Melanoma Surgery in Cornwall, UK: Plain Sailing?

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Introduction and Objectives: In the UK melanoma is the fifth most common cancer¹. Royal Cornwall NHS Trust has a catchment of 500,000, with over 800 melanoma cases annually. Patients are treated with wide local excision (WLE) and sentinel node biopsy (SLNB) if stage 1b or above. Previous data² suggests patients are experiencing neuropathic pain post-operatively, impacting quality of life (QOL). This study aims to obtain quantitative data in Cornwall, to guide patient counselling.

Materials and Methods: Patients with truncal or limbs melanoma, who underwent surgery 2014-2021, were sent Functional Assessment of Cancer Therapy-Melanoma(FACT-M) questionnaires^{3,4}.

The scoring system⁵ provided 4 scores:

- (1) Melanoma Surgery Scale (MSS)
 - (2) Trial outcome index (TOI), for physical wellbeing, functional wellbeing and the melanoma subscale
 - (3) Functional Assessment of Cancer Therapy-General (FACT-G) for physical, social, emotional and functional wellbeing
 - (4) FACT-M scores included all FACT-G factors in addition to the melanoma subscale
- Patients with completion lymphadenectomy or metastatic disease were excluded.
Student t-test was used for statistical analysis.

Results: 117 patients returned the questionnaires, had a median age of 65yrs (21-86 yrs), and a male to female ratio of 0.83 (53/64).

MSS and FACT-M scores were high compared to maximum value. (Table 1).

Early Group (EG) (n=54) had surgery between 2014-2019. Later Group (LG) (n=63) had surgery between 2019 and 2021. EG and LG had similar high MSS scores (94% and 91% of max value, Table 1). LG had higher mean FACT-M total scores, (Table 1), higher TOI and FACT-G score for physical, social, emotional, and functional factors.

SLNB and WLE by location, had high MSS scores (Table 2). Lower FACT-G scores were accounted by physical, social, emotional, and functional factors.

The difference in QAL was not statistically significant.

Conclusion: QOL after melanoma surgery in Cornwall remained high ever since we started SLNB in 2014, with high FACT-M scores compared to maximum value. Neuropathic pain did not impact QOL.

In the latter years, we observed increased physical, social, emotional, and functional wellbeing scores.

Larger studies would be needed to delve into the observed trend for lower QOL for multiple sites or axilla SLNB, and for truncal WLE versus limb WLE.

Table 1
QOL Study Population

	Melanoma Surgery Scale (MSS) Score Mean	Trial Outcome Index (TOI) Mean	FACT-G Total Score Mean	FACT-M Total score Mean	p-value, Student t-test for mean FACT-M
Max Value	32 (100%)	120 (100%)	108 (100%)	172 (100%)	
All patients n=117	29.42 (92%)	112.26 (94%)	95.64 (89%)	157.72 (92%)	
EG* n=54	29.57 (94%)	108.82 (91%)	95.31 (88%)	152.71 (89%)	
					p=0.37 FACT-M
LG** n=63	29.3 (91%)	115.16 (96%)	95.92 (89%)	162.01 (94%)	

*Early Group (EG), surgery dates 2014–2019

**Latter group (LG), surgery dates 2019–2021

Table 2
QOL factors according to SLNB and WLE Site

	Melanoma Surgery Scale (MSS) Score Mean	Trial outcome Index (TOI) Mean	FACT-G TOTAL SCORE Mean	FACT-M Total score Mean	p-value, Student t-test for mean FACT-M
Max Value	32 (100%)	120 (100%)	108 (100%)	172 (100%)	
SLNB single site n=89	29.33 (91%)	113.62 (95%)	96.57 (90%)	160.09 (93%)	
					p= 0.17 FACT-M
SLNB multiple sites n=28	29.71 (94%)	108 (90%)	92.7 (86%)	150.18 (87%)	
SLNB Axilla n=45	30.06 (94%)	107.20 (89%)	93.22 (86%)	150.47 (87%)	
					p= 0.18 FACT-M
SLNB Groin n=44	28.6 (89%)	120 (100%)	100 (93%)	170 (99%)	
Melanoma Limb n=71	30 (91%)	115.75 (96%)	97.70 (90%)	163.2 (95%)	
					p= 0.13 FACT-M
Melanoma Trunk n=46	30.08 (94%)	106.77 (89%)	92.45 (86%)	149.26 (87%)	

A case report of a FGFR activation and genetic variability in metastatic sinonasal mucosal melanoma

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Introduction and Objectives: Common driver mutations in mucosal melanoma are NRAS, KIT, and KRAS. Switches in tumor driver mutation have previously been described in mucosal melanoma.

Results: We present the case of a 44-year-old male patient with stage IV metastasized sinonasal mucosal melanoma. Treatment included primary tumor resection, followed by adjuvant radiotherapy and adjuvant systemic therapy with a PD-1 inhibitor. After a local recurrence, first-line therapy with combination immunotherapy (ipilimumab and nivolumab) was initiated. A switch to second-line Lenvatinib and Pembrolizumab followed due to progressive disease. Progressive disease under second-line therapy lead to a further biopsy for mutational analysis.

An Ion AmpliSeq Cancer Hotspot Panel at diagnosis showed an NRAS mutation and amplification as the driver mutation. Five years after diagnosis, a Foundation One Analysis (FOA) was performed due to progression under therapy, which showed a switch of driver mutation. FGFR-TACC3 rearrangement was found while the previously noted NRAS mutation was no longer detectable. Additionally, an increase in copy number variants (CNVs) was noted, leading to a suspicion of genetic instability within the tumor. Microsatellite status was stable. Retrospectively, a Foundation One Analysis of the biopsy from 2017 was added to confirm the absence of FGFR-3 Rearrangement at this time. According to these results, we have received approval to start Erdafitinib (Balversa®), a specific FGFR1-4 inhibitor.

Discussion: FGFR aberrations and rearrangements have been described in many solid tumors, including melanoma. FGFR-3 rearrangement leads to the activation of the tyrosine kinase, which mediates cell growth and proliferation and leads to tumor progression. Many therapy options are currently being studied and developed to target FGFR specifically. FGFR-3 is a rare mutation in melanoma that is not typically covered in mutational panels. As new targeted therapies are developed, analysis for this specific mutation are becoming more important. In the case of therapy changes due to progressive disease in mucosal melanoma, recurrent mutation analysis could be helpful in the search for new or switched driver mutations.

ARTISTRY-6: nemvaleukin alfa monotherapy in patients with advanced mucosal and cutaneous melanoma

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Introduction and Objectives: Approximately 50% of patients with melanoma receiving checkpoint inhibitors (CPIs) do not respond and some responders ultimately progress. Limited subsequent treatment options underscore the need for novel treatments with durable benefit. Patients with mucosal melanoma (MM) exhibit key efficacy outcomes $\approx 2\times$ lower than those with cutaneous melanoma (CM). Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds to the intermediate-affinity interleukin-2 receptor to preferentially activate CD8⁺ T and NK cells, with minimal expansion of regulatory T cells. Nemvaleukin has US FDA Orphan Drug designation for treatment of MM. In ARTISTRY-1, the intravenous (IV) recommended phase 2 dose (RP2D) for nemvaleukin monotherapy (6 $\mu\text{g/kg}$ on days 1-5 per 21-day cycle) demonstrated durable antitumor activity in patients with advanced melanoma, including MM, previously CPI treated (N=46, overall response rate [ORR] 13.0% [95% CI 4.9-26.3], median duration of response 8.1 weeks [range 6.1-79.0]). In ARTISTRY-2, the subcutaneous (SC) RP2D of 3 mg every 7 days (q7d) demonstrated pharmacodynamic effects consistent with those of IV delivery. These findings support evaluation of nemvaleukin among patients with advanced MM or CM. Additionally, ARTISTRY-3 is evaluating less frequent IV nemvaleukin administration in patients with advanced solid tumors.

Materials and Methods: ARTISTRY-6 (NCT04830124) is an ongoing phase 2, global, multicenter, open-label study, currently enrolling. Eligibility criteria include prior anti-PD-(L)1 +/- anti-CTLA-4 therapy, Eastern Cooperative Oncology Group performance status 0 or 1, and adequate hematologic reserve and hepatic and renal function. In Cohort 1, patients with advanced CM will receive nemvaleukin at the SC RP2D of 3 mg q7d. In Cohort 2, patients with advanced MM will receive nemvaleukin at the IV RP2D of 6 $\mu\text{g/kg}$ on days 1-5 per 21-day cycle. In Cohort 3 (protocol amendment), patients with advanced CM will receive IV nemvaleukin less frequently (1 or 2 doses/cycle) when a less frequent IV RP2D is established in ARTISTRY-3. Treatment will continue until progression or intolerable toxicity. Primary objective: evaluate antitumor activity of nemvaleukin monotherapy (ORR). Additional objectives: evaluate safety, health-related quality of life, predictive biomarkers, pharmacokinetics, immunogenicity, and pharmacodynamics.

Results: Trial in progress.

Conclusions: Trial in progress.

Clinical Activity of the Type II Pan-RAF Inhibitor Tovorafenib in BRAF-Fusion Melanoma

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Introduction and Objectives:

Tovorafenib is an oral, selective, CNS-penetrant, type II pan-RAF inhibitor targeting both monomeric and dimeric forms of RAF without the paradoxical activation of the MAPK pathway reported for type I BRAF inhibitors.¹ Single-agent activity has been observed in melanoma patients harboring *BRAF* and *NRAS* mutations as well as *RAF* fusion-driven solid and brain tumors.^{2,3} Early clinical activity of tovorafenib monotherapy in the first 3 patients with BRAF fusion melanoma as of 8 Feb 2023 is reported.

Materials and Methods:

FIRELIGHT-1 (NCT04985604) sub-study DAY101-102a cohort 1 is an ongoing open-label, multicenter, phase II study of tovorafenib monotherapy in patients ≥ 12 years of age with recurrent or progressive melanoma harboring activating *BRAF* or *CRAF/RAF1* fusions or *CRAF/RAF1* amplifications. Tovorafenib is administered PO once weekly in 28-day cycles. The primary endpoint is overall response rate per RECIST version 1.1.

Results:

Patient 1 is a 53-year-old Asian male with *AGK-BRAF* fusion, Stage III non-Spitzoid cutaneous melanoma who had undergone multiple lymphadenectomies and skin lesion excision surgery. Previous therapy with pembrolizumab provided a best response of stable disease (SD) after 11 weeks of therapy. Following tovorafenib treatment, he had a complete response at the 8-week scan, which was confirmed at 16 weeks.

Patient 2 is a 35-year-old white male with a *TRIM33-BRAF* fusion malignant melanoma, and progressed after treatment with radiation, nivolumab, and nivolumab + ipilimumab. He had a partial response (PR) at the 8-week scan on tovorafenib, which was confirmed at 16 weeks.

Patient 3 is a 71-year-old Asian male with *MKRN1-BRAF* fusion, Stage II non-Spitzoid cutaneous melanoma previously treated with radiation and pembrolizumab (best response of SD after 2 months of therapy). At the 8-week scan, he had a PR on tovorafenib and is awaiting a confirmatory scan.

Treatment-related adverse events for all 3 patients included G1 neck pain, rash, headache, fatigue, urticaria, and hand-foot syndrome, and G2 rash and anemia.

Conclusions:

Early results from the first three patients of this ongoing trial showed tovorafenib is generally well tolerated and has encouraging antitumor activity in *BRAF*-fusion melanoma.

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Key Words:

melanoma, *BRAF* fusion, targeted therapy, pan-RAF inhibitor, tovorafenib, complete response, partial response

Clinical prognostic factors in BRAF mutant metastatic melanoma patients treated with BRAF MEK inhibitors: a real word multicenter experience

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Introduction and Objectives: Multiple systemic treatments (targeted therapies, immunotherapies) are available for BRAF v600 mutant melanoma patients. We collected a real word series of patients treated with BRAF MEK inhibitor targeted therapy (TT) in first line, to evaluate potential prognostic factors associated with better outcome.

Materials and Methods: This is an observational multicenter retrospective study involving 14 Italian Centers.

Results: 425 BRAF mutant metastatic melanoma patients(without brain metastasis) were evaluated. 80% patients were treated with dabrafenib trametinib, 18% with vemurafenib cobimetinib, 2% with encorafenib binimetinib. 73% patients presented baseline ECOG Performance status (ECOGPS) 0, 47% Baseline Neutrophil/Lymphocyte ratio (NLR) >3, 60% baseline LDH (LDH) within normal range, 67% less then 3 metastatic sites (MTS)

Medium follow-up was 38.4 months: Best response was complete response in 20% patients, partial response in 47,5% patients, stable disease in 14.6% patients.

Median PFS was 15 (IC 95% 12.6-17.4) months: in univariate analysis and multivariate analysis independent prognostic factor associated with TT better outcome were: best response ($p < 0.001$), ECOGPS ($p = 0.027$), LDH ($p = 0.041$), MTS ($p < 0.001$), NLR ($p < 0.001$).

Median OS was 26 (IC 95% 19.5-32.4) months: in univariate analysis and multivariate analysis independent prognostic factor associated with TT better outcome were: best response ($p < 0.001$), ECOGPS ($p < 0.001$), LDH ($p = 0.033$), MTS ($p = 0.030$), NLR ($p < 0.001$).

Overall survival calculated post TT progression (time from TT progression to death or last follow-up) was significantly longer in patients with RC as best response ($p = 0.021$), and in patient with TmR (=Time from obtained best response to TT progression) > 9 months ($p = 0.005$)

Conclusions: In real life setting, treatment with BRAF MEK inhibitors appears to be as effective and well tolerated as reported in the pivotal studies. The baseline parameters: LDH, ECOG PS, number of metastatic sites and NLR are able to identify patients with the best prognosis in whom BRAF and MEK inhibitors obtain better efficacy. The depth of response and the maintenance of response have an impact on post-progression survival. The phenomena of rapid progression (with reduced OS) seems more probable in patients with a less marked response and a short lasting response.

Elevated LDH at early stage of adjuvant BRAF and MEK inhibitors therapy does not have diagnostic significance in detecting melanoma recurrence

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Introduction: Lactate dehydrogenase (LDH) is an intracellular enzyme whose concentration in the serum of melanoma patients is a commonly used biomarker for recurrence detection. In this report we evaluated the clinical value of elevated LDH during early stage of adjuvant BRAF and MEK inhibitors in the adjuvant treatment in melanoma patients.

Materials and Methods: Nineteen patients after resection of stage III cutaneous melanoma were included in the analysis. All patients received BRAF inhibitor (dabrafenib) with MEK inhibitor (tarmetynib) in the adjuvant setting. Laboratory tests, including evaluation of LDH level were analyzed at baseline, every 3 first months and then after every 2 months of treatment.

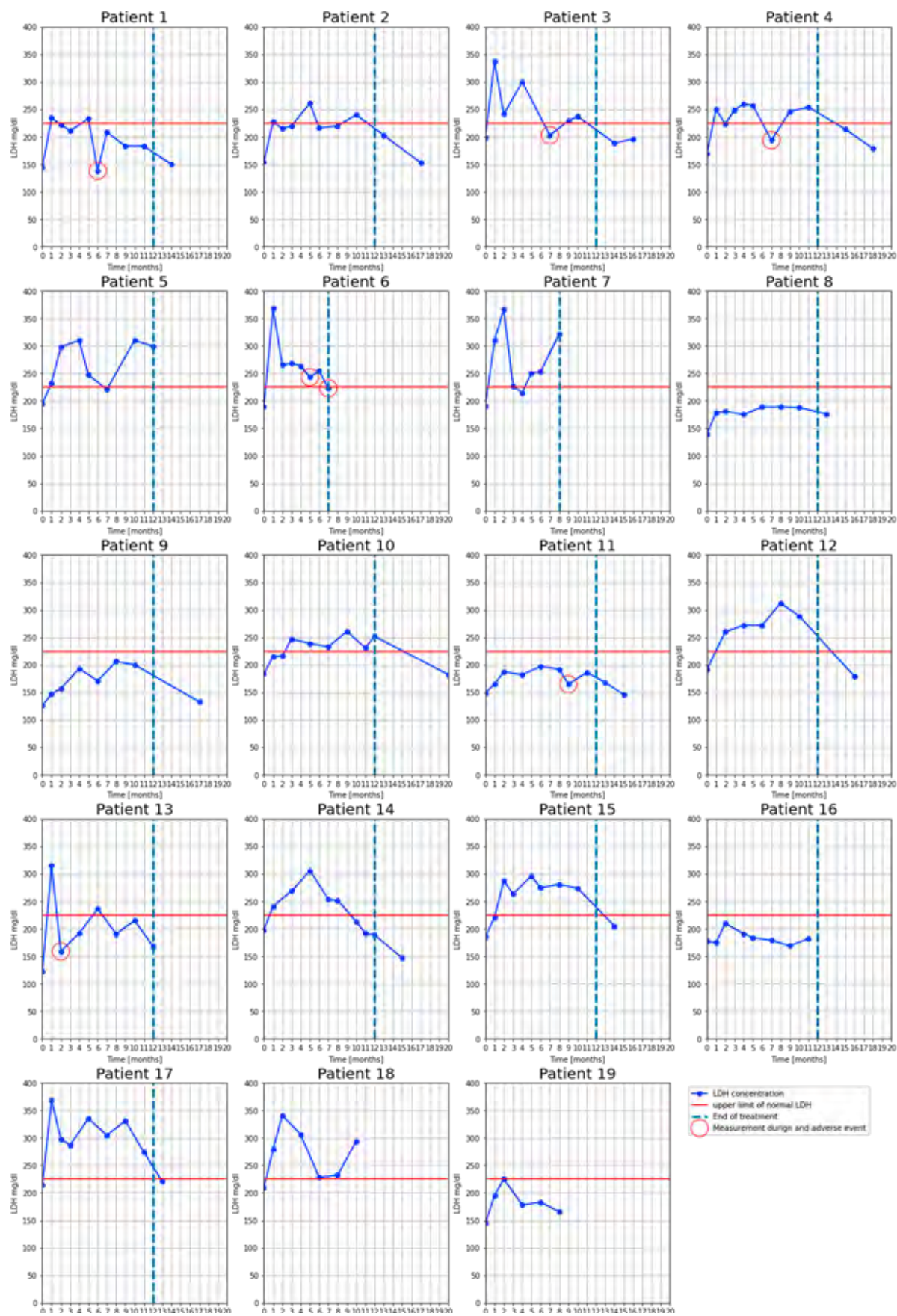
Results: In 15 patients the LDH level was increased in the first assessment, while 4 patients presented normal level. In the last 4 patients, an increase in LDH was also observed, but within the normal laboratory range.

The range of increase in LDH level was from 32 to 193 UI, which was from 18% to 153% of the baseline value. The median increase in LDH in all patients was 108 UI, which is 61% of the baseline value. After discontinuation of dabrafenib with trametinib, a decrease in LDH was observed in all patients except 1, in whom treatment was discontinued due to disease progression. The increase in LDH was not accompanied by leukocytosis, and there was no increase in the inflammatory marker – NLR (neutrophil lymphocyte ratio) between baseline and peak LDH.

To the best of our knowledge, this is the first report demonstrating LDH level increase in melanoma patients receiving adjuvant BRAF and MEK inhibitors which is not linked with disease recurrence. There is also no data allowing to indicate an unambiguous mechanism of the described phenomenon. Our hypotheses include the immunomodulatory effect of BRAF and MEK inhibitors and the effect of these drugs on the MAPK pathway in BRAF wild-type cells.

Conclusion: These preliminary findings need further evaluation in larger patients cohort. After confirming the presented results, the detection of increased serum LDH level in patients undergoing adjuvant target therapy will in many situations allow to avoid additional imaging tests and may prevent unnecessary emotional stress of the patients.

Supporting Document 1



Supporting Document 2

Table 1. LDH value in melanoma patients treated adjuvant targeted therapy

Patient	Baseline LDH UI (ULN – 225UI)	Maximum LDH UI	Δ – absolute value	Δ – %
1	145	234	89	61
2	154	261	107	69
3	199	337	138	69
4	169	260	91	54
5	195	310	115	59
6	189	368	179	95
7	191	367	176	92
8	140	189 N	49	35
9	126	206 N	80	64
10	184	261	77	42
11	149	197 N	48	42
12	191	312	121	63
13	122	315	193	158
14	198	306	108	55
15	185	296	111	60
16	178	210 N	32	18
17	214	369	155	64
18	209	341	132	63
19	145	225	80	55

LDH- lactate dehydrogenase, Δ – difference, N – norm, ULN – upper limit of norm

Long progression free survival in patients on trametinib treatment as 2nd or 3rd line therapy

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Introduction:

The treatment of patients with metastatic melanoma with immune checkpoint blockade (ICB) has significantly increased long term survival, but effective treatments after progression on ICB specifically for BRAF WT patients are lacking. NRAS mutated melanoma has been shown to respond to treatment with the MEK-inhibitor binimetinib, however the PFS of 2,8 months and the median OS of 11 months was not promising [1].

Materials and Methods:

Three BRAF wild-type patients with a NRAS Q61 mutation progressed on PD1 blockade and /or immune combination therapy and were treated with the MEK inhibitor trametinib 2 mg once daily in the Clinic for Dermatology in Rostock. Best response, progression free survival and OS was monitored.

Results: Patient 1: 60-year-old male with a Q61R mutated cerebral, hepatic, lymphatic and cutaneous metastasized melanoma, elevated LDH and S100- β and ECOG of one. Trametinib resulted in a partial response (PR) with an ongoing progression free survival (PFS) of 8 months, overall survival (OS) was not reached. Due to elevated CK trametinib has been reduced to 1 mg daily.

Patient 2: 73-year-old male with a Q61L mutated peritoneal, pulmonary, hepatic, lymphatic and cutaneous metastasized melanoma, elevated LDH and S100- β and ECOG of 2. Best response to trametinib was stable disease with a PFS of 7.5 months and an OS of 9 months. No side effects occurred.

Patient 3: 77-year-old female with a Q61R mutated cerebral, pulmonary, lymphatic, adrenal and cutaneous metastasized melanoma, elevated LDH and S100- β and ECOG of 1. Trametinib lead to a PR, PFS was 9 and OS 15 month. No side effects occurred.

Conclusion: Three patients with high tumor load all benefitted from treatment with trametinib and showed a explicitly longer PFS than the published data. After progression on ICB we therefore recommend to consider MEK-inhibition for NRAS mutated melanoma in selected cases.

Retrospective Single Case Reports on the Treatment of Patients with Advanced BRAFV600-mutated Malignant Melanoma with Encorafenib plus Binimetinib (REMINISCENCE): Focus on Patients with Brain Metastases

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Introduction and Objectives: The definition of an individualized therapy sequence regarding targeted and immune therapies represents one of the challenges to an optimal treatment of advanced, unresectable or metastatic BRAFV600-mutated melanoma. This project aimed to collect exemplary single case reports of patients receiving a combination therapy with encorafenib and binimetinib (EB) as a basis for training and scientific discussions. Here, therapy courses of patients with brain metastases will be reported.

Methods: Cases of adult patients with unresectable or metastatic BRAFV600-mutated melanoma with a therapy sequence including ongoing or completed EB therapy were selected by treating physicians. Eligible patients were documented retrospectively using standardized case report forms after patients' informed consent.

Results: In summary, 17 patients from 5 centers in Germany and Austria were included between July 2020 and February 2022. Five cases of patients with documented brain metastases including patient and treatment profiles, response to therapy and safety will be presented: 1) male, 60 years, progress after long-term remission, EB in 1st-line (best response (BR): durable partial remission (PR) 5 months after end of EB due to toxicities (duration of EB therapy: 7 months); 2) male, 53 years, advanced setting, complex prior therapy lines, EB in late therapy line with parallel brain surgery (therapy duration at cut-off [TC]: 1.4 years; BR: PR); 3) female, 82 years, poor prognosis (brain metastasis, increased LDH and concomitant autoimmune disease), 1st-line EB therapy with PR after surgical intervention and stereotactic radiotherapy (TC: 1 year); 4) male, 75 years, high tumor load (S100 and LDH increased), multiple metastases, EB in 1st-line after previous stereotaxis (TC: 0,3 years, BR: PR); 5) male, 59 years, cardiovascular concomitant disease, multiple metastases, 2nd-line therapy with EB after progress during checkpoint inhibitor therapy (TC: 1,3 years, BR: stable disease of distant metastases, CR of brain metastasis following stereotaxis).

Conclusion: The description of the clinically relevant therapeutic benefits of different EB treatment sequences in patients with brain metastases contributes to the discussion about the optimal management of this patient population usually excluded from clinical studies.

Spatial and molecular heterogeneity in melanoma targeted therapy resistance

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Introduction and Objectives: BRAF and MEK inhibitors have significantly improved the overall survival of melanoma, however resistance remains a large issue as most patients eventually progress.

Materials and Methods: 85 BRAF mutated melanoma cell cultures derived from patient biopsies were tested for sensitivity to encorafenib (LGX818) was assessed using the resazurin assay. We also performed targeted panel DNAseq and RNAseq on 85 melanoma cell cultures. 10 paired biopsies from patients at baseline and progression on BRAF and MEK inhibitors were stained with MLANA, AXL, PTN, GLIS3, NNMT and BRAF V600E using Akoya 6-plex immunofluorescence.

Results: In vitro testing of encorafenib on the 80 melanoma cell cultures revealed 46 cell cultures to be resistant using cutoff of 100 nM. Targeted panel sequencing of all cell cultures revealed NRAS Q61 mutation in 9/46 cell cultures. Differential gene expression between the 34 sensitive and 46 resistant cells revealed melanocytic markers like MITF, MLANA, and TYR to be associated with sensitivity, and dedifferentiation markers like AXL and WNT5A with resistance. Geneset enrichment analysis showed enrichment of the Hoek Proliferative, Verfaillie Proliferative, and Tirosh MITF signatures for sensitive cells and conversely, enrichment for Hoek Invasive, Verfaillie Invasive, and Tirosh AXL signatures for resistant cells. We also discovered new genes like Pleiotrophin (PTN), GLIS family Zinc Finger 3 (GLIS3), and Nicotinamide N-Methyltransferase (NNMT) are genes that distinguish between the resistant and sensitive cells. To investigate if these markers exist in the same cell and same area of the tumor, we performed Akoya 6-plex immunofluorescence on paired biopsies at baseline and progression on BRAF and MEK inhibitors. Tumor heterogeneity was high between the patients as well as between the baseline and progression tumors. The majority of the tumors at baseline consisted of MLANA positive melanoma cells and at progression each patient had multiple subclusters of resistant cells consisting of combinations of PTN, AXL, GLIS3 and NNMT expression.

Conclusions: Our results suggest that there are genetic and non-genetic resistance mechanisms to targeted therapy resistance in melanoma and patients can have their own specific resistance mechanism.

The combination of PI3Ki and MEKi as a promising treatment option for BRAF WT patients

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Introduction and Objectives: In recent years, the development of new therapeutic approaches such as immune checkpoint inhibitors or the targeted use of targeted therapy has improved the overall survival rate of melanoma patients. However, the response rates of current treatment options are limited, and the emergence of resistance mechanisms to immuno-oncology (IO) therapies such as immune checkpoint blockers has become a major challenge in the treatment of melanoma. In-house research as well as studies by colleagues have shown that the PI3K/AKT pathway is deregulated in 70% of melanomas and plays a key role in the development of resistance mechanisms to targeted and IO therapies. Therefore, PI3K may be a promising target for specific inhibitor treatment. In particular, the combination of PI3K and MEK inhibitors that simultaneously target the PI3K/AKT and MAPK pathways may be an effective therapeutic option in metastatic melanoma, as shown in previous in vitro studies by us and others. In monotherapy, the pan-PI3K inhibitor BKM120 (activity against p110 alpha, beta, gamma, and delta isoforms) is able to induce growth inhibition and apoptosis in most of the melanoma models tested to date, whereas BYL719, an alpha-specific inhibitor, has limited antitumor activity as monotherapy. However, both combination treatments of PI3K and an MEK inhibitor resulted in effective growth inhibition and apoptosis in the cellular melanoma models tested, exceeding the effect of MEK inhibition as monotherapy. Initial in vivo test results (in ovo) on chick chorioallantoic membrane (CAM) showed reduced tumor burden and micrometastases by using the p110alpha-specific BYL719 in combination with trametinib. In vivo results in NSG mice injected with either BRAF or NRAS mutated cell lines also showed a synergistic effect of the combination in the NRAS mutated tumors. These data show that the combination of PI3K inhibitors with MEK inhibitors could be a new therapeutic option for melanoma patients. By using PI3K α -selective inhibitors, potential side effects could be reduced compared to pan-PI3K inhibitors.

Trial in progress: A phase 3 study (TILVANCE-301) to assess the efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in combination with pembrolizumab compared with pembrolizumab alone in patients with untreated unresectable or metastatic melanoma

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Introduction and Objectives: Most patients with advanced (unresectable or metastatic) melanoma receiving front-line immune checkpoint inhibitors (ICI) progress within a year (Robert Lancet Oncol 2019; Larkin NEJM 2019; Tawbi NEJM 2022). Early-line therapies are needed to improve the rate of deep and durable responses and increase the proportion of patients with long-term benefit.

Lifileucel demonstrated an ORR of 31.4% and median DOR not reached (median 36.5-mo follow-up) in patients with post-ICI advanced melanoma (Sarnaik SITC 2022). Earlier-line treatment with lifileucel plus pembrolizumab in patients with ICI-naïve advanced melanoma demonstrated an ORR of 67%, including a CR rate of 25% (Iovance Press Release, April 5, 2022; O'Malley JITC 2021). TILVANCE-301 will evaluate the efficacy and safety of lifileucel plus pembrolizumab compared with pembrolizumab alone in patients with untreated advanced melanoma.

Materials and Methods: TILVANCE-301 (NCT05727904) is a phase 3, multicenter, randomized, open-label, parallel group, treatment study that will randomize ~670 patients (1:1) to either Arm A: lifileucel plus pembrolizumab (study intervention includes tumor tissue resection, pembrolizumab, nonmyeloablative lymphodepletion [NMA-LD], lifileucel infusion, an abbreviated course of high-dose IL-2, and thereafter, continued pembrolizumab) or Arm B: pembrolizumab alone. Patients in Arm B who receive pembrolizumab and experience confirmed progressive disease verified by blinded independent review committee (BIRC) have the option to receive lifileucel as immediate next treatment.

Eligible adults have histologically confirmed advanced melanoma; ECOG PS 0–1; estimated life expectancy >6 mo; ≥1 resectable lesion to generate lifileucel and ≥1 remaining measurable lesion; and adequate hematologic parameters and organ function. Neoadjuvant or adjuvant treatment including ICI may be allowed. Exclusion criteria include prior therapy for metastatic disease; symptomatic untreated brain metastases; organ allograft or prior cell therapy; uveal/ocular melanoma; chronic systemic steroid therapy; active systemic infections; or other primary malignancy in the last 3 years.

Dual primary efficacy endpoints: BIRC-assessed (RECIST v1.1) ORR and PFS. Key secondary efficacy endpoint: OS. Additional secondary efficacy endpoints: BIRC-assessed CR rate, DOR, and EFS; investigator-assessed ORR, PFS, CR rate, DOR, EFS, and PFS2; and safety (characterized by severity and seriousness of TEAEs), and relationship to study drug.

The study will enroll globally.

Results: None

Conclusions: None

Vitiligo-like hypopigmentation induced by dabrafenib-trametinib: a potential marker for clinical response

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Introduction: Some immune-related adverse events (irAEs) such as vitiligo-like hypopigmentation (VLH) have been widely reported with the use of immunotherapy (IT) to be associated with favorable outcomes(1,3). However, little is known about irAEs induced by targeted therapy (TT). We present a case of VLH due to dabrafenib-trametinib.

Clinical case: A man in his 60s presented with a superficial spreading melanoma on his trunk classified as a pT4bpN1aM0 stage IIIC melanoma after surgery, PET-CT and lymphadenectomy (Breslow index=6mm, BRAFV600E mutated).

Adjuvant immunotherapy with nivolumab was started. One month after later, the patient progressed with metastases nearby the melanoma scar, the liver, spleen, and bone. Treatment was switched to dabrafenib-trametinib and complete response was achieved after 4 months, assessed by PET-CT.

During follow-up, the patient developed multiple cutaneous manifestations due to TT: acneiform rash after 6 months of treatment, alopecia areata and poliosis on the occipital region after 10 months, and VLH with hypopigmented macules around the mouth, on the melanoma scar and on the left arm after 16 months.

Discussion: Cutaneous irAEs such as VLH and panniculitis have been recently described with TT, suggesting an immune-modulating ability beyond the anti-target effect(2–4). Also, they have been linked to favorable prognosis, showing greater response rates, durability of response and progression-free survival(2–4).

Our patient presented not only VLH but also other cutaneous irAEs (alopecia areata and poliosis) while undergoing exclusively TT. Autoimmune individual predisposition has probably contributed, but TT seems clearly the trigger. It is uncertain if prior nivolumab may have facilitated irAEs development. However, the patient progressed while being on nivolumab whereas remains in complete response on TT. Thus, it seems more plausible for TT to be responsible for irAEs in our patient.

Conclusions:

- We present a case of a patient with metastatic melanoma who developed VLH and alopecia areata while receiving dabrafenib-trametinib and who is currently in complete response after two years of treatment.
- Responders to TT should be studied for signs of VLH to determine its potential role as a predictor of favorable clinical response.

A case of primary adenocarcinoma from apocrine sweat glands

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Introduction and Objectives: Apocrine adenocarcinoma is a rare appendageal neoplasm with nonspecific features. Lack of case reports with dermoscopic images makes the process of diagnosis challenging. We present a case of 56-years-old patient with this type of cancer to fulfill the gaps in field of dermatooncology.

Patient complains about a 3 cm swelling in the right axillary area growing for past 4 years and multiple palpable lesions in breast.

Materials and Methods: Dermoscopy reveals structureless orange area formed by a dense cellular infiltrate. Ulceration in the center. White shiny lines are visible in polarized light. In polarized and non-polarized light clustered small white microcalcification globules are seen in the lumens of tubular structures. Vessels are polymorphic: dotted, short, linear.

According to mammography: compaction of glandular triangle on both sides due to the fibrous component and hyperplasia. Biopsy of the axillary lesion was performed. Two pathologists examined histological slides. Results of immunohistochemistry: Ck8 +; SOX10, Mitf, p63, CK20, tyrosinase negative, HER2 0, ER 0, PR 0, Ki-67 < 20%. This immunophenotype is observed in metastatic breast carcinoma and sweat gland carcinoma. According to another immunohistochemistry: CCR7, AR, GCFP-15 – positive; vimentin, S100 – negative reaction in the tumor.

Histology results led to excision of the tumor and lymphadenectomy of the axillary, subclavian, subscapular lymph nodes (adenocarcinoma metastases were noted in 4 out of 11). 7 samples were taken from breast tissue for exclusion of mammary glands malignant tumor. Histological examination revealed infiltrative growth of tumor from cells with eosinophilic cytoplasm and polymorphic nuclei. Atypical mitoses, decapitation secretion, mucinous and clear cell differentiation of tumor cells, microcalcifications are determined. Perivascular and perineural growth present in subcutaneous fat tissue. In two lymph nodes, metastases from tumor cells of a similar phenotype are detected (with a presence of subcapsular micrometastasis in larger node).

Results: Results of immunohistochemistry: mammoglobin – negative, GATA3 – moderate positive reaction, ER – negative, PR – negative, Ki-67 – positive reaction (17-20%); p63, SMA – the myoepithelial layer is absent around the tumor structures.

Diagnosis: Primary apocrine adenocarcinoma. (T2N2M0).

Better case representation of rare skin tumors may help dermatologists and oncologists in early detection of cutaneous cancer.

A Rare Case of Exophytic Leiomyoma on the Scrotum

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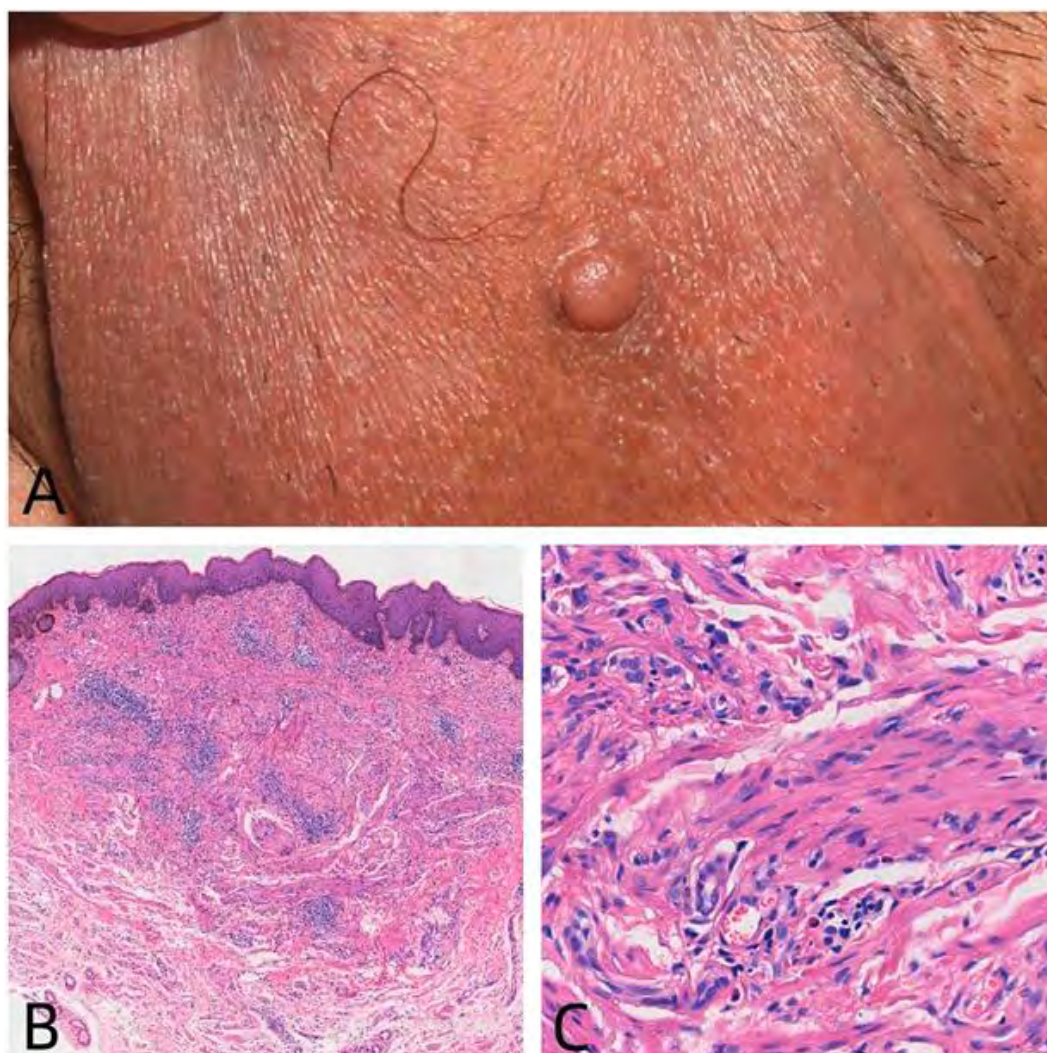
Introduction and Objectives: Scrotal leiomyoma is an uncommon subtype of leiomyoma, mostly located in the scrotum or adjacent to the testis, but extremely rare on the surface of the scrotal skin.

Materials and Methods: Here, we report a case of exophytic growth of scrotal leiomyoma. A 50-year-old male with scrotal nodule for 2 years has no obvious symptoms. Dermatological examination revealed a raised skin-colored nodule with a diameter of about 1 cm on the skin surface of the left scrotum.

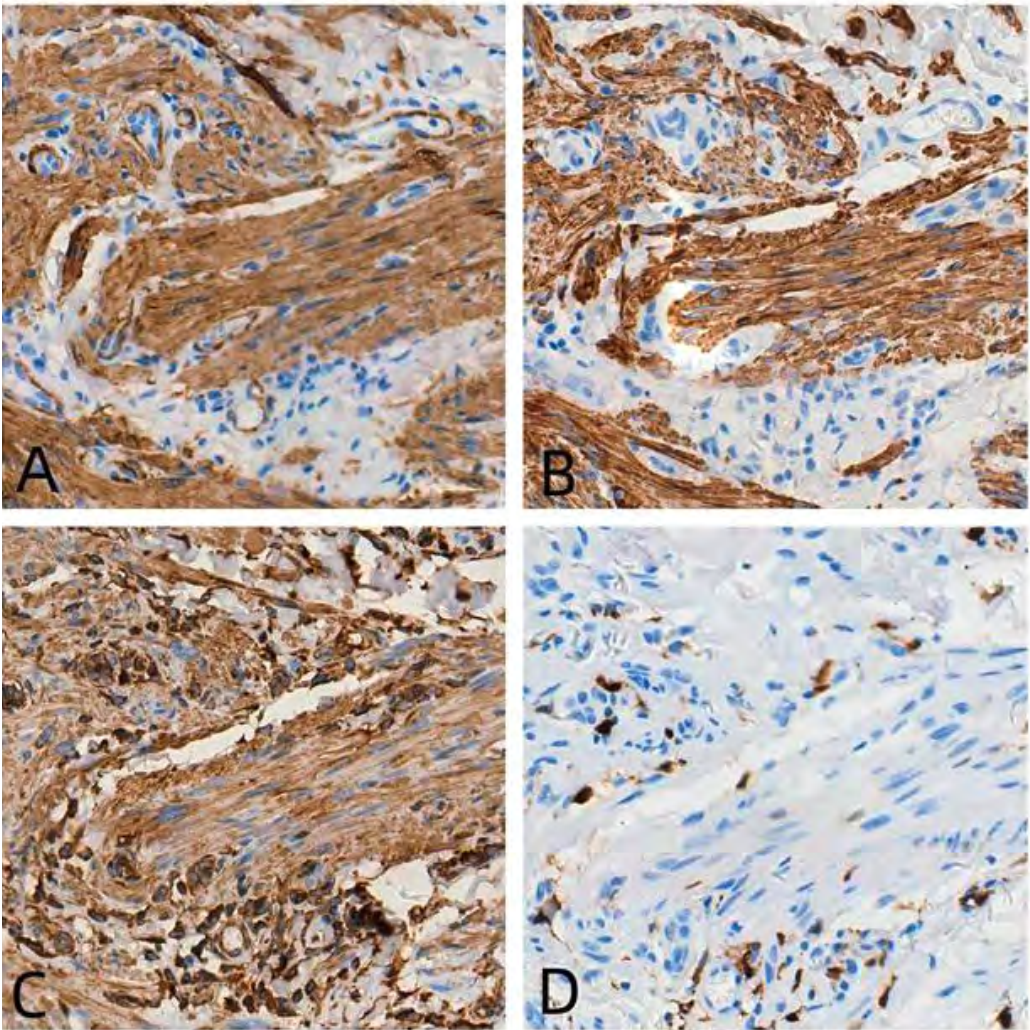
Results: Histopathological examination of skin lesions showed a tumor mass in the entire dermis. The proliferated tumor cells presented are mostly fusiform or spindle-shaped, arranged in crossed bundles, and stained with eosinophilic cytoplasm. The nuclei were elongated, cigar-shaped at both ends, and no mitosis was observed. Immunohistochemistry results were positive for smooth muscle actin (SMA), desmin, and vimentin but negative for S-100 proteins.

Conclusions: The diagnosis of the scrotal exophytic leiomyoma was performed. The patient underwent surgical resection and was followed up for 2 years with no recurrence.

Supporting Document 1



Supporting Document 2



An Indurated Erythematous Rash: Keeping an Open Mind

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Introduction and Objectives: A 71-year-old female patient presented with a three-week history of an erythematous indurated rash with associated papules affecting her right anterior arm (Image 1.0). The patient had a known history of bilateral invasive lobular carcinoma, with known metastases to liver, lung, pancreas and bone, treated with Exemestone and Everolimus. This was Oestrogen receptor and progesterone receptor positive, and Her-2 negative, expressing the PIK3CA gene. On review, an incisional biopsy was taken of the area. Histopathology showed pandermal infiltration by malignant epithelial cells. Immunohistochemistry findings showed Oestrogen receptor positivity; progesterone receptor and Her-2 negativity. This was consistent with metastatic lobular carcinoma of the breast.

Materials and Methods: Breast cancer remains the leading cause of cancer in women and the second highest cause of death, contributing significantly to both morbidity and mortality in women. It is the most common malignancy to result in cutaneous metastasis, with an incidence of approximately 20%¹. Although rare, cutaneous metastasis are associated with a poor prognosis often representing disseminated disease. In addition, distant cutaneous metastasis have been shown to be associated with a poorer survival when compared to local metastasis². Cutaneous metastasis can present with atypical clinical and histopathological findings creating a diagnostic dilemma for physicians^{3,4}. The spectrum of clinical presentation is broad, at times mimicking benign disease.

Results: Currently there is no defined guideline for the treatment of cutaneous metastasis, due in part to the current lack of data examining the immunohistochemical environment of cutaneous metastatic breast cancer. The mainstay of treatments include chemotherapy, radiotherapy, immunotherapy and surgical resection⁵. Sadly, in our case the patient passed away shortly after diagnosis.

Conclusions: In conclusion, cutaneous metastasis can be the first sign of disseminated metastatic disease and a poor prognostic indicator. This case highlights the importance of prompt recognition and treatment of cutaneous metastasis of breast cancer to provide the best outcome and survival for patients.

Supporting Document 1



Atypical fibroxanthoma and pleomorphic dermal sarcoma: Local recurrence and metastasis in a nationwide population-based cohort of 1118 patients

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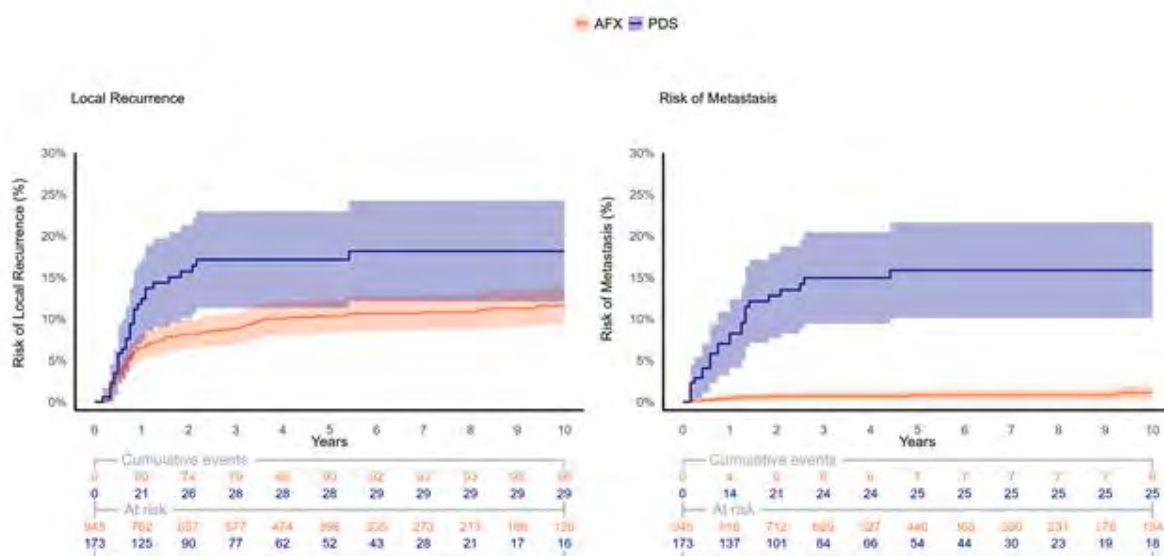
Introduction and Objectives: The prognosis of patients with atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS) remains uncertain and no standardized follow-up programs have been established. The purpose of the study was to provide recommendations for standardized follow-up programs of patients with AFX and PDS based on a nationwide cohort.

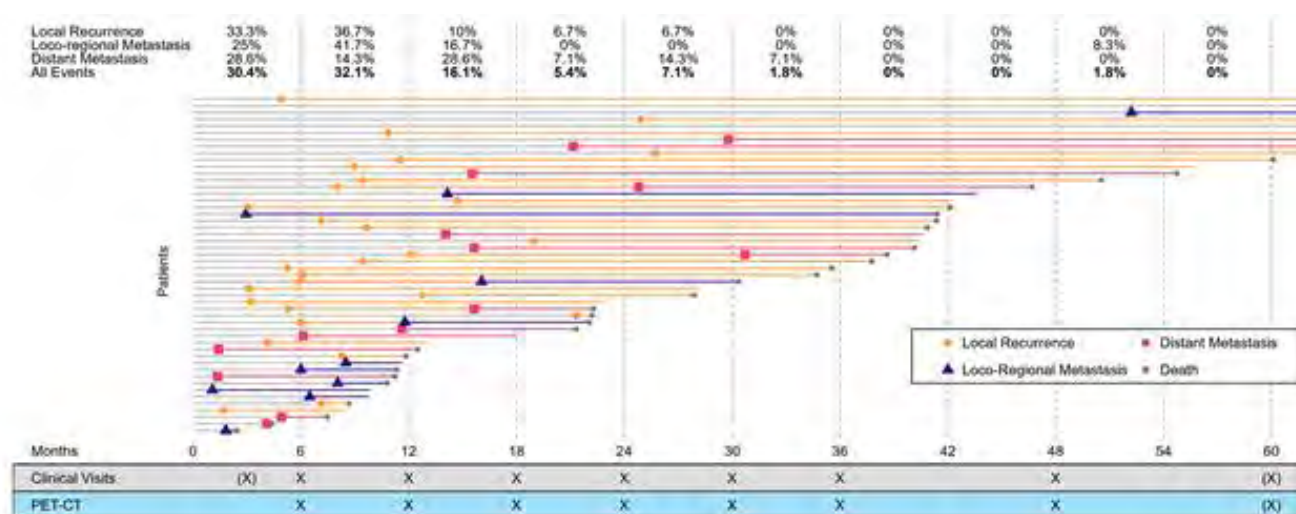
Materials and Methods: All patients with AFX and PDS in Denmark between 2002-2022 were identified in the Danish National Pathology Register. Risks of local recurrence and metastasis were estimated with cumulative incidence functions with all-cause death considered a competing risk. Conditional time-to-event analysis was used to assess the optimal length of the follow-up programs. Multivariable Fine-Gray Regression was used to estimate the association between local recurrence or metastasis and the risk factors; age, sex, anatomical location, margin status, tumor size, invasion depth, necrosis, and perineural/perivascular infiltration.

Results: A total of 945 patients with AFX and 173 patients with PDS were included providing incidence rates of 7.95/1.000.000/year for AFX and 1.45/1.000.000/year for PDS. The 5-year risk of local recurrence was 10% for AFX and 17% for PDS. The 5-year risk of metastasis was 0.8% for AFX and 16% for PDS. The risk of local recurrence or metastasis after four years in both AFX and PDS was <2%. PDS mainly metastasized the first three years in >90% of the patients with 15 distant metastases (54%), nine local metastases (32%) and four regional lymph node metastases (14%). Positive margins significantly increased the risk of local AFX recurrence ($p<0.001$), whereas the main predictors of PDS relapse was invasion beyond the subcutis, perineural/perivascular infiltration and increasing age ($p<0.05$).

Conclusions: The follow-up of patients with AFX can be limited to annual clinical visits for four years due to a risk of metastasis <1%. Patients with PDS have a high risk of both local recurrence and metastasis within the first three years. We recommend that patients with PDS should be followed with clinical visits every six months for three years followed by annual visits for a minimum of one year. All visits should be supplemented with PET-CT due to a high risk of distant metastasis.

Supporting Document 1





Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN): Cutaneous Descriptors and Clinicopathologic Determinants of Survival

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Introduction and Objectives: BPDCN is an aggressive hematologic malignancy which often involves the skin. This disorder has gone through many iterations over the years, being classified initially as a blastic NK-cell lymphoma, then a subset of AML, and finally recognized as a unique myeloid neoplasm. However, due to the poor understanding and the rarity of the disease, we conducted this pooled database analysis to identify the prognostic factors, clinicopathologic characteristics, and therapeutic strategies that influence survival in this disease.

Methods: We compiled a pooled database of 273 cases that fit the diagnostic criteria for BPDCN. Kaplan-Meier survival curves were constructed. Cox proportional hazards model and Log-rank tests were used to assess the influence of demographic and clinicopathologic factors on overall survival (OS).

Results: A total of 273 patients with confirmed BPDCN were identified. The median age was 61.5. Males constituted 80% of the cohort. The median duration of symptoms before diagnosis was 5 months. Eighty-one percent of patients presented with skin lesions, 65% of which were disseminated. BPDCN involved the trunk (23%), head and neck (12%), lower extremities (10%), upper extremities (9%), and multiple anatomical sites (46%). The dermis was always involved either alone (58%), with the subcutaneous tissue (41%), with epidermis (0.5%) or both (0.5%). Involvement of Lymph nodes (LN), bone marrow (BM), spleen, peripheral blood, and CNS occurred in 62%, 73%, 55%, 71%, and 57%. Constitutional symptoms were reported in 13%. The median OS and DFS of the whole group were 16 and 13 months, respectively. Patients younger than 60 had better median OS ($p < 0.0001$). The involvement of LN ($p = 0.03$), BM ($p = 0.007$), spleen ($p = 0.02$), and peripheral blood ($p = 0.01$) was associated with worse OS. While involvement of the extremities had better OS ($p = 0.009$), disseminated skin involvement had worse OS ($p = 0.001$). Compared to no treatment, non-dose intense chemotherapy, dose-intense chemotherapy, and stem cell transplant had incrementally superior OS ($p < 0.0001$). Patients who attained CR as their best response also had a superior median OS ($p < 0.0001$).

Conclusion: This study identifies age, organ involvement, extent of skin involvement, type of therapy, and quality of response to treatment as critical determinants of OS.

Blue unstructured areas, a dermoscopic clue for the identification of sebaceous adenoma

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Introduction: cutaneous adnexal tumors include a group of benign or malignant hamartomas that can originate from the hair follicle, sebaceous glands, eccrine or apocrine sweat glands. Sebaceous adenoma is a benign adnexal tumor that can present as a single or multiple papule located mainly on the head or neck that may have an ulcerated or keratotic center. On dermoscopy, it has been described as a non-melanocytic lesion with a yellowish-pink background, ulceration, and atypical linear irregular or hairpin vessels in focus. Its main differential diagnosis is basal cell carcinoma. Due to its location, normally in a high-risk surgical area, correct histopathological confirmation is essential. It can present as a single cutaneous lesion or be associated with Muir Torre-Syndrome

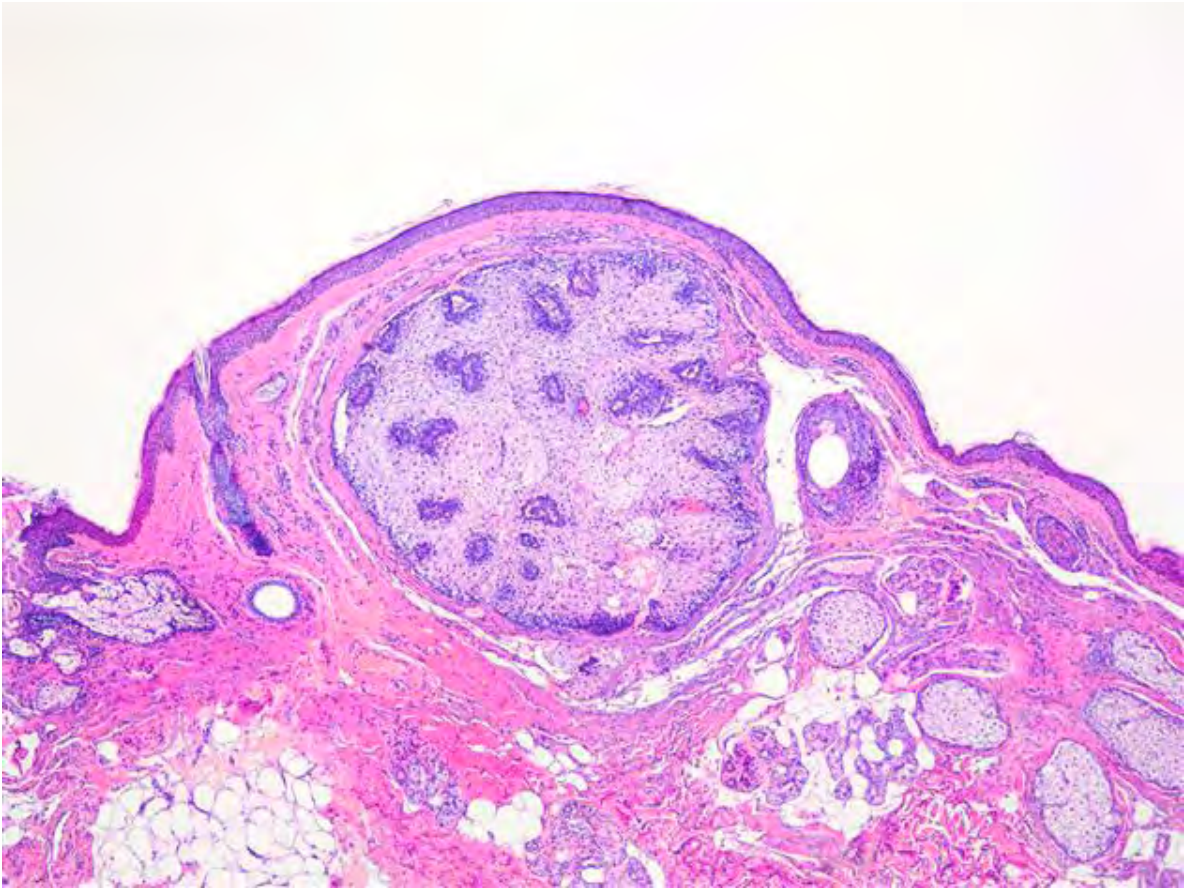
Clinical case: we presented the case of a 93-year-old female patient with a history of lentigo maligna. She was followed in the melanoma unit and in one of her regular checkups a new shiny papular lesion was evidenced on the left cheek. Dermoscopy showed a whitish-pink yellow background with a blue hyperpigmented central area with linear vessels located on the periphery of the lesion that were arranged in a crown without crossing the midline. (Image 1) We decided to excise the lesion and histopathology reported a well-defined nodule in the superficial dermis predominantly of mature sebocytes and basal cells in the periphery without cytological atypia whose diagnosis was sebaceous adenoma. (Image 2) In the multidisciplinary committee due to the advanced age of the patient, clinical follow-up was indicated and no further studies were requested.

Conclusions: The dermoscopy clinical correlation with histopathology is important in order to reach a correct diagnosis that allows adequate treatment. This dermoscopic finding provides one more clue for the identification of this low-incidence entity.

Supporting Document 1



Supporting Document 2



Bronchopulmonary adenocarcinoma revealed by skin ulceration: a case report

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Introduction: Cutaneous metastases are an uncommon secondary location. They may reveal or be synchronous with the diagnosis of the primary disease. They rarely reveal bronchopulmonary cancer (PBC). We report a case of a skin ulceration revealing a bronchopulmonary adenocarcinoma.

Case report: A 63 year old patient, chronically active smoker with 38 pack-years. He presented with a painful ulceration of the lower back, evolving for 6 months. Clinical examination revealed a single ulceration, approximately 4 cm in diameter, located in the lumbar region, deep, with irregular and raised edges, and a budding fundus covered with a yellowish fibrinous coating (Figure 1-2). The pleuropulmonary and other somatic examinations were unremarkable. Pathological examination showed a morphological appearance of a cutaneous location of a moderately differentiated adenocarcinomatous process with an immunohistochemical profile suggestive of a primary bronchopulmonary origin (TTF1 positive). The thoracic CT scan showed a tumour process in the right lung. The extension work-up did not show any other secondary locations. The patient was then referred to pulmonology for further management.

Discussion: Skin metastases are rare with an incidence of 2.9-5.3% for all cancers and 1-12% for lung cancer. Skin metastases occur most often after the discovery of the primary neoplasia. Occasionally, there is a simultaneous occurrence of a skin metastasis and the discovery of its primary neoplasia. Rarely, the metastasis may occur in isolation, before the discovery of its primary cancer. In men, this last situation should orientate the exploration towards lung or kidney cancer as a priority. In women, the kidneys and ovaries should be targeted. The clinical presentations of metastases are varied. Most often in the form of skin nodules, sometimes in the form of bullae or erosions. Rarely, the metastases have an erysipeloid or even sclerotic or armour-like inflammatory appearance. In contrast, skin localisation in the form of ulceration is exceptional.

Conclusion: Cutaneous metastasis of a primary cancer in the form of skin ulceration is exceptional. Histological examination and its immunohistochemical complement often provide the key to the diagnosis.

Supporting Document 1



Supporting Document 2



Clinicopathologic features of epidermoid cysts in the upper and lower extremities, including a case of malignant transformation in the palmoplantar region

Dr Se Yeon Lee¹, Dr Sungmi Jeon¹, How to determine accurate surgical margins for the malignant melanoma? : discrepancy between clinical surgical margin and pathological permanent margin Byung Jun Kim¹, Dr Sung Kwon¹

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Introduction and Objectives: Epidermoid cysts are common benign skin neoplasms derived from the pilosebaceous apparatus that usually develop in hair-bearing regions such as the head and neck. Palmoplantar epidermoid cysts are often confused with warts, calluses, or other cutaneous tumors owing to their rarity. Malignant transformation of epidermal cysts is extremely rare. Here, we present our experience treating palmoplantar epidermoid cysts, including a case of malignant transformation into squamous cell carcinoma.

Materials and Methods: For this retrospective study, we enrolled all patients who underwent excision of epidermoid cysts in the foot and hand from March 2006 to April 2021.

Results: Six patients (five middle-aged males and one female child) were retrospectively reviewed. Cysts were located in the weight-bearing areas of the foot in four cases, and in the palmar aspect of the hand in two cases. The wounds were closed after complete removal in five cases. In the sixth case, 46-year-old male patient with a highly recurrent plantar epidermal cyst was incidentally diagnosed with squamous cell carcinoma arising from the cyst lining after excision of the entire lesion. After a wide excision with a margin of 2 cm, the resulting defect was reconstructed using a free thoracodorsal artery perforator flap.

Conclusions: Palmoplantar epidermoid cysts are rare and knowledge of their pathophysiology, diagnosis, and treatment is limited. Complete excision is necessary to avoid relapse and to confirm the final diagnosis, especially in cases suspected of malignant transformation arising from epidermoid cysts.

Supporting Document 1



Supporting Document 2

Case No.	Sex	Age	Location	Onset	Trauma history	Recurrence history	Size	Pathology	Follow-up period	Outcome
1	M	55	Palm, hypothenar area, Lt.	33YA	+	+	45x23x16mm	Single, round cyst with yellowish keratin material	14Y	No recurrence
2	M	60	3rd finger, middle phalanx, palmar aspect, Lt.	3YA	-	+	10x5x5mm	Single, round cyst with yellowish keratin material	10Y	No recurrence
3	M	69	Sole, ball area, Lt.	(-)	-	-	13x10x6mm	Single, round cyst with grayish keratin material	7Y	No recurrence
4	M	60	Sole, ball area, Rt.	8MA	-	-	15x10x10mm	Single, round cyst with grayish keratin material	11Y	No recurrence
5	M	46	Sole, heel, Lt.	1YA	-	+	35x25x16mm	Multiple unilocular cysts with grayish keratin material (invasive well-differentiated squamous cell carcinoma arising from the cyst wall)	9Y	Recurrence ¹
6	F	6	Sole, ball area, Lt.	4MA	-	-	15x10x7mm	Single, round cyst with grayish keratin material	1Y	No recurrence

Concurrent basal cell carcinoma and Merkel cell carcinoma: a rare clinical case

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Introduction: Merkel cell carcinoma (MCC) is a rare highly aggressive skin cancer which presents neuroendocrine features. It can occur alone or synchronously with several other malignancies, including chronic lymphocytic leukemia, rhabdomyosarcoma, dermatofibrosarcoma protuberans, melanoma and squamous cell carcinoma (SCC). We present a case of a concurrent basal cell carcinoma (BCC) and MCC occurring as a solitary nodule of the sternal region.

Case report: 85-year-old white woman in poor clinical conditions was admitted to the Dermatology ward of University of Cagliari for the excision of a 2 cm x 1 cm bilobate nodule of the sternal region which was very close to a surgical scar of a previously excised epithelioma. The patient reported that the lesion had appeared three months before and no symptoms were associated. She was a smoker during her youth, and she had an history of type II diabetes, hypertension, dyslipidemia and chronic bronchitis. There was not familiarity for malignancies. Routinary blood exams, urinary tests and electrocardiogram did not show any alterations. The histologic exam reported a concomitant nodular BCC and MCC expressing the following immunophenotype: CK8-18+, CD56+, neuron specific enolase +, PAX5+/-, chromogranin -/+, CK20+/-, Ck7+/-, TTF1-, synaptophysin- Margins were free from neoplastic disease. Given the aggressive nature of MCC the patient was referred to the Medical Oncology division of our institution to complete the oncological staging and receive the proper treatment.

Conclusions: MCC is a rare and aggressive tumor arising most frequently on the head and neck of elderly Caucasian people. It is reported that MCC origins from special mechanoreceptors of the human skin called Merkel cells but according to another hypothesis MCC has a pluripotent dermal stem cell as precursor. In similar cases to the one presented, considering the relatively low incidence of MCC collision tumors due to the rarity of MCCs, a shared precursor tumor cell between MCC and BCC could be considered.

Cutaneous Merkel cell carcinoma: prognostic factors influencing the progression of the disease and the response to immunotherapy.

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Introduction and objectives: Merkel cell carcinoma (MCC) can become sometimes a very aggressive rare skin cancer with rapid loco-regional and systemic spreading. The most important prognostic factors influencing this course are clinical, but above all histopathological and molecular features. This presentation focuses on the principal markers to be outlined for the identification of high-risk MCC patients.

Materials and methods: A scientific research drawn from the international literature shows clearly the importance of the clinical and above all histopathological and molecular features to select high-risk MCC patients. Sentinel node biopsy can be the gold-standard to discover the early loco-regional progression as well as the serologic detection of biomarkers (neuron-specific enolase, ctDNA and in particular antibodies anti-MCPyV oncoproteins) can be currently used to diagnose the early systemic spreading and above all to manage better the response to immunotherapy.

Results: Clinical and histopathological features of the primary MCC are strictly correlated with the natural behaviour of the disease, but more recently molecular markers have demonstrated their prognostic role to select high-risk MCC patients because of the rapid progression of the disease and poor response to immunotherapy.

Conclusions: MCC can develop an aggressive course in about 30% cases with rapid and fatal spreading according to its clinical, histopathological and molecular features. Even if further large studies are necessary to define exactly the role of the molecular markers to influence the progression of the disease, nowadays these prognostic factors are already evaluated for the best management of MCC patients, especially in terms of response to immunotherapy.

Cutaneous Metastases As A First Sign Of Gastric Adenocarcinoma: A Case Report

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Introduction and Objectives: Cutaneous metastasis may be the first sign of primary tumor. Lymphatic or hematogenous spread, direct contiguity and iatrogenic implantation are pathways of metastatic dissemination to the skin. Metastases may appear before primary tumor is identified, simultaneously in 25.1% cases, but generally later in the course of the disease. As reported, most affected skin area was anterior thorax region, with abdominal region in second place. Lung cancer was responsible for most cases in men and breast cancer in women. Abdominal region was mainly affected by pancreatic, intestinal, lung, breast and ovarian metastases. Intestine, breasts, stomach and kidneys were the origins of scalp metastases. Metastatic carcinomas can be recognized by histopathology, extensive immunohistochemical examination and anamnestic data. Cutaneous metastases can have wide range of clinical presentation, but mostly present as nodules.

Materials and Methods: We present a case of a patient with cutaneous metastases being the first manifestation of gastric adenocarcinoma.

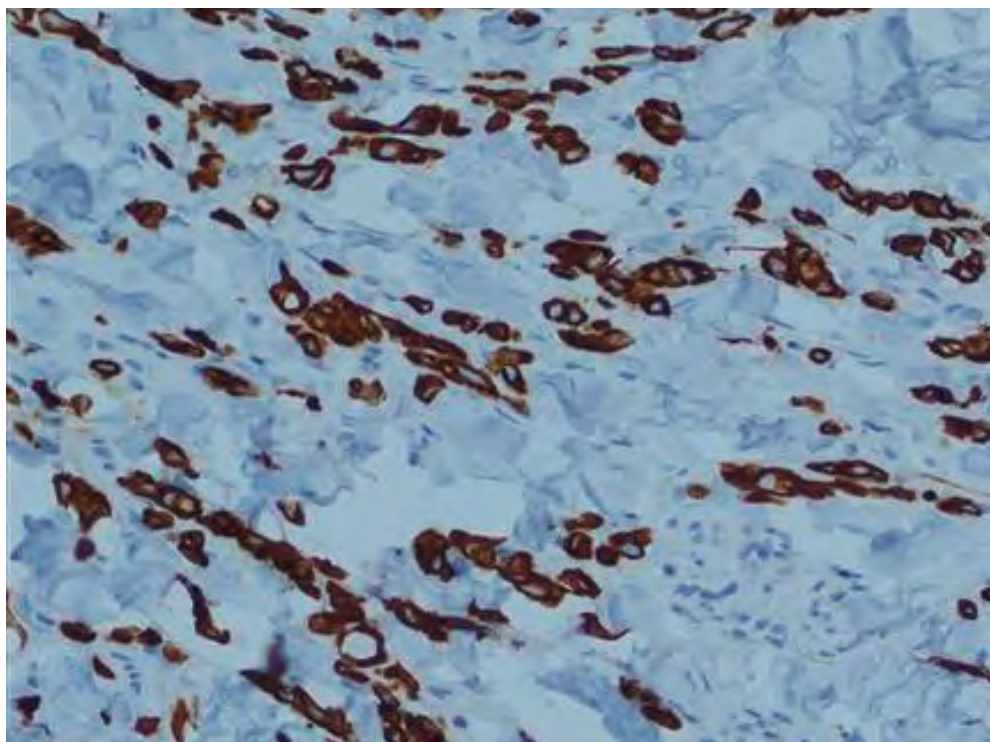
Results: A 61-year-old female patient was referred to our Department because of newly developed erythematous nodules on the skin of the back of her neck (Figure 1). At the same time she reported unintentional weight loss, painful spasms in gastric area and faster intestine transit time. She had no history of any severe diseases. As her symptoms began in the era of coronavirus disease 2019 (COVID-19) pandemic, after a year of extensive diagnostic procedures, she was diagnosed with diffuse gastric adenocarcinoma. Histopathological examination of her skin biopsy revealed cutaneous metastasis, that was confirmed with immunohistochemical cytokeratin (CK)-7 positivity (Figure 2). In the next year-and-a-half our patient underwent surgery, followed by chemotherapy in several cycles. Despite therapy, her metastatic disease progressed extensively. Multiple cutaneous metastases on her trunk were treated with radiotherapy which led to severe post-irradiation reaction. Unfortunately, despite all treatment, she passed away.

Conclusions: If cutaneous lesion is the first representation of silent primary growth, clinical morphology, histopathological and immunohistochemical findings of skin biopsy alongside patient's sex and age are very important for diagnosing primary neoplasm. It is important to emphasize dermatologist's role in early recognition and differentiation of right diagnosis.

Supporting Document 1



Supporting Document 2



Cylindrocarcinoma of the scalp. A case report.

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Dra. Monika Rondan¹, Prof Gabriel Krygier¹**

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Introduction: Cylindrocarcinoma represents a group of extremely rare tumors, reporting less than 80 cases in literature. Malignant transformation of cylindroma is rare. Here we present a case of cylindrocarcinoma of scalp with multiple recurrences.

Presentation of case: A66-year-old woman presented with hyperemic plaque located on his scalp. Resected on multiple occasions, with conventional surgeries and MOSHS techniques with a final diagnosis of cylindrocarcinoma in 2019. In April 2020, MRI revealed meningeal metastasis. She receives concurrent radiotherapy with cisplatin, with complete clinical response (fig.1-2). In May 2021, relapse with pulmonary metastases. She receives carboplatin-paclitaxel and pazopanib since 09/2021 to 10/2022 with stable disease, then progression and dead.

Discussion: Cylindrocarcinoma develops from the adjoining glands of the skin, the benign counterpart being cylindromas (along with eccrine spiradenomas and spiradenocylindromas). It is controversial if they derive from apocrine or eccrine structures. The coexistence of cylindromas and trichoepitheliomas may reflect a common origin in the embryological follicle-sebaceous-apocrine unit. They are usually aggressive tumors. There are no guidelines that support therapeutic behaviors. In localized disease, the cornerstone of treatment is conventional or Mohs surgical resection with wide margins (minimum 2cm). Although the evidence does not come from randomized clinical trials, adjuvant radiotherapy may be indicated to reduce local relapses. There is no evidence of benefit from adjuvant chemotherapy or prophylactic lymph node dissection. In metastatic disease (preferentially lung and pleural disease), different drugs have been evaluated in case reports. It is often suggested that they are chemoresistant. Some drugs evaluated: 5fu, CDDP, and doxorubicin. Although the evidence is scarce, this patient responds to pazopanib.

Conclusion: There is no consensus on the best comprehensive treatment for this tumor, owing to its rarity and limited experience with therapy. In any case, close follow-up for early detection of recurrence and metastases is strongly recommended.

Cytometry and machine learning based approaches for detection of malignant cells in Sézary syndrome

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Introduction and Objectives: Sézary syndrome (SS) is a leukemic variant and an aggressive form of cutaneous T-cell Lymphoma (CTCL), which represents around 15% of CTCL cases. The overall median survival of this disease is 32 months from initial diagnosis. Due to the clinical similarity to benign inflammatory diseases and the heterogeneity of the tumor cells, the current diagnostic methods show limitations and may cause diagnostic delays. Therefore, there is an unmet need for new, more accurate methods to establish diagnosis of the disease. In this study, we explore the potential of combining (I.) label-free imaging flow cytometry (IFC) or (II.) Mass cytometry (CyTOF) with artificial intelligence (AI) algorithms to uncover tumor-defining cells in SS.

Materials and Methods: We established a mass-imaging approach to acquire large-scale single-cell data from peripheral blood. The datasets were analysed by a trained AI model, called CellCnn. CellCnn is a supervised machine learning algorithm that trains a convolutional neural network with a single layer using labelled single-cell data or labelled datasets as inputs. The prediction and classification were done by data-driven analysis. As for the mass-cytometry study, we included a discovery cohort of 60 individuals (20 patients with SS, 20 patients with atopic dermatitis (AD), and 20 HDs) and a validation cohort of 33 individuals (11 individuals of each group). Algorithm performance was assessed with area under the curve (AUC), specificity and sensitivity.

Results: We successfully developed the first machine learning method for morphology based diagnosis for SS samples. The CellCNN approach delivered the best separation of Sezary (84.6% abnormality) and healthy specimens (13.9% abnormality) in comparison with other machine learning models. This is also the first label-free imaging cytometry and weakly-supervised machine learning method to discriminate healthy and diseased samples in general. For a more bench-to-bedside translational approach, we combined mass-cytometry based techniques with AI. Our algorithm can sensitively and specifically identify tumor-defining SS cells in blood according to their pattern.

Conclusions: The result achieved zero false positives and only one false negative prediction with a high accuracy. Our findings pave the way for an easy-to-implement and sensitive diagnostic approach to facilitate early detection of Sézary syndrome and other tumors with blood involvement.

Does atypical fibroxanthoma require more attention than we thought? Importance of the MDT and a need for more guidance.

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Introduction and Objectives: Atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS) are part of the same spectrum of cutaneous malignancy, sharing many clinicopathologic features with some key histological differences, with more aggressive features pointing towards PDS(1). Currently, there is no designated follow-up guidance for AFX/PDS in the UK, although some recommendations exist elsewhere(2,3). We sought to share our experience of this topic to help formulate guidance in this area.

Materials and Methods: We retrospectively reviewed all cases of histologically confirmed AFX and PDS managed at our institution from October 2014 – December 2020, focussing specifically on MDT involvement, recurrence rate and subsequent diagnosis of keratinocyte malignancy.

Results: Our search yielded 28 cases of PDS and 53 of AFX, with key demographic and recurrence data shown in Table 1. Of note, out of the 11 PDS cases that underwent a pre-excision biopsy, 4 biopsies initially diagnosed AFX histologically, and 3 were concluded indistinguishable (AFX vs. PDS). All PDS excision cases went to MDT, where close follow-up was arranged, mirroring that of high-risk SCC. In AFX cases, 20 cases (37.7%) received similar close follow-up as part of an MDT approach. There were 29 AFX cases (54.7%) that had either no formal MDT discussion or were discharged within 1 year of excision. Out of the 7 AFX recurrence cases, 4 were either not discussed at MDT or discharged within 1 year. As many as 47.2% of AFX cases returned for excision of a new keratinocyte neoplasm, with a mean diagnosis time of 23.8 months (range 3-68 months).

Conclusions: Our single-centre experience highlights the need for specific recommendations for AFX/PDS. While AFX is widely considered a less aggressive neoplasm, our experience suggests these cases would still benefit from an MDT approach and close follow-up, particularly regarding the risk of further UV associated cutaneous neoplasms. For example, a proposed 3-year follow-up would have picked up 86% of AFX recurrence and 72% of subsequent keratinocyte neoplasms.

Supporting Document 1

Table 1

	PDS	AFX
Total cases	28	53
Mean age (years)	80.7 (range 62-96)	77.3 (range 42-92)
Sex (M:F)	27:1	49:4
Location (Scalp: Head and Neck: Other)	24:3:1	38:15:0
Mean follow-up duration (months)	26.8 (range 5-58)	31.7 (range 0.06-92)
Recurrence	4 (14.3%) Local skin: 3* Metastasis and mortality: 1	7 (13.2%) Local skin: 5Δ Distant skin: 2
Time to recurrence (months)	19 (range 3-43)	29 (range 7-48)
Subsequent diagnosis of keratinocyte neoplasm	10 (35.7%)	25 (47.2%)

* n=1 presumed, died of prostate cancer before biopsy

Δ n=1 distant PDS

Exploring ‘immunologic pruritus’ in Sézary syndrome and atopic dermatitis using targeted spatial transcriptomics

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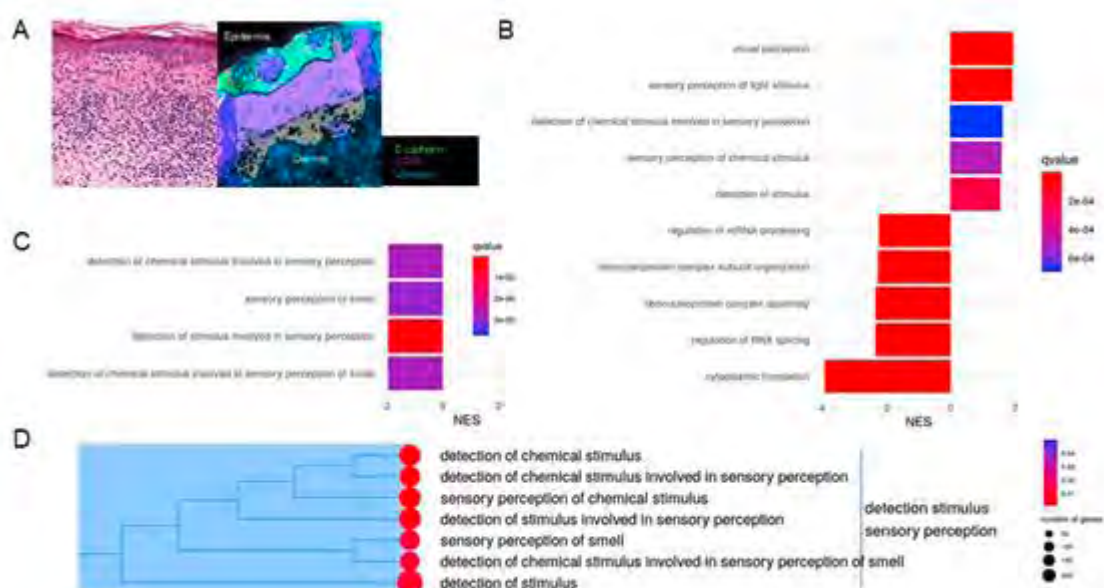
Introduction: Sézary syndrome (SS) is an aggressive type of cutaneous T-cell lymphoma (CTCL), where clones of malignant lymphocytes accumulate in the skin, lymph nodes and blood. >94% of patients report intractable pruritus (itching) leading to a significantly reduced quality of life. However, common antipruritic treatments are ineffective. Similar to SS, atopic dermatitis (AD), a benign inflammatory skin disease, presents with pruritus and characteristic cutaneous infiltration of predominant T-helper 2 (Th2) immune cells. In this project, we investigate the transcriptional signature of immune cells within the cutaneous microenvironment (CME) to identify common pruritic pathways and to assess the potential repurposing of novel antipruritic medication for AD targeting the “immunologic pruritus” in CTCL.

Materials and Methods: Spatial differential gene expression (DGE) of archived skin samples of SS patients (with and without pruritus, n=6), AD (n=3) and age matched healthy donors (n=3) was profiled using GeoMx digital spatial profiler. Immunofluorescent staining of formalin fixed paraffin embedded tissue was used to select epidermal keratinocytes (E-cadherin) as well as subepidermal immune cells (CD45) and fibroblasts (Vimentin) (Figure 1A). In 96 cell-specific regions of interest, Human Whole Transcriptome Atlas with >18'000 genes were quantified.

Results: Comparing networks of hierarchical gene ontology (GO) pathways within the immune cell segment (CD45+) characterized different biologic function of malignancy (SS, downregulated $\alpha\beta$ -T-cell differentiation, p=0.0004) and inflammation (AD, Figure 1B). Clustered analysis of DGE comparing equivalent areas of AD to SS with and without pruritus identified a pruritus-specific gene signature and impaired sensory perception within the immune cell segment (CD45+) in SS (Figure 1C). SS with and without pruritus mainly differed in the neural system activation such as up-regulated sensory perception of chemical stimulus on epidermal level (E-Cadherin+) in pruritic skin samples (Figure 1D).

Conclusion: Applying high dimensional spatial profiling on clinically relevant samples unveils differences in the CME of “immunologic pruritus”. Identified candidate biomarkers will be further validated on protein level. Findings highlight the contribution of the peripheral neuronal system to pruritic sensation in SS suggesting the neuro-immune interaction as a possible therapeutic target in pruritic lymphoproliferative disorders.

Supporting Document 1



Incidence, Local Recurrence and Metastasis of Dermatofibrosarcoma Protuberans: A nationwide Cohort Study of 40 Years

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Introduction and Objectives: Dermatofibrosarcoma Protuberans (DFSP) is a rare, low-grade cutaneous neoplasm with relatively unexplored prognosis. Despite its rarity, it is the most common cutaneous sarcoma. Reliable estimates of incidence, local recurrence, and metastasis are sparse in current literature and data on follow-up examinations is limited. Furthermore, the prognosis of DFSP with fibrosarcomatous transition (DFSP-FS) is unknown. The primary objective was to estimate incidence, local recurrence, and metastasis of DFSP and to propose a standardized follow-up program. The secondary objective was to compare the prognosis of DFSP with DFSP-FS.

Materials and Method: All Danish patients in the period between 1980-2022 with excised DFSP were identified in the Danish National Pathology Register. Annual incidence rates were estimated with the Danish population as reference. The risks of Local DFSP recurrence and metastasis were estimated with cumulative incidence functions with all-cause death as competing risk. The evaluation of risk factors and comparisons between DFSP and DFSP-FS were performed with multivariable Fine-Gray Regression.

Results: We included 603 patients resulting in an incidence of 0.26/100.00/year for DFSP. The median time to follow-up of all patients was 14.6 years (IQR: 7.9-22.7 years). The 5-year risk of local DFSP-recurrence was 6.0% (95% CI: 4.2-8.2) and the 5-year risk of metastasis was 1.2% (95% CI: 0.56-2.4). Positive margins at the primary excision significantly increased the risk of local recurrence, HR 8.07 [95% CI: 3.98-16.4] ($p < 0.001$). Fibrosarcomatous transition significantly increased the risk of local recurrence, HR 4.48 (95% CI: 1.80-11.2), $p < 0.001$ with a 5-year risk of local recurrence of 25.2% (95% CI: 5.5-40.8). Age, sex, and anatomical localization was not associated with a poor outcome in either group.

Conclusions: Patients with DFSP should be followed every four months during the first two years and then twice a year until the fifth year as most of the events occurred within this time period. The value of follow-up beyond five years is limited as the risk of both local recurrence and metastasis after this timepoint is $<2\%$. Further studies are needed to evaluate risk factors such as surgical management to decrease risk of recurrence.

Supporting Document 1

Figure 1



Figure 1: Cumulative incidence functions of the risk of local recurrence for DFSP (yellow) and DFSP-FS (blue) in patients over 20 years. Cumulative events and the total number of patients at risk are provided in the risk tables.

Increased chlormethine induced DNA double stranded breaks in malignant T cells from mycosis fungoides skin lesions

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Background: Mycosis fungoides (MF) is a type of cutaneous T-cell lymphoma. Chlormethine (CL) is recommended as first line therapy for MF, with a major purpose to kill tumor cells through DNA alkylation.

Materials and Methods: To study the extent of treatment susceptibility and tumor specificity, we investigated the gene expression of different DNA repair pathways, DNA double-stranded breaks, and tumor cell proliferation of clonal TCR Vb+ tumor cell populations in cutaneous T-cell lymphoma skin cells on direct exposure to CL.

Results: Healthy human T cells were less susceptible to CL exposure than two T-lymphoma cell lines, resulting in higher proportions of viable cells. Interestingly, in T cells from MF lesions, we observed a downregulation of several important DNA repair pathways, even complete silencing of RAD51AP1, FANC1, and BRCA2 involved in homologous recombination repair. In the presence of CL, the double-stranded DNA breaks in malignant MF skin T cells increased significantly as well as the expression of the apoptotic gene CASP3.

Conclusion: These data point toward an important effect of targeting CL on MF skin tumor T cells, which support CL use as an early cutaneous lymphoma treatment and can be of synergistic use, especially beneficial in the setting of combination skin-directed therapies for cutaneous T-cell lymphoma.

Intralesional T-VEC in cutaneous B-cell lymphoma

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Introduction and Objectives: Primary cutaneous B-cell lymphomas (pCBCL) are a group of lymphoid malignancies, primarily presenting on the skin. Intralesional oncolytic virotherapy with Talimogene laherparepvec (T-VEC) showed efficacy and is approved for cutaneous melanoma. Previous studies with oncolytic virotherapy in cutaneous lymphomas showed positive results; hence, we investigated intralesional T-VEC in patients with CBCL.

Materials and Methods: Patients with CBCL were enrolled into the single centre, single arm, open label phase I clinical trial with intralesional T-VEC (NCT03458117). The first intratumoral injection of $\leq 4\text{ml} \times 10^6$ PFU/ml was followed by an increased dose of $\leq 4\text{ml} \times 10^8$ PFU/ml 3 weeks later and then every two weeks for up to 8 injections. We assessed clinical response of injected and non-injected lesions using response criteria for intratumoral therapies, and safety by CTCAE v5 criteria. To assess T-VEC induced tissue changes, we collected tumor biopsies prior and during treatment. We performed multiplex immunohistochemistry for CD3, CD8, CD79a, CD56, CD11c and FoxP3 and used Akoya Bioscience technology for evaluation.

Results: Nineteen patients with three pCBCL subtypes were enrolled into the trial: marginal zone lymphoma (8pts), follicle center lymphoma (8pts) and diffuse large B-cell lymphoma (3pts). The median age was 60y (range, 33-85y). Eighteen patients have received at least one T-VEC injection with a median of seven injections, one patient withdrew consent before treatment start. Twelve patients (67%) demonstrated response of injected lesions, two (11%) were complete responses. Treatment related adverse events (trAEs) occurred in 73% of patients, one of them grade 3. Most common trAE were fever and flu-like symptoms (32% each). Tissue for analysis was available in 12 cases. CD79a+ cells decreased in all samples after 2 T-VEC injections. CD8+ cells increased and FoxP3+ cells decreased in responding lesions, compared to marginal changes in non-responding lesions. T-VEC led to an increase of CD56+ cells in all analyzed samples.

Conclusions: Intralesional T-VEC induces clinical responses and activates immune response in CBCL lesions. The treatment was well tolerated without any unexpected toxicities in this patient population. T-VEC merits investigation in larger controlled clinical trials.

Long-term clinical outcomes of Spitz-type lesions in adults: a single institution retrospective cohort review

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Background: The lack of information on clinical outcomes of Spitz-type lesions, means that their management remains a contentious issue, with some centres opting for a purely conservative, observational approach, while others mandate further surgery and long-term follow-up. Our aim was to therefore determine the long-term clinical outcome of classic Spitz and spitzoid naevi, atypical Spitz tumours (ASTs) and spitzoid melanomas, with a view to finding evidence to support a unified management approach.

Methods: We conducted a retrospective cohort review of Addenbrooke's Hospital patients aged ≥ 18 years with a histopathologic diagnosis containing the term "Spitz", from 1991 through 2020. Sentinel lymph node biopsy (SLNB) results, metastases and fatality were assessed.

Results: 126 patients with Spitz-type proliferations and follow-up information were identified (mean age:35.9, SD:11.6). There were 86 (68.3%) classic Spitz or spitzoid naevi, 12 (9.5%) ASTs, 27 (21.4%) spitzoid malignant melanomas and 1 (0.8%) melanoma that arose in a previously-excised Spitz naevus. SLNB findings were positive in 3 of 7 but none of the 10 individuals with ASTs and spitzoid melanomas, respectively. There were 4 cases of invasive non-Spitz melanomas occurring in those with Spitz-type lesions, all of whom also had either classic Spitz and spitzoid naevi. Following a median follow-up of 46 months (range: 1-304), only 1 patient with an AST, who had a distinct malignant melanoma (2.4mm, level 4), developed distant metastases with 100% survival.

Conclusions: While no fatalities or subsequent melanomas were identified in those with ASTs, the positive SLNBs and case of distal metastasis suggests a need for careful surveillance. Whereas, the relatively indolent course of spitzoid melanoma cases indicates that a re-evaluation of the 5-year follow-up approach is reasonable. Similarly, the benign clinical behaviour of classic spitz and spitzoid naevi supports reconsideration of recommendations for more aggressive management such as wide local excision and SLNB. These finding support previous work and extend the findings to a large European cohort for the first time.

Lymphomatoid papulosis in pediatric population: results of a multicenter retrospective cohort study

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Background: Lymphomatoid Papulosis (LyP) is a rare cutaneous T-cell lymphoproliferative disorder. Comprehensive data on LyP in the pediatric population is scarce.

Objectives: To better characterize epidemiological, clinical, histopathological and prognostic features of pediatric LyP.

Methods: This was a retrospective, multicenter international cohort study including 87 cases of children and adolescents with LyP diagnosed between 1998 and 2022. Patients from 0 to 18 years old at disease onset were included. Diagnosis was made in each center based on clinicopathological correlation.

Results: Eighty-seven patients from 12 centers were included. The mean age at onset was 7.1 years (range 3 months-18 years) with female to male ratio 1:2. The mean time between onset of first cutaneous lesions and diagnosis was 1.3 years (range 0-14 years). Initial misdiagnosis concerned 26.4% of patients. LyP was most commonly misdiagnosed as PLEVA, insect bites, or mollusca contagiosa. Erythematous papules or papulonodules were the most frequent morphological presentation, occasionally accompanied by ulceration. The main histology subtype was A in 56.4% of the cases. If analyzed, monoclonal TCR rearrangement has been found in 76.5% of the skin biopsies. The overall survival rate was 100% with follow up at 5 years available for 27 patients and at 15 years for six patients. A development of associated Hematological Malignancy (HM) occurred in 9.6% of the cases (7/73), with primary cutaneous Anaplastic Large Cell Lymphoma diagnosed in 2 patients, Mycosis Fungoides in 4 cases, and one case of Acute Myeloid Leukemia. Diagnosis of associated HM preceded the diagnosis of LyP in one case, was co-diagnosed with LyP in 2 patients and occurred after for the others, once more than 10 years after LyP onset.

Conclusions: We report epidemiological data from a large cohort of children and adolescents with LyP. Due to increased risk of associated HM, a long-term follow-up should be recommended for LyP patients.

Merkel Cell Carcinoma with Atypical Location and Presentation

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Introduction and Objectives: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine cutaneous malignancy with high propensity for recurrence and metastases. MCC typically presents in older immunocompromised individuals with lightly pigmented skin, as a rapidly expanding, deep red, cherry-shaped, asymptomatic nodule in a sun-exposed head and neck area. We present an atypical case of a MCC presenting as a long-standing large plaque on the axillae.

Materials and Methods: A 60 year old Chinese woman with a past medical history of hypertension, aortic regurgitation and essential thrombocythemia presented with a 2 year painful scaly erythematous plaque on her right axillae. The lesion was increasingly tender and became nodular 2 weeks prior to presentation. She was not on immunosuppressives. Her skin phototype was IV. Examination of the right axillae showed a large 6x7cm erythematous plaque with a 2cm fleshy erythematous fungating weepy nodule centrally (Fig 1). There was associated right axillary lymphadenopathy.

Results: Skin biopsy was performed. Histopathological examination shows psoriasiform epidermal hyperplasia with ulcerations, and dermal proliferations of atypical basaloid cells with hyperchromatic nuclei and brisk mitoses that were diffusely positive for cytokeratin 20 (CK20) and weakly positive for chromogranin. No lymph-vascular invasion was seen in histology. Positron emission tomography and computed tomography (PET-CT) scan showed a moderately F-fluorodeoxyglucose (FDG)-avid cutaneous nodule in the right anterior axilla with a cluster of enlarged hypermetabolic right axillary nodes suspicious for nodal metastases. The patient was diagnosed with Stage III merkel cell carcinoma. She underwent sentinel lymph node evaluation, wide local excision of the primary tumour and adjuvant radiotherapy to the right axillae.

Conclusions: While MCC commonly manifests as deep red nodules in the head and neck areas, it may also present as a plaque in sun-protected sites. Patients may not be immunocompromised as well. Given the low incidence and variable appearance, diagnosis of MCC can be challenging. Early lymphogenic spread often leads to locoregional metastases and poorer prognosis, therefore early histopathological examination and diagnosis is crucial. Following initial definitive therapy, patients with MCC should be reviewed closely due to high rates of recurrent disease.

Supporting Document 1



Merkel Cell Polyomavirus Prevalence in a Cohort of 54 Merkel Cell Carcinoma Patients: Correlation with Clinical and Prognostic Data

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Merkel cell carcinoma (MCC) is a rare and aggressive tumor. It's frequently encountered in elderly and immunosuppressive patients, caused by solar damage and Merkel cell polyomavirus (MCPyV). The prevalence of MCPyV in MCC varies depending on the geographical region, with rates of 70-80% in North America and Europe, and 20% in Australia. The aim of this study was to assess the prevalence of MCPyV in Turkey and investigate the clinical, immunohistochemical and prognostic differences between MCPyV(+) and MCPyV(-) subgroups.

Patients diagnosed with MCC at our institution over a 20-year period were scanned from the archives. Immunohistochemical studies were conducted using primary antibodies directed to MCPyV (with two clones: Ab3 and CM2B4), Cytokeratin 20 (CK20) and Ki67. Clinical data were retrieved from patient files.

The study group consisted of 54 patients, aged 24-91 years (mean age 67). Four patients, including the youngest of the group were organ transplant recipients and were under immunosuppressive treatment. Cutaneous tumors were found on extremities (50%), head-neck (33.3%) and trunk (16.7%). Twelve cases with no cutaneous lesion but MCC in lymph nodes were diagnosed as nodal MCC. At admission, 18.5% of patients were in stage I, 25.9% in stage II, 46.3% in stage III and 9.3% in stage IV.

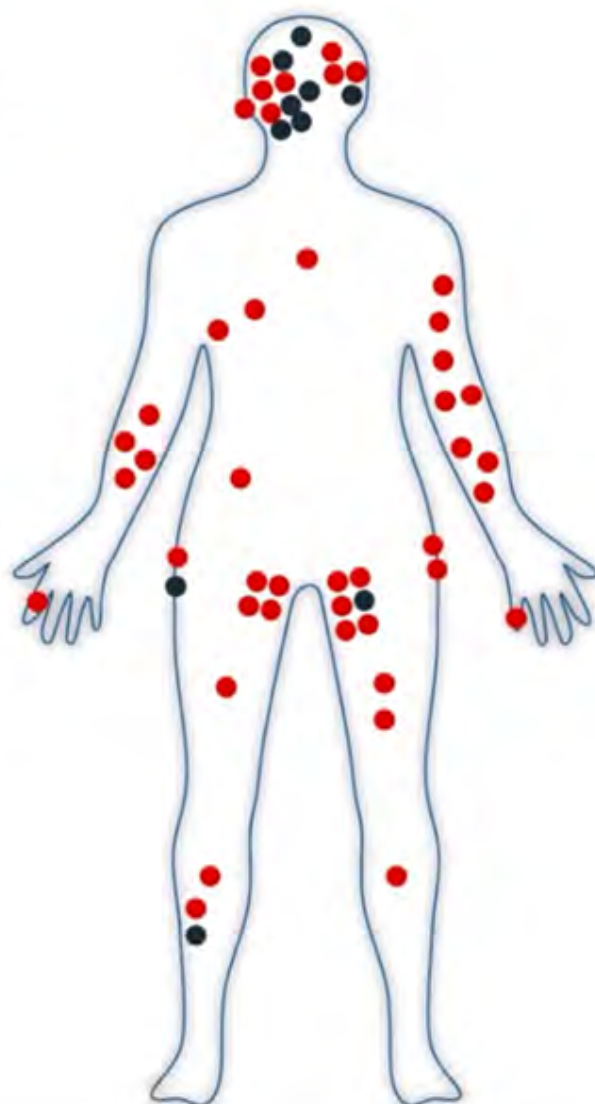
Immunohistochemical study using MCPyV clone Ab3 revealed that 44/54 (81.5%), including 11/12 nodal cases, were MCPyV(+). In five cases, MCPyV clone CM2B4 was negative, but Ab3 was positive. Only two cases were negative with CK20, and these cases were also MCPyV(-). The mean Ki67 scores were assessed as 54.7% in MCPyV(+) and 71.3% in MCPyV(-) groups ($p=0.020$). Distribution of primary tumors with respect to MCPyV status is shown in Figure (A). In this series, disease-related death rate was 39.6%, mean expected survival time was 111.5 months for MCPyV(+) patients, whereas 50 months for MCPyV(-) patients ($p=0.393$).

MCPyV prevalence in this cohort from Turkey was similar to those reported from Europe. Our study revealed higher Ki67 scores and shorter survival times for MCPyV(-) cases. Moreover, we demonstrated that MCPyV Ab3 is a more sensitive clone than CM2B4 and can facilitate the diagnosis of MCC, particularly in nodal cases.

Supporting Document 1

MCPyV (+): ●

MCPyV (-) : ●



Molecular Profiling To Guide Treatment For Eccrine Carcinoma

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Eccrine carcinomas represent a rare subset of skin cancer thought to arise from cells lining the eccrine sweat ducts. There are several types of eccrine carcinoma which range on a spectrum of locally aggressive tumors to those with metastatic potential.¹ As with other cutaneous malignancies influenced by ultraviolet damage, eccrine carcinomas may be associated with a high tumor mutational burden (TMB) resulting in promising response rates to immune checkpoint inhibitors (ICIs) or may have actionable mutations for which a targeted therapy is available.²⁻⁵ To date, there is no standard of care for the treatment of metastatic eccrine carcinoma. We present data from one institution highlighting the potential use of molecular profiling to guide therapy in these complex patients.

Patients with unresectable or metastatic skin cancer at the University of Pennsylvania were queried from 2016 to 2023. Data on treatment and outcome were collected on patients with eccrine carcinoma.

We identified 6 patients with a diagnosis of unresectable or metastatic eccrine carcinoma [Table 1]. Five (5) patients (83%) underwent molecular profiling of their tumor. One (1) patient with metastatic porocarcinoma and high TMB treated with anti-PD1 therapy had a near complete response. There was also 1 patient identified with a BRAF V600E mutation who responded to BRAF inhibitor therapy. An additional 4 patients had no actionable mutations and were treated with ICIs. Only one of those patients had stable disease (SD).

These data, although limited, identify the importance of molecular profiling in patients with eccrine carcinomas to help guide treatment. Particularly in the case of metastatic porocarcinoma, high TMB may be associated with improved outcomes. Next generation sequencing (NGS) may also reveal targetable mutations such as our patient with a BRAF mutation. While expansion is needed, molecular profiling is an important tool which should be obtained in all patients with unresectable eccrine carcinomas to offer the best potential treatment options.

Supporting Document 1

Histology	Molecular profiling	Treatment	Best response
Eccrine carcinoma	BRAF p.V600E c.1799T>A TP53 p.? c.559+1G>T	Dabrafenib + Trametinib	Partial response
Acralsyringeal carcinoma	STK11 p.P281Rfs*6 c.842delC TP53 p.F109S c.326T>C ERBB4 p.G936V c.2807G>T	Cemiplimab	Stable disease
Porocarcinoma	CDH1 p.S851* c.2552C>G FBXW7 p.S546* c.1637C>G RB1 p.K577Rfs*34 c.1730delA TP53 p.Y220N c.658T>A FBXW7 p.? c.1419-1G>C JAK1 p.S198* c.593C>G STAG2 p.S1256* c.3767C>G TSC2 p.A607V c.1820C>T	Pembrolizumab	Near complete response
Microcystic adnexal carcinoma	DNMT3A p.Y623* c.1869C>G PTCH1 p.Y204* c.612delC TP53 p.R213* c.637C>T BRIP1 p.S895F c.2684C>T MED12 p.H458Y c.1372C>T NOTCH1 p.S137L c.410C>T RAC1 p.P34S c.100C>T RET p.E428K c.1282G>A TGFB2 p.G424R c.1270G>A	Cemiplimab	Progression of disease
Apocrine adnexal carcinoma	TP53 p.R158H c.473G>A TP53 p. c.376-1G>C CTNNB1 A116V c.347C>T NF2 p.R338C c.1012C>T	Pembrolizumab	Progression of disease
Apocrine adnexal carcinoma	No NGS	Pembrolizumab + carboplatin + paclitaxel	Progression of disease

Phase II clinical trial of docetaxel and trastuzumab for HER2-positive advanced extramammary Paget's disease (EMPD-HER2DOC)

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Purpose: Currently, there is no consensus on the optimal chemotherapy for metastatic cases of extramammary Paget's disease (EMPD), a rare cutaneous adenocarcinoma, due to the lack of solid evidence. This phase II single-arm trial was designed to evaluate the benefit of the docetaxel and trastuzumab combination for HER2 positive metastatic EMPD, and to establish the first evidence for the use of chemotherapy for EMPD.

Patients and Methods: Thirteen Japanese HER2-positive metastatic EMPD patients received intravenous trastuzumab (loading dose of 8 mg/kg and maintenance dose of 6 mg/kg) and docetaxel 75 mg/m² administration every 3 weeks for up to 2 years. Docetaxel dose was reduced or discontinued according to its toxicity. The primary endpoints were objective response rate (ORR) after 3 cycles and safety throughout the study period.

Results: All of 13 patients completed 3 cycles of combination therapy. The ORR after 3 cycles was 76.9% (n = 10/13; 90% CI: 50.5-93.4) including 5 complete responses (38.5%) and 5 partial responses (38.5%). 12 patients continued treatment and 3 patients (23%) maintained an initial response at the data cut-off point. The median progression free survival was 9.3 months (95% CI: 5.8-30.4) and the median overall survival (OS) could not be estimated because the estimated OS at the last time of 49.3 months was over 50% and three-year survival rate was 53.7% (95% CI: 20.1% to 78.6%). Frequently observed adverse events were neutropenia (100%), hypoalbuminemia (84.6 %), alopecia (76.9 %) and mucocutaneous infection under neutropenia (84.6 %), all of which were well managed. There was no treatment related death.

Conclusion: This study demonstrated that a favorable clinical effect and acceptable tolerability of docetaxel and trastuzumab combination for HER2 positive metastatic EMPD. Further trials including larger populations will be necessary to establish the true safety and efficacy of this treatment.

Phosphaturic Mesenchymal Tumor Along the Hallux side Inducing a Chronic non-Healing Wound: A Case Report

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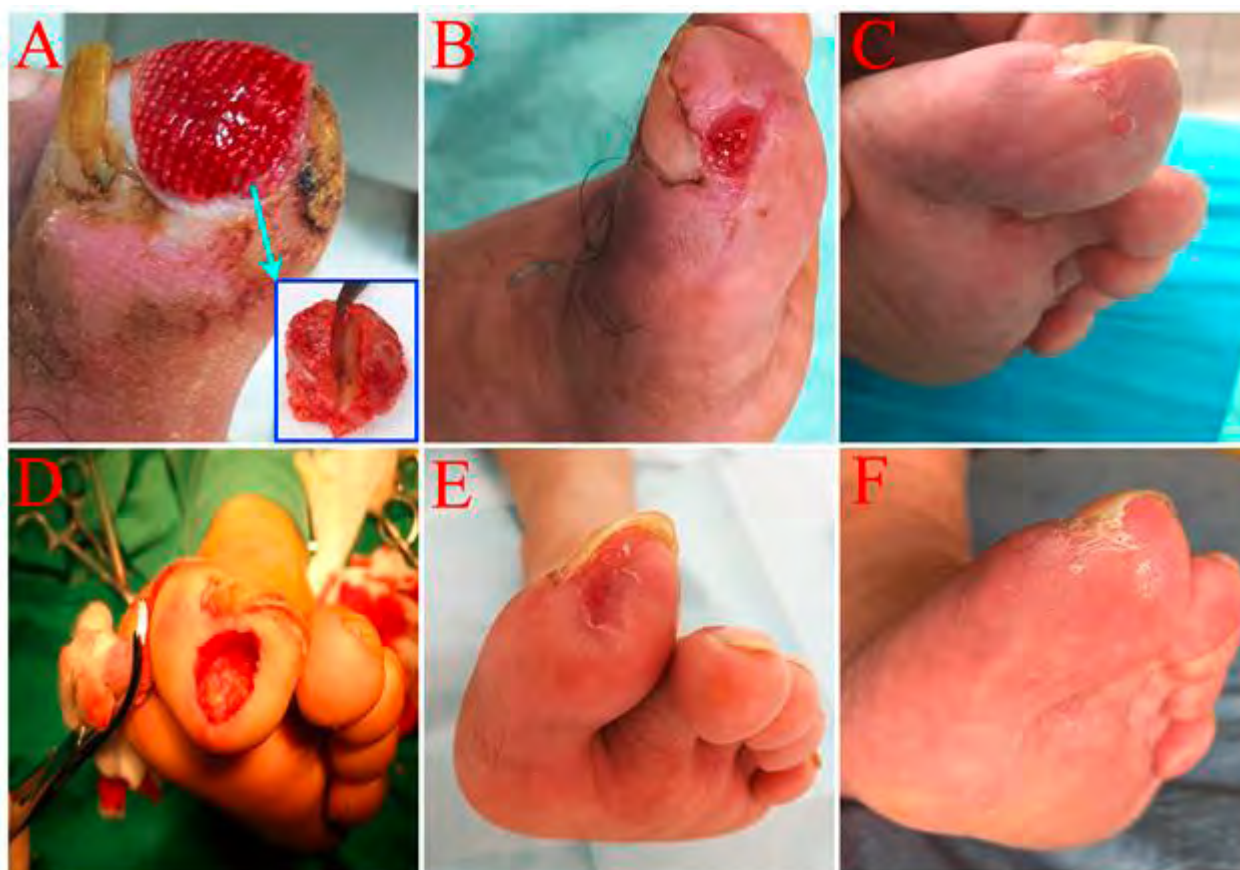
Introduction: Phosphaturic mesenchymal tumor (PMT) is a rare tumor that originates from mesenchymal tissue. PMT produces a substance known as fibroblast growth factor 23 (FGF23). Most patients suffer from fatigue, bone pain, pathological fractures, hypophosphatemia, phosphaturia, and osteomalacia. The diagnosis of PMT is very difficult because of its insidious and small size, especially, when it appears in subcutaneous tissue with a chronic non-healing wound.

Methods: We report a rare case of a 38-year-old man with a chronic non-healing wound on the left hallux for approximately eight months. Complete surgical resection of the tumor is believed to be the most effective treatment measure. Radiographic images, Pathologic examination, immunohistochemistry, ELISA, and RT-PCR were used to investigate the association between PMT and chronic non healing wound.

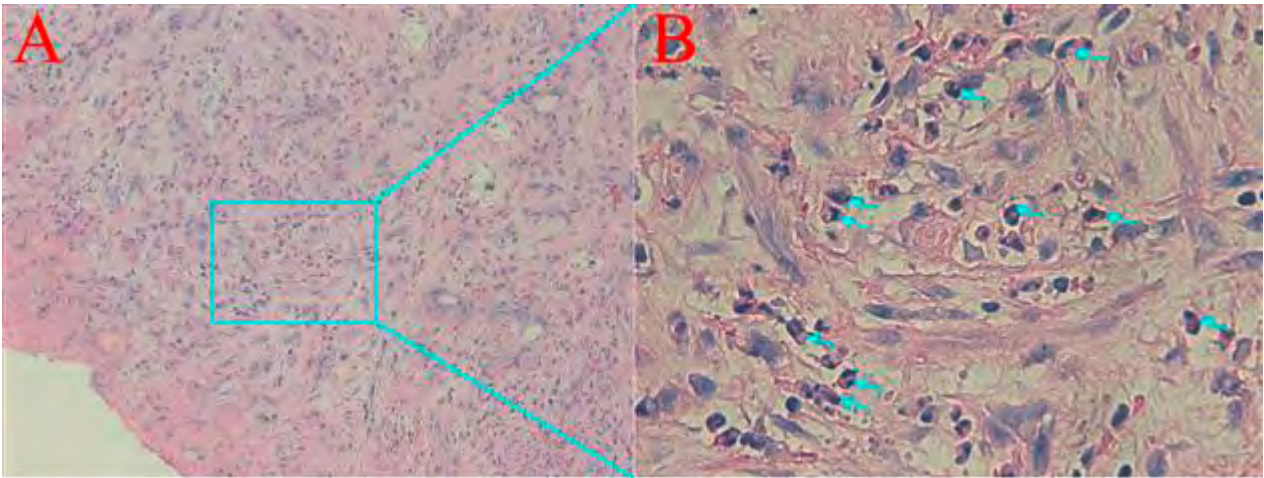
Results: Plain radiographic images and magnetic resonance imaging (MRI) revealed a cystic radiolucent shadow in the left distal phalanx. Bone scan observations also showed increased uptake in the same location. Histologically, this tumor was composed of numerous spindle cells with clusters of giant cells. The serum FGF23 level was significantly higher before surgery, with higher FGF23 levels closer to the tumor. RT-PCR and immunohistochemistry further confirmed the high expression of FGF23 in tumors. The tumor was CD56- and D2 to 40-positive and CD31-negative.

Conclusions: The diagnostic basis of PMT mainly includes gross evidence, pathological evidence, and even immunohistochemical evidence. FGF23 may be a potential causative factor of PMT. The serum FGF23 levels might be useful for the diagnosis of PMT and localization of the tumor. The non-healing wound caused by PMT might be attributed to the invasive growth of the tumor, destruction of intercellular junctions, and decrease in the number of endothelial cells.

Supporting Document 1



Supporting Document 2



Pleomorphic dermal sarcoma – a diagnostic and therapeutic challenge

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Introduction: Pleomorphic dermal sarcoma (PDS) is a rare tumor of mesenchymal tissue that predominantly affects sun-exposed areas of older adults, with a predilection for the scalp. This neoplasm shares characteristics with atypical fibroxanthoma, however it is more associated with aggressive biological behavior, frequently with local recurrence and possible distant metastasis.

Material, Methods, and Results: An 84-year-old male presented to the dermatology department with a one-year history of multiple slowly enlarging lesions on his left shoulder. He also reported a weight loss of 15% in this period. He denied local or other systemic symptoms. He had a personal history of prostate cancer in remission but no previous skin cancers. We observed a conglomerate of erythematous-brown, firm, and ill-defined nodules in the anterior region of the left shoulder and axilla, occupying a maximum of 7 cm in length. Incisional biopsy revealed a dermal neoplasm with focal extending to the adipose tissue, characterized by pleomorphic spindle-shaped cells with several mitotic figures. Immunostaining was positive for CD10, CD68 and smooth muscle actin, but CK7, CK20, S100, SOX10, beta-catenin, STAT6, MUC4, CD10, CD34, TLE-1, GLUT-1, PSA, desmin and h-caldesmon were negative. These findings suggested pleomorphic dermal sarcoma. Magnetic resonance imaging revealed tumor infiltration up to the muscular plane, mainly in the clavicular portion of the deltoid muscle and in the lateral fibers of the pectoralis major muscle. Computed tomography ruled out regional or distant metastasis. The lesion was submitted to a wide local excision, but tumoral involvement of deep margins was noted. The patient was evaluated by a sarcoma multidisciplinary team, and it was decided to start adjuvant radiotherapy. 3D-Conformal Radiation Therapy was performed with a total dose of 66Gy (6MV photons). Within 4 months of radiotherapy, he remains without clinical or radiological evidence of recurrence.

Discussion: Currently, there are no published guidelines directed to the diagnosis, management, and follow-up of PDS. Surgical treatment with wide location excision remains the first-line therapy and adjuvant radiotherapy and/or systemic therapy agents should be considered for advanced disease. This case represents an atypical localization for PDS with aggressive local behavior, that needed combined therapies to achieve remission.

Polymorphic cutaneous post-transplant lymphoproliferative disorder in a lung transplant patient

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Background: Post-transplant lymphoproliferative disorders (PTLD) are lymphoid and plasmacytic proliferations that can occur in individuals who have received solid organ or allogeneic hematopoietic cell transplants, due to the immunosuppression and decreased T cell immune surveillance. In most affected patients, PTLD is caused by the proliferation of Epstein-Barr virusinfected B cells and can present as a wide range of clinical manifestations, from benign lymphoid hyperplasia to aggressive lymphomas.

Methods: We present the case of a 69-year-old man who underwent a lung transplant in 2020 for idiopathic pulmonary fibrosis. He sought medical attention due to the appearance of a plaque on his left knee about three months prior to the visit. The physical examination revealed an erythematous violaceous plaque with indurated hyperkeratotic nodules that were painless and mildly pruritic.

Results: A skin biopsy was performed on one of the nodules which showed a mixed polymorphic infiltration with a plasmacytic and B lymphocytic component (CD20+, CD79a+) associated with a T-type lymphocytic component (CD3+). There were also some areas of necrosis and scattered Reed-Stenberg type cells (CD30+). Evaluation using in situ hybridization methods with RNA probe (EBER) highlighted the presence of EBV in many lymphoid elements, while the molecular investigation revealed a clonal rearrangement for the immunoglobulin heavy chains. Based on the morphological, immunohistochemical, and molecular characteristics (EBER mRNA), a diagnosis of EBV-related PTLD was made.

Conclusions: Polymorphic PTLD (P-PTLD) is characterized by the presence of a monoclonal infiltrate of B lymphocytes in all stages of maturation, which subverts and destroys the architecture of the affected tissue but does not fully meet the diagnostic criteria for lymphoma. Immunophenotypically, B lymphocytes show monoclonal rearrangement of immunoglobulin genes, and EBV is usually evident within tumor cells by in situ hybridization. P-PTLD can occur at any time after transplantation, and reducing immunosuppression is the main therapeutic strategy.

Patients who do not respond to this treatment may require more aggressive therapeutic options, such as immunotherapy with monoclonal antibodies (rituximab), chemotherapy, or a combination of both.

In conclusion, despite its rarity, PTLD should be considered in the differential diagnosis of lateonset skin complications in solid organ transplant recipients.

Primary Cutaneous B-cell Lymphomas: Treatment Results of 33 cases and Atypical Presentations

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Introduction and Objectives: Primary cutaneous B-cell lymphomas (PCBCL) represent approximately 20-25% of all cutaneous lymphomas. Management and prognosis vary between subtypes. The aim of this study is to present a report on demographics, classification, treatment and outcomes of PCBCL patients in Greece, as well as to present cases with atypical clinical presentation.

Materials and Methods: This study consists of PCBCL patients who were monitored in the National Centre of Excellence of cutaneous lymphoma in Greece, for 4 years, from December 2018 to December 2022, classified according to the WHO-EORTC criteria. Diagnosis was verified with the aid of histopathological and immunohistochemical analysis. Further examination with computed tomography (CT) and bone marrow examination, to exclude systemic involvement, was performed in compliance with the European guidelines.

Results: 33 patients were included, 16 male and 17 female, aged 27-88 years (median 41) at diagnosis and without extracutaneous involvement. The distribution among the different PCBCL subtypes was as follows: 19 patients with primary cutaneous marginal zone lymphomas (PCMZL), 12 patients with primary cutaneous follicle center lymphomas, 2 patients with primary cutaneous diffuse large B-cell lymphomas. Treatment management included surgical excision (n = 8), localized radiotherapy (n = 14) and systemic therapy with rituximab (n=4) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone, n=2), but also 'wait and see' (n = 4), intralesional steroids (n=5) and topical steroids. 24 patients achieved complete remission and 9 achieved partial remission. During the follow-up of 4 years there were six cutaneous relapses but no nodal or metastatic spread.

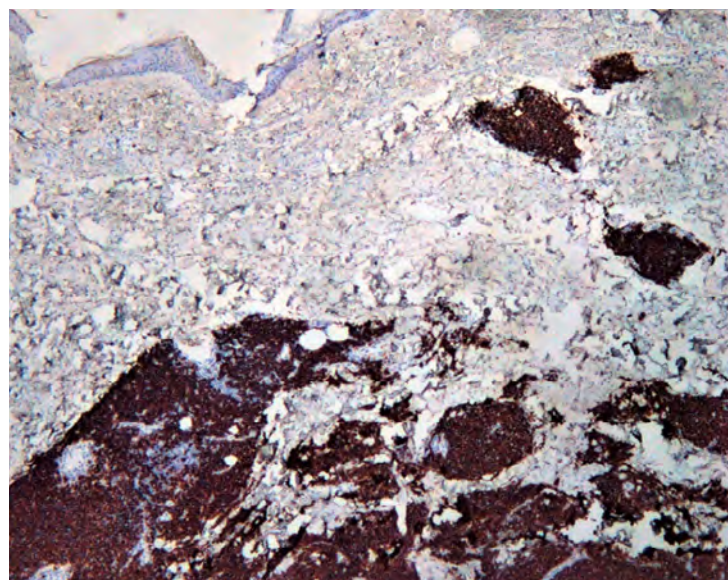
2/19 PCMZL cases presented with subcutaneous nodules. The histology reveals a B-cell lymphoid infiltration in subcutaneous cell tissue, without epidermal changes, and with immunohistochemical studies of CD20+, CD79+, Bcl2+, Bcl6-, CD10-, CD5-, CD23-, Ki67 15-30%. These two cases appear to have a more aggressive behavior, with resistance to radiotherapy and rituximab and frequent cutaneous relapses.

Conclusions: Most of PCBCL patients present with solitary or clustered nodules, however we present an atypical presentation with subcutaneous nodules. Surgical excision and radiotherapy are highly effective in marginal zone and follicular center PCBCL, although there are some cases that appear to be resistant to treatment.

Supporting Document 1



Supporting Document 2



Primary cutaneous mucinous carcinoma in an elderly woman: A rare entity

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Introduction: Primary cutaneous mucinous carcinoma (PMCM) is a rare malignant tumor of sweat gland origin. In general, PCMC is a slow-growing tumor with an indolent behavior, which predominantly affects the face and scalp of elderly male patients. This tumor can be difficult to diagnose due to its clinical and histological similarities to other skin conditions, including metastatic breast and colon mucinous adenocarcinomas.

Material, Methods, and Results: We report a case of an 80-year-old female patient with no significant medical history, who presented to our dermatological department with a 2-years nodule on the scalp. The nodule was increasing gradually in size with occasional mild pain, but without bleeding or discharge. Dermatologic examination revealed an 18x15mm, elevated, dome-shaped, erythematous-violaceous tumor on the left occipital region. Clinical examination and extensive laboratory, radiographic, and endoscopic studies did not reveal distant primary disease. The lesion was resected with free tumor margins. Histopathology revealed a circumscribed tumor with large amounts of mucin compartmentalized by fibrous septa and scattered floating islands of tumor cells in the dermis. Immunohistochemical studies stained positive for CK7. According to the observed clinical and laboratory characteristics, PMCM diagnosis was assumed. No local recurrence, regional lymph node involvement, or distant metastasis was observed during the follow-up.

Discussion and Conclusion: Clinical and radiological evaluation, histology, and immunochemistry play a crucial role in the diagnosis of PCMC. Microscopically, it is characterized by nests of neoplastic epithelial cells floating in mucinous lakes, with more organized nests, less hyperchromasia, and less mitosis compared to secondary mucinous carcinoma deposits from other tissues. Immunohistochemical markers, such as CK7, CK20, CDX2, TTF1, D2-40, and p63, aid in the diagnosis, but still inconsistently differentiate PCMC from metastatic mucinous adenocarcinomas of the breast. Exclusion of metastatic disease is crucial, so complementary evaluation, such as mammography, colonoscopy, computed tomography and/or PET, should be performed. This report case highlights the diagnostic complexity of this rare adnexal tumor.

Primary cutaneous osteosarcoma of the scalp. Presentation of one case and review of the literature

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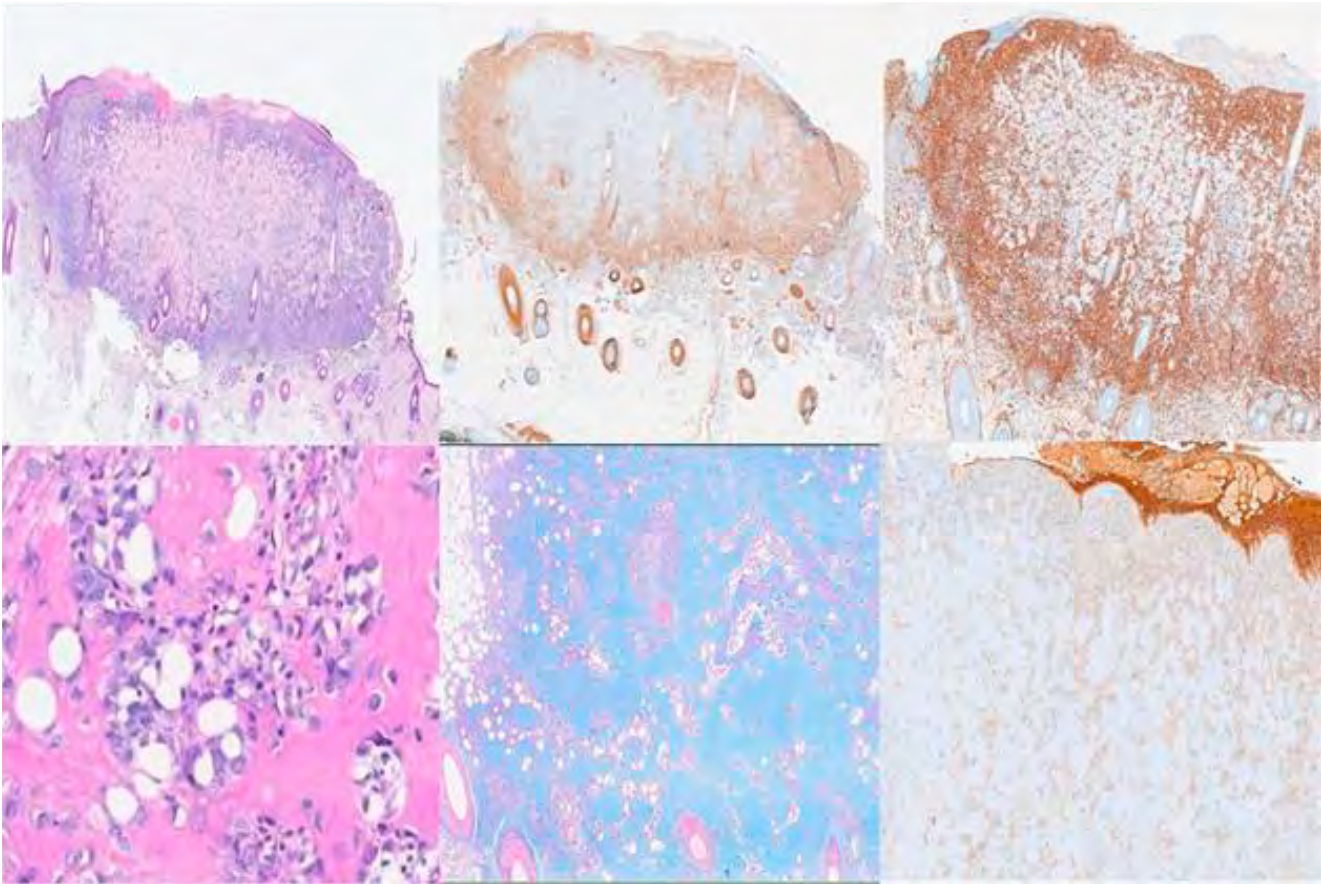
Clinical case: A 90-year-old woman with no significant medical history presented with a rapidly growing solitary nodule in the midfrontal region. The nodule had a keratotic surface and a diameter of 15 mm with a crateriform appearance. There were no palpable locoregional adenopathies. Histology revealed a well-defined, ulcerated tumor in the superficial/mid dermis. The lesion was composed of a proliferation of occasionally spindle-shaped polygonal cells surrounding extensive eosinophilic areas of osteoid matrix and surface calcification. The tumor cells exhibited abundant mitotic figures and expressed SATB2 and vimentin with a high proliferation index (Ki-67). However, they did not express cytokeratins (CK20, CK7, AE1-3, 34 beta E12, and CAM5.2), CEA, EMA, CDX2, p40, caldesmon, smooth muscle actin, muscle-specific actin, desmin, p63, p40, S100, SOX10, GATA-3, ERG, CD34, CD31, or CD68. Fluorescence in-situ hybridization (FISH) with the double probe MDM2 (12p15)/CEP12 did not show amplification. The extension study (cervical and thoraco-abdominal CT) did not reveal any evidence of extracutaneous involvement. Primary cutaneous osteosarcoma (PCO) was the definitive diagnosis. A surgical excision with 7mm oncological was performed. At the 6-month follow-up, the patient did not show any clinical or radiologic sign of recurrence.

Discussion: PCO is a rare subtype of extraskeletal osteosarcoma. Differential diagnosis should consider rare variants of melanoma, atypical fibroxanthoma with bone metaplasia, metaplastic carcinoma (carcinosarcoma), sarcomatoid basal cell carcinoma, and metastatic cutaneous osteosarcoma. In this case, the histopathological and immunohistochemical findings, and the absence of an underlying bone/extraskeletal osteosarcoma, allowed for the establishment of the diagnosis. Surgery remains a crucial and potentially curative treatment for this type of sarcoma, which has a better prognosis than other types of tumors in the same lineage. The benefit of other approaches such as Mohs surgery has been reported in isolated cases. In conclusion, this case provides an opportunity to review the clinicopathological characteristics of PCO, including its diagnostic challenges, treatment, and prognosis.

Supporting Document 1



Supporting Document 2



Role of neutrophils to lymphocyte ratio (NLR) in patients with mycosis fungoides

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Background: the neutrophil/lymphocyte ratio (NLR) at diagnosis, has been shown to correlate with advanced disease and to be a prognostic factor in many tumors. However, its role as a prognostic factor for mycosis fungoides (MF) has not been yet clarified.

Objective: our study aimed to evaluate the correlation of NLR with stages of disease in patients with MF, to define whether or not higher values of this marker correlate with a more aggressive disease.

Methods: we retrospectively analyzed NLR in a total of 302 newly diagnosed MF patients. NLR was calculated using the complete blood count (CBC) data.

Results: median NLR among patients with the non-advanced disease (low-grade IA-IB-IIA) was 1.88, while the median NLR for patients with advanced disease (IIB-IIIA-IIIB) was 2.64. Statistical analysis showed positive associations of advanced MF stages with NLR higher than 2.3.

Conclusions: our analysis demonstrates that NLR represents a cheap and easily available parameter which could be used as a marker for advanced MF. This could help identify patients with advanced stages of disease requiring a strict follow-up.

Squamoid Eccrine Ductal Carcinoma: a rare tumor

Squamoid Eccrine Ductal Carcinoma: A Rare Tumor Carla Bochi¹, **Squamoid Eccrine Ductal Carcinoma: A Rare Tumor** Paulo Marcos Ribeiro Sampaio¹, **Squamoid Eccrine Ductal Carcinoma: A Rare Tumor** Ciro Paz Portinho¹, **Squamoid Eccrine Ductal Carcinoma: A Rare Tumor** Ana Paula Barreto Garcia¹, **Squamoid Eccrine Ductal Carcinoma: A Rare Tumor** Sabrina De Stefani¹, **Dr Eduardo Bertolli²**, **Squamoid Eccrine Ductal Carcinoma: A Rare Tumor** Sérgio Luís Thiesen Hilgert¹, **Squamoid Eccrine Ductal Carcinoma: A Rare Tumor** José Neri da Silva¹, **Squamoid Eccrine Ductal Carcinoma: A Rare Tumor** Juliana Ribeiro Bertelli¹, **Squamoid Eccrine Ductal Carcinoma: A Rare Tumor** Roberta Barcellos Venturella¹

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Introduction and Objectives: Squamoid eccrine ductal carcinoma (SEDC) is a poorly documented skin adnexal carcinoma with sweat duct differentiation, first described in 1997. Most cases were reported in small series with limited follow-up information. The tumors are largely confined to sun-damaged skin, particularly of the head and neck. It usually happens in the elderly. This disease has a high rate of local recurrence, regardless of completeness of excision. This is likely due to the deep and diffusely infiltrative growth of the tumor and the frequent presence of perineural infiltration.

Material and Methods: A 75-year-old woman was first diagnosed with a squamous cell carcinoma on the nose after a skin biopsy. A Mohs Micrographic surgery was performed. In the third phase, bone invasion was identified, and biopsy diagnosis was questioned as deeper aspects of the tumor started evidencing sweat duct differentiation. The surgery was interrupted as we needed to wait for hematoxylin and eosin-stained sections review and immunohistochemistry results for carcinoembryonic antigen and epithelial membrane antigen to achieve the validation of diagnosis. It is not uncommon for this tumor to be taken as a squamous cell carcinoma due to the superficial aspects, these tumors show only squamous differentiation with epidermal connection. Generally, diagnosis is validated when the tumor is fully analyzed.

Results: The SEDC was excised with 1 cm margins given the tumor extension. The resection margins were tumor-free. The nasal reconstruction with forehead flap was safely performed. Adjuvant radiotherapy was indicated because of perineural invasion. This patient has now been followed for three months without recurrence.

Conclusions: An accurate and reliable diagnosis of SEDC is particularly challenging. Considering the potential for aggressive behavior and the associated implications for treatment, a well-grounded diagnosis is needed.

Supporting Document 1



Supporting Document 2



Tertiary lymphoid structures and chemokine landscape in virus-positive and virus-negative Merkel cell carcinoma

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Introduction and Objectives: Merkel cell carcinoma (MCC) is a rare malignant skin cancer with potentially high immune activity. MCC is treated with immune checkpoint inhibitors (ICIs), but the response rate is only about 30%, and many patients exhibit no benefit. Tertiary lymphoid structures (TLSs) are used as biomarkers in many cancers for assessing the response to ICIs. In Merkel cell carcinoma (MCC), TLSs have only been examined in MCPyV-positive cases. We investigated the usefulness of TLS as a biomarker in a cohort that included MCPyV-negative MCC.

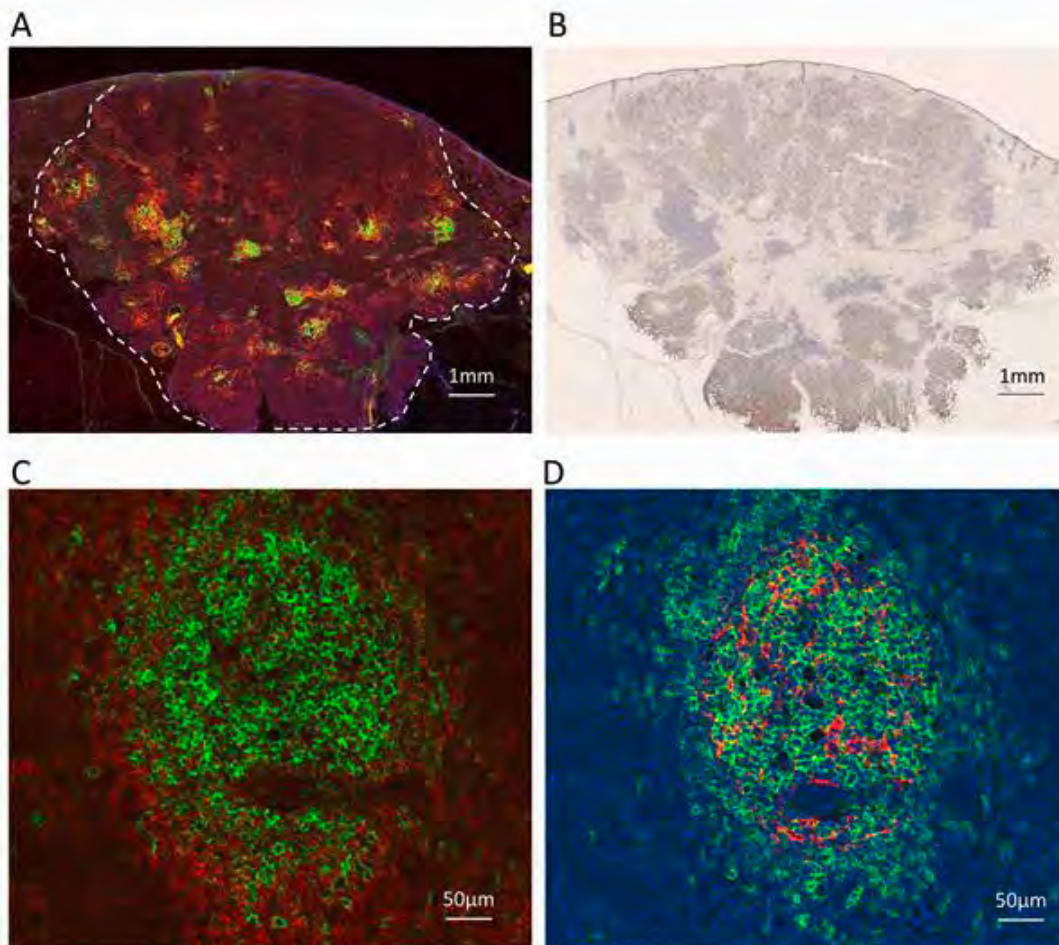
Materials and Methods: We examined 71 samples from 61 Japanese patients with MCC diagnosed histologically based on biopsy or surgical resection samples obtained in 9 facilities. We also comprehensively analyzed the chemokines associated with TLS formation using next-generation sequencing.

Results: TLS-positive samples had a significantly better prognosis than TLS-negative samples. MCPyV-positive samples had a good prognosis with or without TLSs, and MCPyV-negative/TLS-positive samples had a similarly good prognosis as MCPyV-positive samples. Only MCPyV-negative/TLS-negative samples had a significantly poor prognosis. Interestingly, all cases with spontaneous regression after biopsy were MCPyV-positive/TLS-positive. The RNA sequencing results revealed 5 chemokine genes, CCL5, CCR2, CCR7, CXCL9, and CXCL13, with significantly high expression in TLS-positive samples compared with TLS-negative samples in both MCPyV-positive and MCPyV-negative samples. Among them, two chemokine genes, CXCL13 and CCL5, were specific for TLS formation. On the other hand, 2 chemokine genes, CXCL10 and CX3CR1, had significantly different expression levels on whether MCPyV was positive or negative. Patients with high CXCL13 or CCL5 expression have a significantly better prognosis than those with low expression.

Conclusions: TLSs can be a useful prognostic marker in MCPyV-negative MCC, which is ultraviolet-induced and has many genetic mutations and neoantigens. On the other hand, MCPyV-positive MCCs seem to have a different mechanism of tumor immune activation. Elucidation of this mechanism will help us understand tumor immunity in MCC, which is strange compared to other tumors. Chemokine profiles may help us understand the tumor microenvironment in patients with MCPyV-positive or MCPyV-negative MCC and may be a useful prognostic marker in their own right.

Supporting Document 1

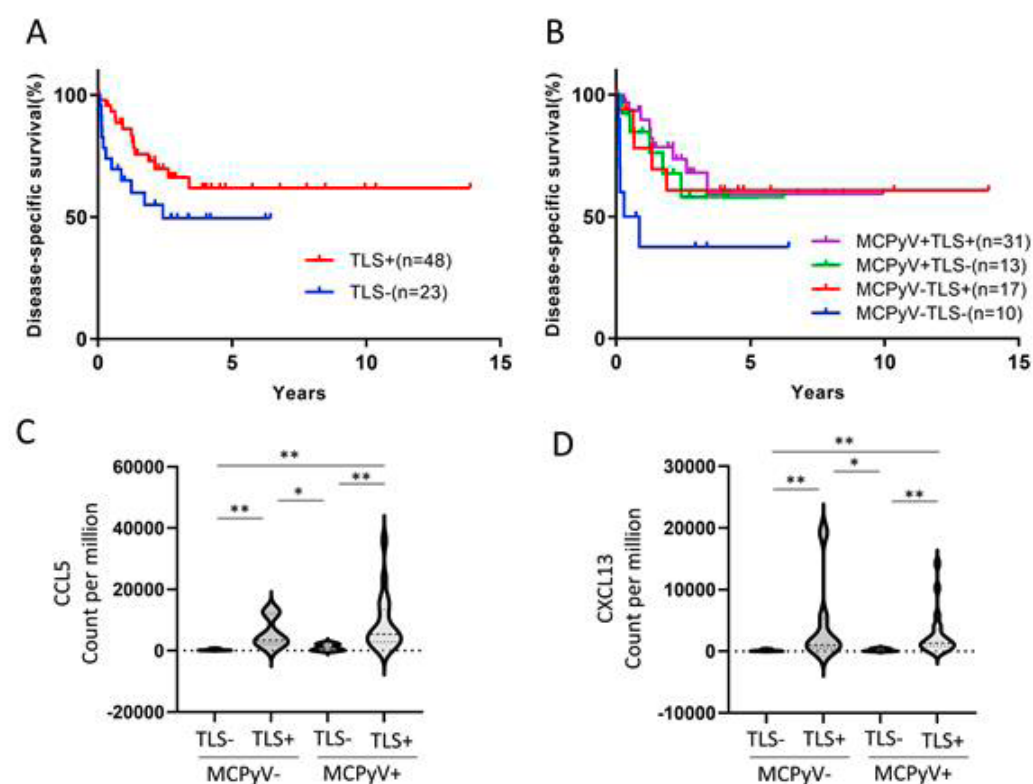
Figure 1

**Figure 1**

(A) TLSs in Merkel cell carcinoma. Triple immunofluorescence staining for CD20 (green), CD3 (red), and DAPI (blue). The broken line indicates the tumor border. Scale bar, 1 mm. (B) Immunohistochemical staining for MCPyV large T antigen (CM2B4, brown). Scale bar, 1 mm. TLSs were observed inside the tumor's stroma, but not in the surrounding area. (C) Representative high magnification image of the mature TLS. CD20 (green), CD3 (red), Scale bar, 100 μ m. A cluster of CD20-positive cells is surrounded by CD3-positive cells. (D) Representative high-magnification image of the same mature TLS. CD20 (green), CD21 (red), and DAPI (blue). Scale bar, 100 μ m. CD21-positive follicular dendritic cells (FDCs) were observed within a cluster of CD20-positive cells.

Supporting Document 2

Figure 2

**Figure 2**

(A) Kaplan-Meier curves for the samples with or without TLSs. Gehan-Breslow-Wilcoxon test, $p=0.0468$. (B) Kaplan-Meier curves for the samples with or without TLSs and MCPyV infection. Logrank test for trend, $p=0.0497$.

(C, D) Violin plots of CCL5 and CXCL13 were highly expressed in TLS-positive samples. * $p \leq 0.05$, ** $p \leq 0.01$, Steel-Dwass test

Therapeutic Outcomes and Survival Analysis of Extramammary Paget's Disease: A multicentre retrospective study of 249 patients.

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Introduction and Objectives: Extramammary Paget's disease (EMPD) is an uncommon skin disorder with potential to become invasive and/or metastatic over time. Evidence regarding long-term therapeutic outcomes and disease-specific survival (DSS) in EMPD is limited. The aim of this presentation is to assess the clinical course, DSS, treatment schedules and outcomes of surgical and nonsurgical therapeutic modalities in a large cohort of EMPD patients.

Materials and Methods: Retrospective chart review of EMPD patients visiting 20 Spanish tertiary-care hospitals between 1990-2022.

Results: Data on 249 patients with a median follow-up of 60 months (range 6-324) were analyzed. The median age at diagnoses was 71 years (range: 37-95), and the most common affected site was the female genitalia (57.4%). Dermal invasion was observed in 22.1% of patients (Table 1). The estimated 5, 10 and 15-year DSS was 95.9%, 92.9%, and 88.5% respectively. The presence of deep dermal invasion (≥ 1 mm) and metastatic disease were the unique variables significantly associated with decreased DSS ($p < 0.05$). A $\geq 50\%$ disease improvement was achieved in 100%, 91.3% and 75.3% of patients treated with surgery, radiotherapy and topical therapies (including imiquimod, 5-fluorouracil and photodynamic therapy), respectively. Regarding the histological margin status, tumor-free resection margins were obtained in only 42.4% of the patients treated with wide local excision (WLE). The 5-year recurrence-free survival (RFS) after Mohs micrographic surgery (MMS), WLE with tumor-free margins, WLE with positive margins, radiotherapy and topical treatments was 63.0%, 51.4%, 20.4%, 30.1% and 20.8%, respectively (Figure 1).

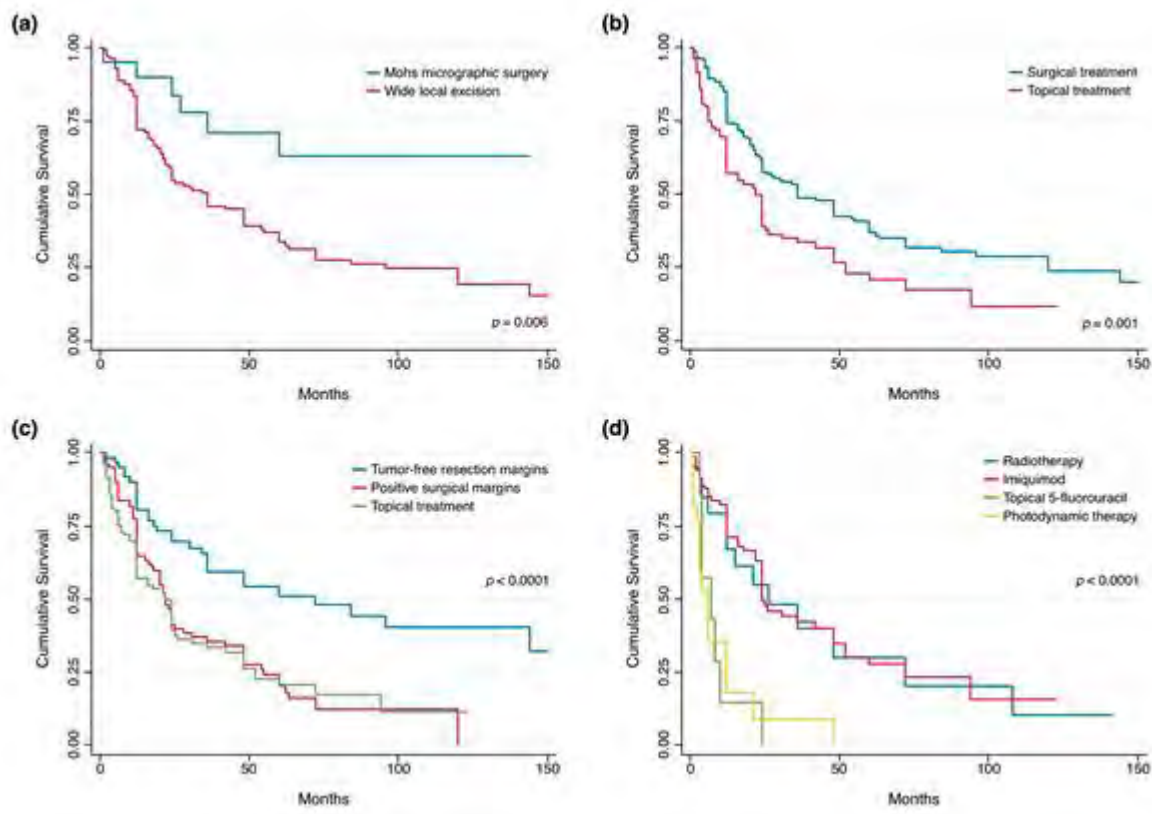
Conclusions: EMPD is usually a chronic condition with a favorable prognosis. MMS represents the therapeutic alternative with the greatest efficacy and RFS of the disease. A high percentage of patients treated with WLE exhibit positive margins after surgery, and local recurrence rate in such scenario is similar to the one observed in subjects treated with topical agents. The knowledge of the clinical course and the long-term therapeutic outcomes of the different treatment modalities of EMPD could help clinicians in the management of this condition.

Supporting Document 1

Table 1. Clinical and demographic features of study population

Characteristic	
Sex	
Female, <i>n</i> (%)	178 (71.5%)
Male, <i>n</i> (%)	71 (28.5%)
Median age at diagnosis, years (<i>range</i>)	71 (37-95)
Median diagnostic delay, months (<i>range</i>)	12 (0-240)
Site of presentation	
Female genitalia, <i>n</i> (%)	143 (57.4%)
Perianal, <i>n</i> (%)	60 (24.1%)
Inguinal, <i>n</i> (%)	38 (15.3%)
Male genitalia, <i>n</i> (%)	31 (12.5%)
Perineum, <i>n</i> (%)	17 (6.8%)
Others, <i>n</i> (%)	25 (10.0%)
≥1 site, <i>n</i> (%)	49 (19.7%)
Median lesion size, mm (<i>range</i>)	50 (3-200)
Associated malignancies, <i>n</i> (%) ¹	41 (16.5%)
Dermal invasion ²	
All, <i>n</i> (%)	55 (22.1%)
< 1mm, <i>n</i> (%)	24 (57.1%)
≥ 1mm, <i>n</i> (%)	18 (42.9%)
Lymphovascular invasion, <i>n</i> (%)	9 (3.6%)
Regional and/or distant metastases, <i>n</i> (%)	20 (8.0%)
Median number of treatments, <i>n</i> (<i>range</i>)	2 (0-13)
Initial treatment	
Wide local excision, <i>n</i> (%)	149 (59.8%)
Mohs micrographic surgery, <i>n</i> (%)	15 (6.0%)

Supporting Document 2



Vogt-Koyanagi-Harada disease associated with Primary Cutaneous Anaplastic Large Cell Lymphoma

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Introduction: Vogt-Koyanagi-Harada disease is a rare disorder of unknown origin that affects many body systems, including the eyes, ears, skin and the covering of the brain and spinal cord. The disease is initially characterized by headaches, very deep pain in the eyes, dizziness, vertigo, and nausea. These symptoms are followed by uveitis, blurring vision and in a few weeks the retina may detach.

Materials and Methods: We present the case of a 54 years old female diagnosed in 2015 with Vogt-Koyanagi-Harada disease. The disease begun with severe headache, eye inflammation and blurring. Some weeks later exudative retinal detachment was noticed. The testing modalities as FFA, ICG and OCT assisted the diagnose of Harada disease. In 2021 she presented several large painful, exudated and purulent ulcers on the back and limbs. The edges of the ulcers were undermined. They started as very painful small pustules which developed slowly. The pathergy test was positive and the biopsy confirmed the presence of a neutrophilic infiltrate compatible with Pyoderma Gangrenosum. 2 months after the ulcers of Pyoderma Gangrenosum were almost healed, she presented 2 large painful firm abscesses in the femoral region. The histological examination confirmed the diagnoses of Primary Cutaneous Anaplastic Large Cell Lymphoma. The patient started the treatment and death occurred 4 months later due to an Acute Renal Insufficiency.

Discussion: Pyoderma Gangrenosum is an uncommon, ulcerative cutaneous condition of uncertain etiology. It is associated with systemic diseases in at least 50% of patients who are affected mainly with Inflammatory Bowel disease, Rheumatoid Arthritis, Leukaemia and Monoclonal Gammopathy, usually IgA. There is no evidence since now in which Pyoderma Gangrenosum is associated with rare diseases. Also, there are no strong evidences that show the association of Vogt-Koyanagi-Harada disease with Lymphoma. There are publications that suggest that some manifestation of Lymphoma can resemble or mimic a Vogt-Koyanagi-Harada disease.

An invasive squamous cell carcinoma within a plaque of Mycosis Fungoides; An extremely rare case.

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Introduction and Objectives: Mycosis Fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma (CTCL). Cutaneous squamous cell carcinoma (SCC) is a common type of keratinocytic or non melanoma skin cancer. Despite the fact that patient with MF have increased risk for both primary hematologic malignancies and secondary solid tumors; development of SCC in skin affected by MF is extremely rare. As reported in the literature, SCC might accompany MF secondarily after skin-directed therapies for MF, including total skin electron beam radiation, topical nitrogen mustard, ultraviolet A and narrowband ultraviolet B light (NB-UVB) therapy. Last is used increasingly in MF patients because of its good toleration and well established management. Herein we report a case of a patient who developed a giant SCC on mycosis fungoides plaque with no prior anticancer therapy.

Materials and Methods: A 70-year-old male patient consulted our clinic because of large confluent, hyperpigmented, erythematous, pruritic patches and plaques on trunk, upper and lower extremities. Physical examination revealed a giant of >8cm diameter tumor on a plaque on the right patient's arm. Patient was immunocompetent and his medical history was only notable for hypertension and dyslipidemia. Diagnostic biopsy and immunohistochemistry from both tumor and plaque were performed.

Results: Coexistence of MF and SCC of histological thickness greater than 5mm, poorly differentiated with invasion of the subcutaneous tissue was revealed. Stage of the tumor was assessed to T3N0M0 while stage of MF was assessed to IIB. Treatment consisted of surgical excision of SCC and adjuvant radiotherapy along with systemic methotrexate.

Conclusions: Although increased risk for both cutaneous and internal malignancies in patients with CTCL have been reported, concomitant MF and SCC within the same lesion is extremely rare. Majority of reported cases of SCC in MF patients have been described following treatment with skin directed therapies. However the development of a secondary malignancy in an active CTCL without prior anticancer treatment is of unknown origin. Our patient was immunocompetent and never in the past had received anticancer or immunosuppressant therapy. This case suggests that physicians should be alert and screen for possible cutaneous malignancy in active CTCL lesions.

CemiplimAb-rwlc Survivorship and Epidemiology (CASE): A prospective study of the safety and efficacy of cemiplimab in patients with advanced cutaneous squamous cell carcinoma in a real-world setting

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Introduction and Objectives: Cemiplimab is the first programmed cell death-1 inhibitor to be approved for the treatment of patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or radiation. The aim of this study was to evaluate the use of cemiplimab in real-world conditions in a subgroup of patients with CSCC enrolled in the CASE study (NCT03836105).

Materials and Methods: In this observational study, patients received commercially available cemiplimab 350 mg intravenously every 3 weeks according to standard of care. Prospective data were captured using an electronic case report form. Data collected from 43 US academic and community centers between June 2019 and October 2021 were evaluated and the data relating to objective response rate, survival, and safety (all per investigator assessment) are presented here. Recruitment is ongoing.

Results: As of October 1, 2021, 188 patients were enrolled, of which most were white (>90%) and male (>75%). The cohort was elderly, with a median age of 76 years (range, 33–98), and 19.1% considered either immunocompromised or immunosuppressed. Median duration of cemiplimab exposure for all patients was 22.1 weeks (interquartile range, 9.1–46.4; range, 0–117). Efficacy was evaluated in patients enrolled before Cycle 3 (n=164), when a clear treatment outcome could be established. Objective response rate in the overall population was 42.1% (95% CI, 34.4–50.0) and in the immunocompromised or immunosuppressed population (n=27) objective response rate was 44.4% (95% CI, 25.5–64.7).

Of the 164 patients, treatment-related adverse events were categorized as immune-related for 47 (25.3%) and serious for eight (4.3%). Cemiplimab was generally well tolerated in immunocompromised or immunosuppressed patients. Overall, 95 (48.2%) patients discontinued treatment.

Conclusions: At this timepoint, the safety, tolerability, and effectiveness of cemiplimab in this real-world study of patients with advanced CSCC were consistent with results observed in the registration clinical trial.

Depletion of the Dyskerin/snRNA complex in cutaneous squamous cell carcinoma promotes metastatic spread by enhancing lipid metabolism.

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Introduction and Objectives: Metastatic cutaneous squamous cell carcinomas (MSCCs) usually involve regional lymph nodes, and occur in approximately 4–5% of patients. In this study we aimed to identify epigenetic mechanisms involved in the dissemination of MSCC and to identify prognostic markers of clinical value that could help identify those patients at increase metastatic risk.

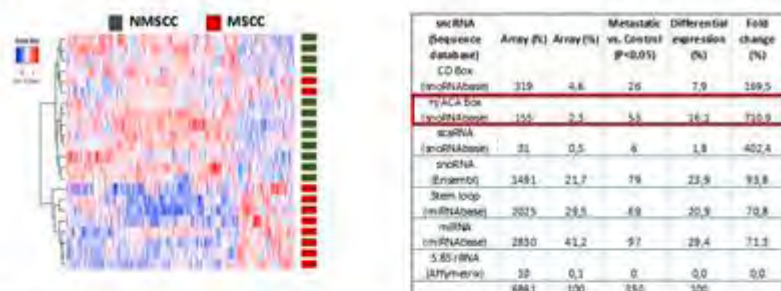
Materials and Methods: The expression of small non-coding RNAs was analyzed in 22 primary cSCC (10 from cSCCs that had evolved to histologically confirmed metastases, and 12 from a cSCC control group who had not developed any metastasis in a 5-year follow-up period). The effects of dyskerin (DKC1) depletion were studied in cSCC cell lines using proteomic, transcriptomic and metabolomic approaches, and the results were functionally validated in vitro. Immunohistochemistry was used to assess protein expression in 107 primary cSCCs and in 39 metastatic samples.

Results: Primary metastasizing cSCCs showed an overall impoverishment in small nucleolar RNAs (snoRNAs) when compared to non-metastasizing cSCCs. Accordingly, the expression of DKC1, the protein that provides stability to snoRNAs, is reduced throughout the progression of cSCC. Downregulation of DKC1 expression in cultured cSCC cells induced a metabolic switch to the mevalonate pathway, potentially increasing cholesterol biosynthesis and the acquisition of metastatic traits in cSCC cells. Treatment of DKC1-depleted cells with simvastatin, an inhibitor of the mevalonate pathway, effectively reduced the levels of proteins involved in migration and metastasis and impaired their metastatic abilities, indicating that the changes at the functional level were due to the metabolic rewiring. Quantitative scoring of the expression of the lipid enzyme HMGCS1 (3-Hydroxy-3-Methylglutaryl-CoA Synthase 1) in primary cSCCs tumors and metastatic samples showed that the mevalonate pathway is associated with cSCC progression, underscoring the relevance of the in vitro data and their translational potential for the clinical management of cSCC patients.

Conclusions: Loss of DKC1 function results in a rewiring of the metabolism and the acquisition of invasive features in cSCC. Our results show the importance of the mevalonate pathway for metastatic dissemination, and will allow new therapeutic strategies exploiting this potential vulnerability of the cancer cell.

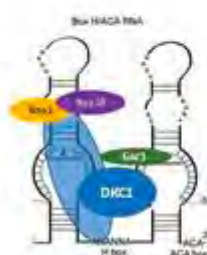
Supporting Document 1

A



sncRNAs differentially expressed in primary metastasizing vs. non-metastasizing cutaneous squamous cell carcinomas (MSCC and NMSCC respectively), identified with the miRNA 4.0 array (Applied Biosystems).

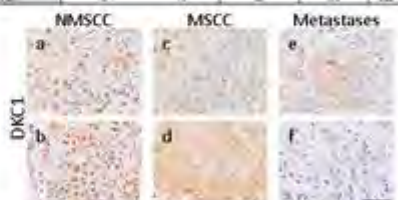
B



H/ACA ribonucleoprotein (RNP) complex

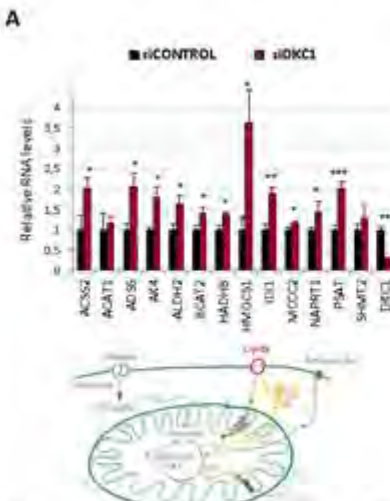
C

	NMSCC n(N)	MSCC n(N)	Primary SCC (NMSCC & MSCC) n(N)	Metastases n(N)	Total
DKC1 positive	16 (71%)	25 (69%)	62 (70%)	27 (33%)	72
DKC1 negative	12 (29%)	11 (27%)	27 (30%)	23 (27%)	50
Total	28	41	89	50	108



DKC1 expression in TMAs of primary NMSCC and MSCC, and in metastases. Initial cohorts: 56 MSCC, 51 non-MSCC and 39 metastases. Below, representative images showing DKC1 immunodetection in independent TMA samples of NMSCC (a, b), MSCC (c, d) or lymph metastases (e, f). Scale bar, 50 μ m.

Supporting Document 2

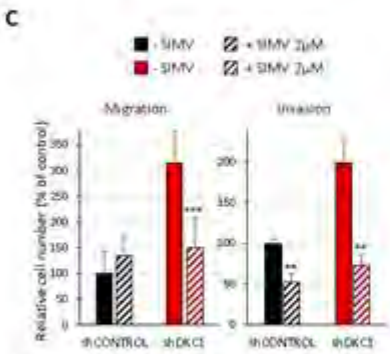


Expression of lipidic genes in the cutaneous SCC cell line UT-SCC12A depleted from DKC1, determined by qRT-PCR. *, $p < 0,05$; **, $p < 0,005$. Below, a drawing that illustrates the metabolic switch in cells following DKC1 depletion.

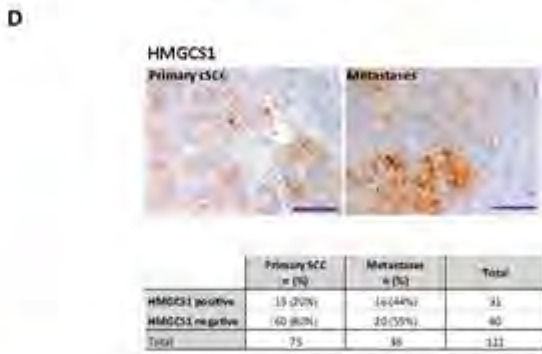
B

	Negative (n = 60)	Positive (n = 15)	Total (n = 75)	p-value
Pathological variables				
Differentiation, n (%)				0.388
Good	17 (28.3)	6 (40.0)	23 (30.7)	
Moderate	36 (60.0)	9 (60.0)	45 (60.0)	
Poor	7 (11.7)	0 (0.0)	7 (9.3)	
Tumor thickness (mm)				0.063
Mean (SD)	6.39 (3.60)	8.22 (3.47)	6.74 (3.63)	
Median (Q1, Q3)	6.5 (4.0, 7.8)	9.0 (4.5, 10.5)	7.0 (4.0, 8.0)	
Min, Max	0.7, 19.0	3.3, 14.0	0.7, 19.0	
N (% Non-missing)	60 (100.0)	15 (100.0)	75 (98.7)	
Tumor size (cm)				0.001
Mean (SD)	2.13 (1.51)	3.24 (1.06)	2.32 (1.50)	
Median (Q1, Q3)	1.8 (1.2, 2.5)	3.0 (2.4, 4.0)	2.0 (1.4, 3.0)	
Min, Max	0.6, 10.0	1.5, 5.1	0.6, 10.0	
N (% Non-missing)	58 (96.7)	13 (86.7)	71 (93.4)	
Clark level, n (%)				0.547
3	12 (20.3)	2 (14.3)	14 (19.2)	
4	28 (47.3)	6 (42.9)	34 (46.6)	
5	9 (15.3)	1 (7.1)	10 (13.7)	
6	10 (16.9)	5 (35.7)	15 (20.5)	
Staging systems, n (%)				
TNM (AJCC)				0.012
T1	28 (48.3)	1 (7.7)	29 (40.8)	
T2	27 (45.8)	11 (84.6)	38 (53.3)	
T3	5 (5.2)	1 (7.7)	6 (8.6)	
TNM (Brigham)				0.100
1	37 (37.9)	2 (14.3)	39 (53.3)	
2a	28 (48.3)	7 (50.0)	35 (48.6)	
2b	3 (5.2)	1 (7.1)	4 (5.6)	
3	5 (8.6)	4 (35.7)	9 (12.5)	

Correlation analysis of HMGCS1 expression and pathological features. Statistical analyses were performed with Mann-Whitney U-test and Fisher exact test for continuous and categorical variables, respectively.



Effect of simvastatin on the *in vitro* migration and invasion abilities of control and DKC1-depleted cells; **, $p < 0,005$; ***, $p < 0,001$.



HMGCS1 expression in cSCC, detected by immunohistochemistry. Below, contingency table of HMGCS1 expression in primary cSCC and metastases. Scale bars, 100 µm

Different surgical margins in T1 squamous cell carcinomas of the lip: a Dutch retrospective multicenter cohort study

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Background: Currently patients with T1 squamous cell carcinoma (SCC) on the lip are treated by excision with either a 5mm or a 10mm clinical tumor-free margin.

Objective: To compare groups of patients with T1 SCC on the lip treated with 5mm versus 10mm clinical margins with respect to risk factors for recurrence and/or metastasis.

Methods: Relevant data from surgically treated patients were retrospectively derived from the Dutch Pathological Anatomical National Automated Archive between 2010 and 2018.

Results: Data were available for 173 and 67 patients treated with a 5mm and 10mm clinical margin, respectively. Patients in the 5mm group were more often treated by a dermatologist (59.0% vs 3.0%, $p<0.001$) and less often had a location on the lower lip (60.7% vs 82.1%, $p=0.001$) or mucosal involvement (4.3% vs 18.2%, $p=0.003$). Median infiltration depth was lower (2.2 mm vs 2.9 mm, $p=0.056$). After excision, the median histological margin was 4.0 mm (range: 1.6-5.0) in the 10mm group versus 3.0 mm (range: 1.5-4.6) in the 5mm group ($p=0.257$).

Conclusion: The results reflect selective referral of patients with worse prognosis to excision with 10mm instead of 5mm clinical margin. However, the use of a wider clinical margin in these patients did not result in a significantly higher median histological margin, which is a prognostic factor according to the literature. The 5mm group was more frequently treated by dermatologists, who appear to be able to demarcate a tumor more precisely by using dermoscopy, resulting in more accurate clinical margins.

Epidermal growth factor receptor (EGFR) inhibitors in advanced cutaneous squamous cell carcinoma (cSCC): A systematic review and meta-analysis

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Introduction: PD-1 inhibitors are associated with high objective response rates (ORR) of approximately 45% in patients with advanced cutaneous squamous cell carcinoma (cSCC), however they are not appropriate for every patient. These include solid organ transplant recipients (SOTRs) who develop cSCC 65-to-250 times more frequently than the general population who risk allograft rejection.

Method: We conducted a systematic review and meta-analysis investigating epidermal growth factor receptor (EGFR) inhibitors in advanced cSCC (PROSPERO registration CRD42023394300). Data were extracted by two investigators including study design; EGFR inhibitor studied; demographic information; and efficacy outcomes (ORR, progression-free survival (PFS) and overall survival (OS)).

ORR was pooled using the inverse variance method and a random effects model. Published Kaplan-Meier OS and PFS curves were used to construct summary OS and PFS plots, from which median values, 6-month PFS proportions and 12-month OS proportions were derived.

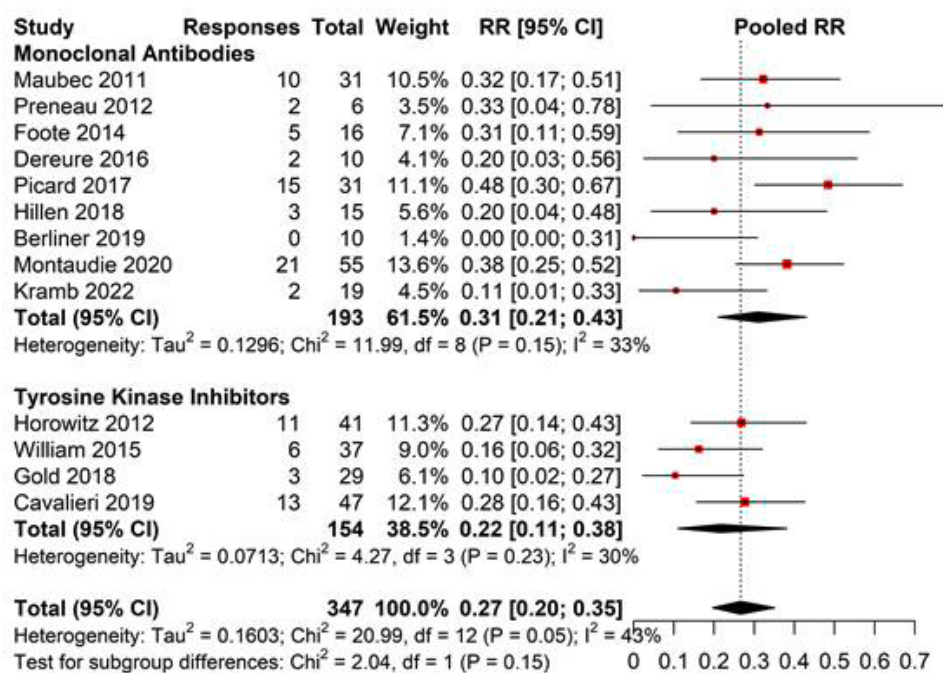
All analyses were conducted using R, version 4.2.

Results: A total of 13 studies (7 prospective, 6 retrospective) met inclusion criteria, reporting on 365 patients. The pooled ORR was 27% (95% CI 20-35) (Figure 1), and was not significantly different between studies of monoclonal antibodies versus tyrosine kinase-inhibitors (TKIs) – 31% (95% CI 21-43) versus 22% (95% CI 11-38), respectively, $P=0.15$.

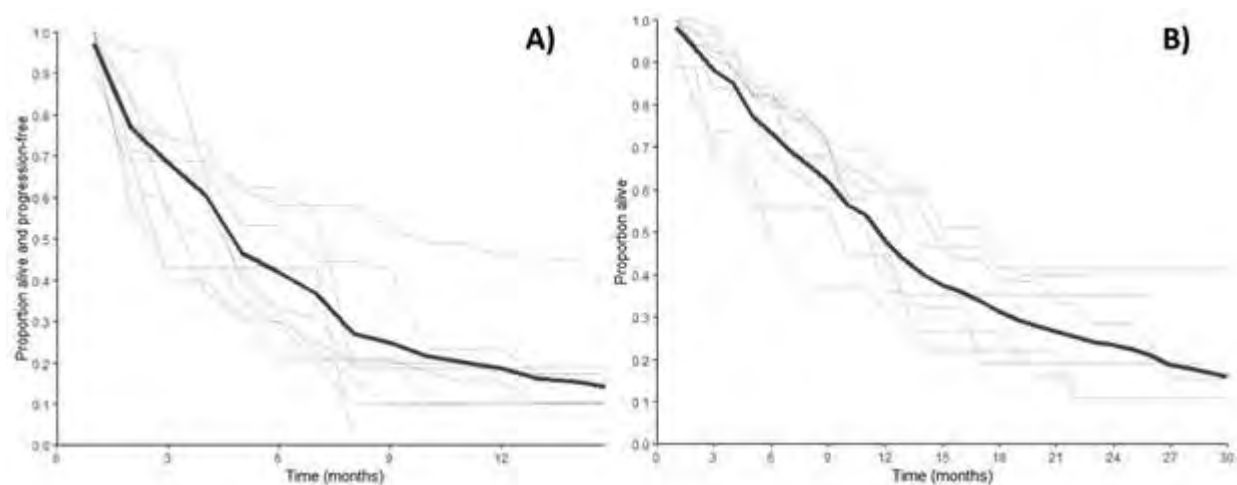
A summary PFS curve was constructed using available data from 9 studies ($n=263$ patients), and a summary OS curve using data from 9 studies ($n=288$ patients) (Figure 2a,b). Pooled median PFS was 4.8 months (95% CI 3.9-6.6), and the 6-month PFS rate was 42% (95% CI 32-55). Pooled median OS was 11.7 months (95% CI 9.2-14.1), and the 12-month OS rate was 48% (39-60). These were not significantly different between studies of monoclonal antibodies versus TKIs ($P=0.27$ for PFS and $P=0.42$ for OS).

Discussion: EGFR inhibitors are associated with modest clinical efficacy in advanced cSCC, although our results are inferior to those reported for PD-1 inhibitors. Prospective studies in patients who are ineligible for anti-PD-1 (e.g. SOTRs) and in those who have previously progressed on immunotherapy will be critical in incorporating EGFR inhibitors into the contemporary treatment paradigm for advanced cSCC.

Supporting Document 1



Supporting Document 2



Immunological deficiency in cutaneous squamous cell carcinoma of patients with recessive dystrophic epidermolysis bullosa

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Introduction: Cutaneous squamous cell carcinoma (cSCC) is one of the most devastating complications of recessive dystrophic epidermolysis bullosa (RDEB). We have recently demonstrated a reduction in immune cell peritumoral infiltration in cSCC of RDEB patient with a reduction of CD3+, CD4+, CD68+ and CD20 compared to primary and secondary cSCC in patient without RDEB.

New molecules such as high mobility group box 1 (HMGB1), T cell immunoglobulin and mucin domain 3 (TIM-3) and Heme oxygenase-1 (HO-1) play a role in the antitumoral immunity.

Objectives: The OH1-HMGB1-TIM3 activation axis, as correlated to the T lymphocytes cell count, was assessed in biopsy samples from cSCC and from pseudoepitheliomatous cutaneous hyperplasia of RDEB patients and from primitive cSCC.

Materials and Method: A retrospective study on 31 consecutive cases was performed: 12 cases of cSCC in RDEB patients; 12 consecutive cases of primitive cSCC and 7 cases of pseudoepitheliomatous cutaneous hyperplasia in RDEB patients.

Results: In cSCC and pseudoepitheliomatous hyperplasia of RDEB patients the expression of CD4 T helper lymphocytes is lower than in the peritumoral infiltrate found in primitive cSCC. CD8 cytotoxic T lymphocytes were increased in primitive cSCC compared to the other two groups. An increased HMGB1 expression was evident in primitive and RDEB cSCC. TIM3 expression was higher in cSCC of RDEB patients compared to the other two groups. A significantly reduced immunohistochemical expression of OH-1 in the tumoral microenvironment of cSCC-RDEB compared to those of primitive cSCC was evident.

Conclusions: These data confirm a reduction in immune cell peritumoral infiltration in RDEB patients that can justify the particular aggressiveness of cSCC in RDEB patients.

Immunotherapy for locally advanced and metastatic cutaneous squamous-cell carcinomas in a real-world Australian cohort

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Introduction and Objectives: Immunotherapy has revolutionised the management of advanced cutaneous squamous cell carcinoma (CSCC)(1-5). However, the stringent inclusion criteria of clinical trials results in key populations with advanced CSCC being excluded or underrepresented in the key registrational studies. This includes the elderly, who owing to frailty, comorbidity and poorer overall performance status (PS) are often underrepresented, and the exclusion of the immunocompromised, those with autoimmune disease and organ transplant recipients. This has generated interest in reviewing real-world populations treated with immunotherapy via access schemes, however, to date many of these reports have been limited by small patient numbers (6-9). To our knowledge this is the largest real-world report of advanced CSCC patients treated with immunotherapy.

Materials and Methods: This was a multi-centre national retrospective review performed across 15 Australian institutions of trial-ineligible patients with advanced CSCC who received immunotherapy via an access program. The primary endpoint was the best overall response rate (ORR) as per standardised assessment criteria using the hierarchy of Response Evaluation Criteria in Solid Tumors 1.1, modified World Health Organisation clinical response criteria or Positron Emission Tomography Response Criteria 1.0. We assessed toxicity as per Common Terminology Criteria for Adverse Events version 5 and correlated baseline clinico-pathological features with both overall (OS) and progression free survival (PFS).

Results: 286 patients were analysed. Median age was 75.2 years (range 39.3-97.5); 81% were male, 31% immunocompromised, 9% had an autoimmune disease and 21% were ECOG >2. ORR was 63% with 28% complete responses, 35% partial responses, 22% stable disease and 16% with progressive disease (Table 1). Median follow-up was 12 months. The 12-month OS and PFS were 78% (95%CI 72-83) and 65% (95%CI 58-70) respectively. In multivariate analysis poorer ECOG PS and immunocompromised status were associated with worse OS and PFS (Table 2). 19% of patients reported grade 2 or higher immune-related adverse events. There were no treatment related deaths.

Conclusions: This study demonstrates that immunotherapy is effective and well-tolerated in a real-world cohort of trial ineligible advanced CSCC patients. Comparable efficacy was seen to what has been demonstrated in clinical trials with similar toxicity.

Supporting Document 1

Table 1: Response rates

Characteristic	Total (n = 286)
Best response (RECIST 1.1 + WHO + PET)	
Complete response	74 (28% [23, 34])
Partial response	92 (35% [29, 41])
Stable disease	57 (22% [17, 27])
Progressive disease	41 (16% [11, 20])
Missing	22
Best RECIST 1.1 response	
Complete response	34 (22% [15, 29])
Partial response	65 (41% [34, 50])
Stable disease	36 (23% [17, 30])
Progressive disease	22 (14% [9, 20])
Missing	129
Best WHO response	
Complete response	18 (24% [15, 35])
Partial response	30 (39% [28, 51])
Stable disease	16 (21% [13, 32])
Progressive disease	12 (16% [8, 26])
Missing	210
Best PERCIST response	
Complete response	43 (45% [35, 56])
Partial response	26 (27% [19, 37])
Stable disease	11 (12% [6, 20])
Progressive disease	15 (16% [9, 25])
Missing	191

Supporting Document 2

Table 2: Cox Regression for Overall Survival

Variable	Level	N	Events	Univariable		Multivariable	
				HR (95% CI)	p-value	HR (95% CI)	p-value
Age	Per 5 years increase	286	66	1.2 (1.0, 1.3)	0.015	1.0 (0.9, 1.2)	0.674
Sex	Male	232	57	ref	0.298	ref	0.181
	Female	54	9	0.7 (0.3, 1.4)		0.6 (0.3, 1.3)	
H&N primary site	No	55	16	ref	0.205	ref	0.101
	Yes	231	50	0.7 (0.4, 1.2)		0.6 (0.3, 1.1)	
ECOG	Per unit increase	277	65	2.7 (2.0, 3.8)	<0.001	3.0 (2.0, 4.3)	<0.001
Immunosuppressed	No	197	35	ref	0.015	ref	0.025
	Yes	88	30	1.8 (1.1, 3.0)		1.8 (1.1, 3.0)	
Disease type	Locally advanced only	188	42	ref	0.873	ref	0.706
	Metastatic disease	98	24	1.0 (0.6, 1.6)		0.9 (0.5, 1.6)	
Prior nodal RT	No prior nodal RT	191	41	ref	0.355	ref	0.383
	Prior nodal RT	95	25	1.3 (0.8, 2.1)		1.3 (0.7, 2.2)	

Inhibitory Effect of 13-Butoxyberberine Bromide on Metastasis of Skin Cancer A431 Cells

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Introduction and Objectives: Cancer metastasis is the major cause of cancer-related death. Therefore searching for a compound that could inhibit cancer metastasis is necessary. 13-Butoxyberberine bromide is a berberine derivative that has not been reported on the anti-metastatic effect on skin cancer cells. This study aims to investigate the anti-metastatic effect of 13-butoxyberberine bromide on skin cancer A431 cells.

Materials and Methods: The effect of 13-butoxyberberine bromide on A431 cell viability was examined by MTT assay. Suppression of cell migration and invasion in A431 cells were determined by a wound healing assay, transwell migration assay, and transwell invasion assay.

Results: The result demonstrated that 13-butoxyberberine bromide decreased A431 cell viability in a dose-dependent manner. In addition, sub-toxic concentrations of 13-butoxyberberine bromide suppressed cell migration and invasion in A431 cells.

Conclusions: 13-Butoxyberberine bromide could inhibit A431 cell metastasis. These findings may be useful in the development of 13-butoxyberberine bromide as an anti-metastatic drug in the future.

Invasive squamous cell carcinoma of scalp: treatment, challenge and result

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Introduction and Objectives: Scalp squamous cell carcinoma often originates from previous skin lesions such as chronic inflammation, ulcers, burn scars, traumatic scars, etc., in patients with many chronic diseases. The cancer progresses rapidly and tends to invade the skull and meninges making it difficult to treat. Treatment is mainly surgical, focusing on extensive excision combined with reconstruction. The large-sized, high-vibration pedicle flaps are of great advantage for complex scalp lesions due to squamous cell carcinoma.

Materials and Methods: This study included 9 patients diagnosed with squamous cell carcinoma invading the skull from December 2018 to November 2020. The tumor was extensively resected to a negative margin. Meningeal defects are reconstructed with femoral fascia, craniofacial defects are reconstructed with the outer layer of skull bone or titanium mesh. Scalp defects were reconstructed with pedicle flaps. Clinical and laboratory symptoms, treatment methods, surgical results were collected, analyzed and evaluated.

Results: 7/9 patients had cancer that developed from previous skin lesions, 4 patients had chronic comorbidities. Two cases had to be re-operated, of which one case was due to local recurrence, one case of long-healing incision. The area of the scalp defect after tumor resection is from 54cm² to 168cm² and the skull defect is from 6cm² to 64cm². One case had to reconstruct the meninges with femoral fascia. Eight cases were reconstructed craniofacial defects with titanium mesh and one case with cranial exoskeleton. Scalp defects were reconstructed by pedicle flaps, including seven scalp flaps, one rotation flap and three trapezius skin flaps. All flaps survived completely.

Conclusion: Scalp squamous cell carcinoma often develops from previous lesions, presenting challenges for both tumor resection and reconstruction. Excision of the tumor should be extensive until the resection area is negative. The pedicle flap is a good material for reconstructing scalp defects caused by squamous cell cancer.

Key demographics, real world responses and safety data for the UK REACT-CEMI (Real-world Evidence of Advanced CSCC Treatment – with CEMiplimab) study

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Introduction and Objectives: Cemiplimab was licensed in 2019 in the United Kingdom (UK) as the first systemic treatment for patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiotherapy (herein referred to as advanced CSCC [aCSCC]). Real-world experience of cemiplimab post-marketing authorization has not been investigated in a UK multicentre study. Here, we describe key demographics, response rates and safety events for the 'Real-world Evidence of Advanced CSCC Treatment-with CEMiplimab' (REACT-CEMI; NCT05493826) study.

Materials and Methods: This UK non-interventional study involved retrospective data collection from medical records at 10 cancer centres in 105 adult (≥ 18 years) patients treated with ≥ 1 dose of cemiplimab for aCSCC according to routine clinical practice between 02/07/2019 and 30/11/2020.

Results: Patient records were analysed for a period of up to 36 months. 70% of patients were male; 31% had locally advanced disease and 61% were metastatic. 69% had received prior treatment. Median age at index was 78.6 years (range: 55.5-93.3). 80 patients had ECOG performance status (PS) assessments: 89% (71/80) were PS 0-1 and 11% (9/80) PS >2 . 17% of patients were immunocompromised and 1 patient had a history of organ transplant. Primary endpoint, overall response rate (ORR) within 12 months post cemiplimab initiation, was 42% (95% CI: 32%-51%); ORR for the study was 45% (95% CI: 35%-54%) with 15% achieving a complete response. Median time to best response was 3.5 months (range: 0.7-23.0). Median duration of response was 22.3 months (range: 0.7-34.3). Disease control rate within 12 months was 62%.

Any grade immune-related adverse reactions (irARs) were experienced by 19% of patients, leading to treatment interruptions in 6% of patients. At data cut-off, 84% had discontinued treatment. Demographics, efficacy and safety, including reasons for discontinuation, are summarised in Tables 1 and 2.

Conclusions: These results provide new insights into the real-world clinical effectiveness and safety of cemiplimab in the UK for aCSCC patients, including patients normally excluded from clinical trials. The results are similar to those reported in the EMPOWER-CSCC-1 study and complement existing evidence, which will help to inform treatment decisions for aCSCC.

Supporting Document 1

Table 1: Patient Demographics and Cemiplimab Treatment Response	
Demographics¹	
Age at treatment initiation [median (range)]	78.6 (55.5-93.3)
Sex	70% male; 30% female
Ethnicity	90% white; 1% mixed; 10% not stated
Stage of disease (n=104)	31% locally advanced; 61% metastatic; 8% other ⁵
Comorbidities ²	62% no comorbidity; 26% 1 comorbidity; 12% ≥2 comorbidities
ECOG PS (n=80)	26% PS0, 63% PS1, 10% PS2, 1% PS4
Immunocompromised	17%
History of organ transplant	1%
Prior treatment(s) ³	32% no treatment, 53% 1 treatment, 15% >1 treatment
Responses (post-initiation of cemiplimab)¹	
Overall Response Rate within 12 months	42% (95% CI, 32% – 51%)
Overall Response Rate ⁴	45% (95% CI, 35% – 54%)
- Complete Response and Partial Response	17%; 28%
Disease Control Rate within 12 months	62%
Time to Best Response ⁶ , median (range), n=47	3.5 months (0.7 – 23.0)
Time to Partial Response, median (range), n=39	2.8 months (0.7 – 19.2)
Time to Complete Response, median (range), n=16	9.1 months (2.4 – 23.0)
Duration of Response, median (range), n=47	22.3 months (0.7 – 34.3)
¹ Denominator is n=105, unless otherwise stated. ² Not mutually exclusive, patients could have had more than one comorbidity. ³ Prior treatment included: Surgery (n=48), Radiotherapy (n=36), Chemotherapy (n=1) or Other (n=3). Patients could have received more than one type of treatment. ⁴ Over the entire study period. ⁵ Includes 'not recorded'. ⁶ Best Response includes Partial Response and Complete Response. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; 95% CI, 95% confidence interval.	

Supporting Document 2

Table 2: Safety	
	N=105
irAR (any grade), n (%)	20 (19%)
Treatment interruptions (due to experiencing an irAR), n (%)	6 (6%)
Number of cemiplimab interruptions (overall), n (%)	15 (14%)
- Number of interruptions (per patient), n (%)	12 (11%) 1 interruption; 3 (3%) >1 interruption
Permanent discontinuations, n (%)	88 (84%)
	N=88
Reason for permanent discontinuation, n (%)	
- Treatment course completed	16 (19%)
- Disease progression	30 (35%)
- irARs	15 (17%)
- Other adverse reactions (non-immune related)	3 (3%)
- Death (any cause)	10 (12%)
- Patient decision	5 (6%)
- Other ¹	7 (8%)
- Missing	2 (2%)
Patients with interruptions before discontinuation, n (%)	77 (88%) no interruption; 11 (13%) >1 interruption(s)
¹ Includes atrial flutter (n=1), infection (n=1), toxicity (n=1), hospitalisation (n=1), patient with clinical deterioration/decline in health (n=2), Patient quality of life/frailty of age' (n=1). Abbreviations: irAR, immune-related adverse reaction.	

Locally advanced and metastatic cutaneous squamous cell carcinoma treated by Immunotherapy: observational study of our experience

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Introduction: Cutaneous squamous cell carcinoma (cSCC) is the second most common non-melanoma skin cancer after basal cell carcinoma¹. The majority of cSCC are cured with surgery, but locally advanced and metastatic disease may require radiation and systemic therapy. 1-3 Here, we describe our experience using immunotherapy for locally advanced or/and metastatic cSCC in a Dermatology Department.

Methods: We retrospectively reviewed all medical records between December 2018 and February 2023 from patients who received immunotherapy for non-radiable and unresectable with healing intention advanced cSCC. Immunotherapy agents included were cemiplimab, nivolumab and pembrolizumab. The following data was collected: age, gender, tumour location, response, prior therapies, progression-free survival (PFS) and immune-related adverse events (CTCAE 5.0 irAEs).

Results: A total of 12 patients were identified (Table 1). The patients were predominantly male (66.7%), with median age 85 years (range 82–89). The median duration of follow-up was 9 months (range 4–48). Primary tumors were located on the head/neck (75%), trunk (16.7%) and extremities (8.3%). Therapies prior to receiving immunotherapy included surgery (83.3%) and radiotherapy (33.3%).

Among all patients, 10 (83.3%) received pembrolizumab and 2 (16.7%) cemiplimab. Nine (75%) patients achieved objective complete clinical response (OCR), 1 (8.3%) achieved partial response, 1 (8.3%) had stable disease and 1 (8.3%) did not respond. The median time to achieve a clinical response was 2 months (range 0.25–4.75) and the median PFS was 28 months (range 42–3). Among the patients with OCR, 2 patients were able to discontinue therapy and remained disease free for 32 months afterwards.

Five patients experienced irAEs. Three patients presented grade 1-2 rheumatologic irAEs, which were managed with prednisolone and hydroxicloroquine. One patient developed a grade 4 hepatitis after the third cycle of immunotherapy and one patient suffered a grade 5 myocarditis.

Conclusion: We highlight the high rate of OCR presented in our series (75%) and the 3 cases which remained with OCR after more than 28 months from the withdrawal of immunotherapy. Our experience supports the effectiveness of the immunotherapy for advanced sCC treatment, showing a reasonable safety profile which was similar to that reported in clinical trials.

Oncolytic viruses to augment PD-1 inhibition in metastatic cutaneous squamous cell carcinoma: A case report and review of the literature

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Introduction: Cutaneous squamous cell carcinoma (cSCC) is the second most common malignancy in Caucasian populations, with an increasing incidence worldwide. The advent of immune checkpoint inhibitors in the preceding decade has allowed for unprecedented disease control in various solid organ malignancies, including cSCC. While high objective response rates of approximately 45-60% are observed in trials of PD-1 blockade in cSCC, complete responses are infrequent (0-15%) (ref 1-3). Therefore, there is a need for the development of strategies to augment PD-1 inhibition in the treatment of advanced cSCC, particularly in the context of resistant disease.

Case presentation: A 62-year-old Caucasian man was referred to the Phase 1 oncology clinic with an extensive background of non-melanoma skin cancers. This included a 2-year history of metastatic cSCC which had progressed on cemiplimab, cisplatin plus capecitabine, vismodegib (due to a germline PTCH1 mutation) and multiple courses of radiotherapy. At time of referral, disease involvement included a right parotid mass (30x20mm, SUV-max 12.1) and right medial supraclavicular node (19x15mm, SUV-max 6.6) (Figure 1a,b). Due to a lack of standard-of-care treatment options, the patient was enrolled on a Phase 1 clinical trial of 3-weekly intratumoral injections of an oncolytic reovirus to the supraclavicular node in combination with pembrolizumab (200mg intravenously, q3-weekly).

Other than Grade 1 injection site pain, there were no significant treatment-related toxicities. After 12 cycles of treatment, repeat PET-CT showed a complete metabolic response in both the parotid bed and nodal metastases (Figure 1c,d). This was associated with improvement in ECOG performance score, decreased pain and reduced analgesic requirements. Due to closure of the trial, the patient was transitioned to ongoing maintenance cemiplimab.

Discussion: Oncolytic viruses are preferentially replicate within and trigger CD8+ T-cell mediated cytotoxicity against solid tumours, and may augment PD-1 inhibition in cancer immunotherapy by increasing CD8+ and decreasing regulatory T-cells in the tumour microenvironment. Therefore, in patients with advanced or metastatic cSCC who progress on anti-PD-1 therapy, addition of oncolytic virus therapy may be an effective treatment option. However, prospective studies are needed to validate the safety and efficacy of this combination compared to PD-1 inhibition alone in these patients.

Optimal duration of cemiplimab therapy in advanced cutaneous squamous cell carcinoma

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Background: PD-1 Immune checkpoint inhibitor therapy is effective for advanced CSCC, but there is little published data to inform decision-making regarding duration of treatment.

Methods: We performed a 5-year retrospective cohort study of patients who received cemiplimab for advanced CSCC. Descriptive analyses were performed comparing treatment response with duration of treatment. Univariate Cox regression was performed to calculate progression-free survival.

Results: 93 patients received cemiplimab, of whom 46 (49%) received <6 months, 26 (28%) received 6-12 months, and 21 (23%) received ≥12 months of treatment. The overall response rate was 53% and disease control rate was 60% at time of cemiplimab discontinuation. After removing patients who discontinued treatment due to progression, we analyzed outcomes in cohorts according to the duration of treatment. Compared to patients receiving 6-12 months of treatment, there was no significant difference in progression-free survival for patients receiving 12-18 and ≥18 months of treatment (HR: 12.0 p=0.08; HR: 1.5, p=0.30, respectively). Patients who received ≥12 months of treatment experienced a larger percentage of adverse events (<6 months: 12%, 6-12 months: 48%, ≥12 months: 71%; p<0.001)

Conclusion: In this retrospective analysis, there was no benefit to cemiplimab treatment for more than 6-12 months, suggesting that 12 months of treatment is a reasonable stopping point for non-progressing patients.

Phase 2 confirmatory study of cemiplimab 350 mg intravenous every 3 weeks in patients with locally advanced or metastatic cutaneous squamous cell carcinoma: Study 1540 Group 6

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Introduction and Objectives: While most patients diagnosed with cutaneous squamous cell carcinoma (CSCC) are cured with local therapies, a small percentage develop life-threatening advanced CSCC. In Phase 1 (NCT02383212) and pivotal Phase 2 (NCT02760498) clinical trials, cemiplimab—an anti-programmed cell death-1 antibody—was the first systemic therapy to demonstrate significant antitumor activity in patients with advanced CSCC. Here, we report results from Group 6 of the pivotal Phase 2 trial.

Materials and Methods: This group comprised patients with advanced CSCC who received cemiplimab IV every 3 weeks for at least 27 weeks without experiencing disease progression, and who then had the option to receive cemiplimab by subcutaneous injection for up to 108 weeks. The primary endpoint was objective response rate according to independent central review. Secondary endpoints included duration of response, progression-free survival, and overall survival by central and investigator review, and safety and tolerability.

Results: As of October 25, 2021, 167 patients were enrolled, of whom 165 received at least one dose of cemiplimab and were followed up for a median of 8.7 months (range: 0.0–19.5). Of 167 enrolled patients, five received prior systemic therapy. According to independent central review, the objective response rate was 44.3% (95% CI: 36.6, 52.2) with complete response in 5.4% of patients, partial response in 38.9%, and duration of response not reached (95% CI: 13.0 months, not evaluable). Among treated patients, median progression-free survival was 14.7 months (95% CI: 10.4, not evaluable) and median overall survival was not reached (95% CI: 17.6 months, not evaluable).

The most common treatment-emergent adverse events of any grade were fatigue (26.1%), diarrhea and pruritus (each 21.2%), and nausea (17.0%). The most common Grade ≥ 3 treatment-emergent adverse events were hypertension and pneumonia (each 3.6%), and general physical health deterioration (3.0%).

Conclusions: The Group 6 primary analysis demonstrated a safety and efficacy profile consistent with that of earlier groups in the study.

Phase 2 study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma: Final analysis from EMPOWER-CSCC-1 Groups 1, 2, and 3

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Introduction and objectives: Previous analyses from the EMPOWER-CSCC-1 Phase 2 study (NCT02760498) demonstrated substantial clinical benefit and an acceptable safety profile with cemiplimab in patients with locally advanced and metastatic cutaneous squamous cell carcinoma (CSCC). Here, we present the final analysis of 5-year data for patients in study Groups 1, 2, and 3 of the EMPOWER-CSCC-1 study.

Materials and Methods: Patients received cemiplimab 3 mg/kg intravenous every 2 weeks for up to 96 weeks (Group 1, metastatic CSCC; Group 2, locally advanced CSCC) or cemiplimab 350 mg intravenous every 3 weeks for up to 54 weeks (Group 3, metastatic CSCC). The primary endpoint was objective response rate (ORR; complete + partial response) according to independent central review (ICR). This is the final analysis with the final database lock occurring on March 1, 2022.

Results: A total of 193 patients were enrolled (Group 1, n=59; Group 2, n=78; Group 3, n=56). Tumor ORR according to ICR was: Group 1: 50.8% (95% CI: 37.5–64.1); Group 2: 44.9% (95% CI: 33.6–56.6); Group 3: 46.4% (95% CI: 33.0–60.3). Median progression-free survival in months was: Group 1: 18.4 (95% CI: 7.3–53.2); Group 2: 18.5 (95% CI: 11.1–43.8); Group 3: 21.7 (95% CI: 3.8–43.3).

Median overall survival (months) was: Group 1: 57.7 (95% CI: 29.3–not evaluable [NE]); Group 2: not reached; Group 3: 48.4 (95% CI: 29.5–NE). Findings remained generally consistent with the previous update with data cutoff of October 11, 2020. Overall survival at 48 months was 61.8% (95% CI: 54.0–68.7). Median duration of response was 41.3 months.

Fatigue (34.7%) was the most common treatment-emergent adverse event of any grade, with hypertension (4.7%) being the most common Grade ≥3 treatment-emergent adverse event.

Conclusion: The final update of the EMPOWER-CSCC-1 Phase 2 study at 5 years confirms the durable response, safety, and efficacy of cemiplimab in patients with advanced CSCC. There were no new safety signals identified on longer follow-up. Cemiplimab remains a standard of care option for advanced CSCC.

Phase 3 KEYNOTE-630: Adjuvant Pembrolizumab in High-Risk Locally Advanced (LA) Cutaneous Squamous Cell Carcinoma (cSCC)

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Introduction and Objectives: Better treatment options are needed for patients with high-risk, LA cSCC who experience recurrence after surgery. The PD-1 inhibitors pembrolizumab and cemiplimab have shown antitumor activity in advanced metastatic cSCC. KEYNOTE-630 (NCT03833167) is a randomized, double-blind, placebo-controlled, phase 3 trial of adjuvant pembrolizumab in patients with resectable, high-risk, LA cSCC.

Materials and Methods: Eligible patients have LA cSCC as the primary site of malignancy and have undergone complete macroscopic resection of all disease with ≥ 1 high-risk feature: histologically involved nodal disease with extracapsular extension, with ≥ 1 lymph node > 2 cm in diameter or ≥ 2 lymph nodes involved; any gross cortical bone, skull base, and/or skull base foramen invasion; any index tumor with ≥ 2 of the following: tumor ≥ 4 cm with > 6 -mm depth or invasion beyond subcutaneous fat, multifocal perineural invasion for nerves < 0.1 mm in diameter (≥ 3 foci) or any involved nerve ≥ 0.1 mm in diameter, poor differentiation and/or sarcomatoid and/or spindle cell histology, recurrent disease (recurrence within 3 years in the previously treated area), or satellite lesions and/or in-transit metastases, lymphatic or vascular involvement. Patients must have received adequate postoperative dose of hypofractionated or conventional radiotherapy, including a BED EQD2 > 48 Gy, have ECOG performance status of 0 or 1, and completed adjuvant radiotherapy ≥ 4 and ≤ 16 weeks from randomization. Patients will be randomly allocated 1:1 to pembrolizumab 400 mg IV every 6 weeks or placebo for approximately 1 year (≤ 9 cycles). Randomization will be stratified by extracapsular extension, cortical bone invasion, and prior systemic therapy (all, yes vs no). Patients receiving placebo may be eligible to cross over to receive pembrolizumab (≤ 18 cycles) if first biopsy-proven recurrence occurs within 5 years. In the pembrolizumab arm, eligible patients may receive pembrolizumab retreatment for up to 18 cycles. Primary end point is recurrence-free survival per investigator assessment. Secondary end points include overall survival, health-related quality of life, and safety.

Results: Planned enrollment is approximately 570 patients, and recruitment is underway at sites in Asia, Australia, Europe, and North and South America.

Conclusions: Results will help elucidate the role of adjuvant pembrolizumab in patients with high-risk, LA cSCC.

Prevalence of Human Polyomaviruses 6, 7, Merkel cell polyomaviruses, β -papillomaviruses and Trichodysplasia Spinulosa-associated polyomaviruses in Actinic Keratosis and Squamous Cell Carcinoma: one-year data from clinical practice

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Introduction and Objectives: To date, human polyomaviruses (HpyVs) and papillomaviruses (HPV) have a controversial role in non-melanoma skin cancer (NMSC) [1]. Among them, Merkel cell polyomaviruses (MCPyV), human polyomaviruses (HpyV6, HpyV7) and Trichodysplasia Spinulosa-associated polyomaviruses (TSPyV) present a skin tropism, but a causal role in skin diseases has been established only for MCPyV as causative agent of Merkel cell carcinoma (MCC) and TSPyV as etiological agent of Trichodysplasia Spinulosa (TS) [2]. In this study, we investigated the prevalence of β -HPV, MCPyV, HpyV6, HpyV7 and TSPyV in actinic keratosis (AK) and squamous cell carcinoma (SCC).

Materials and Methods: 37 consecutive patients with clinical diagnosis of AK or SCC have been recruited in our center. A lesional and a non-lesional skin biopsy have been performed in each patient to confirm clinical diagnosis and to investigate the prevalence of the viruses.

Results: Among 37 patients enrolled, 3 are women (8.1%) and 34 men (91.9%). According to positive histology for SCC or AK alone (11 patients with SCC and 23 with AK), MCPyV was present in 4 SCC samples and 7 AKs while HpyV6 was detected exclusively in AKs. Considering 19 patients without SCC, MCPyV was present in both AKs and unaffected skin. HpyV6 was found to be more present in unaffected skin than in AKs. MCPyV DNA was found in 11 lesional tissue samples and 11 non-lesional biopsy samples. Considering β -HPV, two patients showed the presence of oncogenic genotypes both on healthy and damaged skin. Also, there were 6 patients who had no oncogenic genotypes. All patients who presented oncogenic genotypes of β -HPV on lesion biopsy received a histological diagnosis of SCC. Moreover, subjects with SCC had more oncogenic genotypes of β -HPV than subjects with only AKs ($p < 0.017$).

Conclusions: HpyV6 is, like MCPyV, part of the skin microbiota whereas, the absence of HpyV6 and HpyV7 in AK and SCC samples could confirm that are not involved in cutaneous malignancies. Moreover, subjects with SCC had more oncogenic genotypes of β -HPV than subjects with only AKs. Future research would clarify a possible role of virome in cutaneous tumours.

Prognostic factors of satellitosis or in-transit metastasis in cutaneous squamous cell carcinoma. A multicentric cohort study

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Introduction and Objectives: Satellitosis or in-transit metastasis (S-ITM) has clinical outcomes comparable to node-positivity in cutaneous squamous cell carcinoma (cSCC). There is a need to stratify risk groups. Hypothesizing that not all S-ITMs in cSCC are equal, the present study aims to determine which prognostic factors of S-ITM are associated with an increased risk of relapse and specific death in order to give guidance on stratifying risk groups.

Materials and Methods: Retrospective multicenter cohort study. Patients with cSCC developing S-ITM were included. Patients with prior or concurrent nodal or visceral metastasis were excluded. Follow-up time started at the date of diagnosis of the S-ITM. End points were relapse and specific death. Multivariate competing risk analysis evaluated which factors were associated with relapse and specific-death.

Results: Of a total of 111 patients with cSCC and S-ITM, 86 patients were included for analysis. Median (interquartile range) follow-up was 9.6 (4.2-20.4) months.. Relapse and specific death cumulative incidences at 3-year follow-up were 64% and 38%, respectively. An S-ITM size ≥ 20 mm, >5 S-ITM lesions and a primary tumor deep invasion were associated with an increased cumulative incidence of relapse [sub-hazard ratio (SHR): 2.89 (95% CI 1.44-5.83, $p=0.003$), 2.32 (95% CI 1.13-4.77, $p=0.021$), 2.863 (95% CI 1.25-6.55, $p=0.013$)] respectively. A number >5 S-ITM lesions was also associated with an increased probability of specific death [SHR: 3.48 (95% CI 1.18-10.2, $p=0.023$)]. An S-ITM ≥ 20 mm had an SHR of 2.4 (95% CI 0.97-5.93, $p=0.058$) for specific death.

Conclusions: This study demonstrates that the size (≥ 20 mm) and the number of lesions (>5) of S-ITM are the two main prognostic factors associated with a poor outcome in patients with cSCC presenting with S-ITM. Distance between S-ITM and primary tumor and time from primary tumor to S-ITM appearance, as well as other primary tumor (except for a deep tumor invasion) and patient risk factors do not increase the risk of relapse or specific-death. In cases where S-ITM is incorporated into future cancer staging systems, these results could provide guidance on stratifying risk groups and consequently could assist clinicians with treatment and management decisions.

Proteome sampling with pulsed electric fields carries features discriminating between cutaneous squamous cell carcinoma and basal cell carcinoma

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Clinical misclassification between cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) affects treatment plans and carries risks of potential for reoccurrence, metastases and mortality. We report the development of a novel tissue sampling approach with molecular biopsy using electroporation. The method, coined e-biopsy, enables non-thermal permeabilization of cells in the skin for efficient vacuum-assistant extraction of informative biomolecules for rapid diagnosis. We used e-biopsy for ex vivo proteome extraction from 3 locations per patient in 21 cSCC and in 21 BCC pathologically validated human tissue samples. The total 126 extracted proteomes were digitalized with mass spectrometry. The obtained mass spectra presented significantly different proteome profiles for cSCC and BCC with several hundreds of proteins significantly differentially expressed in each tumor in comparison to another. Notably, 17 proteins were uniquely expressed in BCC and 7 were uniquely expressed in cSCC patients. Statistical analysis of differentially expressed proteins found 31 cellular processes, 23 cellular functions and 10 cellular components significantly different between cSCC and BCC. Machine Learning classification models constructed on the sampled proteomes allowed separation of cSCC patients from BCC with 81% accuracy, 78.7% precision and 92.3% recall, which is comparable to manual initial diagnostics in clinical setup. Finally, the protein-protein interaction analysis of 11 most informative proteins, derived from Machine Learning framework, enabled detection of a novel protein-protein interaction network valuable for further understanding of skin tumors. Our results provide evidence that the e-biopsy could potentially be used as a tool to support cutaneous tumors classification with rapid molecular profiling.

Real-world patient characteristics, treatment patterns, and outcomes among patients with advanced cutaneous squamous cell carcinoma (aCSCC) treated with cemiplimab at US oncology clinical practices

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Background: Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer in the United States (US). Most cases of CSCC are cured by surgery/radiation, but an estimated 1% to 5% of patients will develop advanced CSCC (aCSCC), which is associated with poor prognosis. Prior to Food and Drug Administration approval of cemiplimab in 2018, median overall survival (OS) for adult patients with aCSCC receiving systemic therapy was 8 to 15 months. Limited real-world data are available on cemiplimab for this indication in the United States (US).

Materials and Methods: This retrospective cohort study included adult patients with aCSCC initiating cemiplimab monotherapy in the US between 2018 and 2021 in the Flatiron Health database. A trial-like subcohort was also identified using select clinical trial (EMPOWER CSCC-1) inclusion/exclusion criteria. Time to treatment discontinuation (TTD), time to next treatment (TTNT), and OS were estimated using Kaplan–Meier methods. Cox proportional hazard models were used to examine potential prognostic factors associated with OS: univariate models assessed magnitude/significance of baseline variables, with known prognostic factors and significant variables carried forward to a multivariate model.

Results: The main cohort included 622 patients (n=240 in trial-like cohort). In the main cohort, median age was 78 years, 77.8% were male, 21.4% were immunocompromised, and 63.8% had metastatic CSCC. Median (95% CI) TTD and TTNT were 8.0 (6.6-9.0) months and 16.4 (13.3-21.0) months, respectively. Median (95% CI) OS was 24.8 (21.8-29.1) months in the main cohort (not reached in trial-like cohort). In multivariable analyses, younger age, lower Eastern Cooperative Oncology Group performance status and primary CSCC location in the head and neck only (vs extremities) were associated with better OS.

Conclusion: These findings confirm the effectiveness of cemiplimab among a heterogeneous, real-world aCSCC patient population and substantiate the efficacy of cemiplimab as observed in clinical trials.

Risk of cutaneous squamous cell carcinoma local recurrence, metastasis, and disease-specific death in solid organ transplant recipients: a nationwide matched case-control study

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Introduction and Objectives: Cutaneous squamous cell carcinoma (cSCC) is one of the most common post-transplant malignancies in solid organ transplant recipients (SOTR). SOTR has previously been associated with a poor prognosis but has not been compared directly to a matched control group of immunocompetent patients with cSCC. The aim of this study was to compare the risk of cSCC local recurrence, metastasis, and disease-specific survival in SOTRs with that of immunocompetent controls.

Materials and Methods: All patients diagnosed with cSCC between January 1980 and October 2018 were identified by means of the Danish national health registries. Patients who had received transplantation prior to their first cSCC diagnosis were considered cases. Patients with cSCC who had never received any systemic immunosuppressive medicine served as controls. Cases and controls were matched 1:4 using exact matching on age, sex, and Charlson Comorbidity Index. All comparisons were performed with multivariable Fine-Gray regression adjusted for age, sex, tumour location, and number of tumours.

Results: 22747 patients with cSCC were identified. A total of 287 SOTRs were included (kidney, n=206; lung, n=88; heart, n=29 and liver, n=19) and compared with 1148 immunocompetent controls. The 5-year disease-specific survival for SOTRs was 98% (95%CI 95-99) compared with 99% (95%CI 98-99) for controls. The 5-year risk of metastasis for SOTRs was 10% (95%CI 6.9-15) compared to 3.9% (95%CI 2.8-5.3) for controls. SOTR status significantly increased the risk of local recurrence ($p<0.001$) but was not independently associated with metastasis or death from cSCC ($p=0.2$ and $p=0.5$). The number of primary tumours significantly increased the risk of local recurrence, metastasis, and disease-specific death ($p<0.001$).

Conclusions: SOTRs had a 3-fold increased risk of cSCC-related death compared to immunocompetent patients with cSCC. SOTRs had a significantly higher risk of local recurrence, metastasis, and disease-specific death. The higher risk was primarily attributed to a higher number of primary tumours in SOTRs which significantly increased the risk of local recurrence, metastasis, and death from cSCC, suggesting a mediating effect in the number of primary tumours. Future studies should address the combined effect of tumour number, tumour T-stage, and immunosuppression.

Skin Cancer Risk in Kidney Transplant Patients: Analysis of EUSCAP Registry

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Introduction and objectives: Nonmelanoma skin cancer (NMSC) is the most common cancer in renal transplant patients, accounting for 95% of all skin cancers. Cutaneous squamous cell carcinoma (cSCC) is the most common type of NMSC, with incidence rates 20-200 times higher than in the general population. On average, it takes around 8-10 years for cSCC to develop after a transplant. The basal cell carcinoma (BCC) to cSCC ratio is 1:4, which is the opposite of the general population. Therefore, in this study, we aimed specifically to identify risk factors, particularly lifetime sun exposure, associated with skin cancer development in kidney transplant patients.

Materials and Methods: We conducted a retrospective observational study using data from the skin cancer risk factor register "EUSCAP," which collects information on patients undergoing skin cancer screening at our institution. The register includes demographic and lifestyle factors, physical examination, and pathology results. In this study, we analyzed data related to skin cancer risk in kidney transplant patients. We also plan to provide details on the post-transplant nephrological follow-up of the kidney transplant patients in a future study.

Results: We included all 54 renal transplant patients enrolled in the general skin cancer EUSCAP registry (total of 500 patients). All transplant patients were under immunosuppressive treatment with bitherapy or tritherapy, including corticosteroids, calcineurin inhibitors, antimetabolites, and/or mTOR inhibitors. Among the transplant patients, 28 (52 %) were female, with a mean age of 62 years (range 26 – 82 years). The majority of patients were of White/Caucasian ethnicity (72 %). 162 cSCCs, 72 BCCs, and 3 malignant melanomas were diagnosed. We found that 28% of patients developed BCC (with an average of 5 lesions), and 39% developed cSCC (with an average of 8 lésions). The time between the first transplant and the first skin cancer diagnosis was 12 years.

Conclusion: Our study supports the high risk of skin cancer development, particularly cSCC, in kidney transplant patients. Regular skin cancer screening and early intervention are crucial. Our future work will analyze data on sun exposure in immunosuppressed patients to better understand this risk.

Squamous cell carcinoma in a burn scar: a case report

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Introduction: Burn scar degeneration is rare but not exceptional as 1-2% of skin cancers develop on burn scars. It occurs preferentially on the limbs. We report a case of squamous cell carcinoma arising on a burn scar.

Case report: An 80-year-old patient with a history of childhood burns on the upper right thigh, presented with a painful ulceration on the burn scar that had been evolving for 7 years. Clinical examination revealed a single ulceration, 14×7 cm in diameter, located on the upper 1/3 of the anterolateral aspect of the right thigh, with a budding base, well-bounded and slightly raised margins, and peri-lesional skin with a scleroatrophic appearance sequelae of a burn (Figure 1-2). Pathological examination showed large irregular clusters of polyhedral squamous cells with enlarged nuclei, coarse nucleoli, and numerous mitoses. The stroma was highly inflammatory. The surface of the tumour was ulcerated and the tumour was underlain by a dermal-epidermal fibrous scarring associated with a dermal inflammatory infiltrate. This concluded to be a squamous cell carcinoma. The patient was then referred to plastic surgery for further management.

Discussion: Squamous cell carcinomas on thermal burn scars are serious and rare conditions, often caused by domestic and professional accidents or criminal acts. They occur preferentially in the folds of the limbs and rarely metastasise. Conservative treatments are accompanied by a 30% recurrence rate. Cancers in male subjects, occurring on thermal burns, developed on an untreated reulceration or scarring sclerosis.

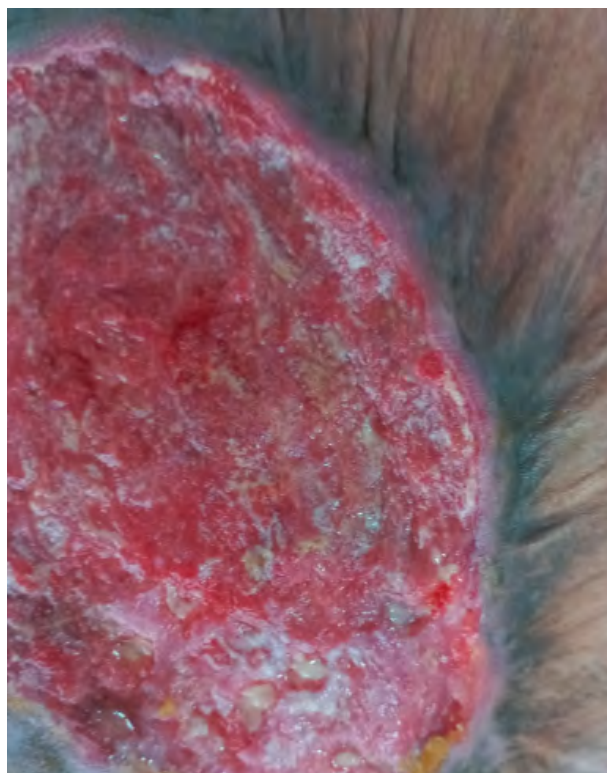
Its treatment is primarily preventive, preventing the transformation of burns by excision of scar tissue. In addition, in the case of suspicious lesions, surgical treatment must be radical from the outset.

Conclusion: The occurrence of squamous cell carcinoma in burn scars is an uncommon but formidable complication.

Supporting Document 1



Supporting Document 2



Squamous cell carcinoma of the inter-toe space: a case report

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Introduction: Squamous cell carcinoma is an infiltrative and destructive skin tumour. It has a predilection for photo-exposed areas. Localization in the inter-toe space is very rare. We report a case of squamous cell carcinoma occurring in a context of chronic intertrigo.

Case report: a 73-year-old female patient, without any notable pathological history, who presented with an intertrigo of the 4th inter-toe space of the right foot for 6 years and refractory to antifungal treatment, evolving to a protruding lesion. Clinical examination revealed a bulging nodular lesion, filling the entire 4th inter-toe space, 2 × 1.5 cm in size, with a small ulceration and crusts on the surface and the lesion associated with deep cracking of the inter-toe space (Figure 1-2-3), without satellite adenopathy. Histological examination showed a tumour proliferation of squamous cells of the epidermis, with hyperchromatic and nucleolated enlarged nuclei, with infiltration of the underlying dermis, in favour of an invasive squamous cell carcinoma. The patient was then referred to plastic surgery for further management.

Discussion: Squamous cell carcinoma is the second most common skin cancer, occurring in elderly patients with a light phototype in light-exposed areas. Localization in the inter-toe space is rare. It should be considered in the presence of any intertrigo that is resistant to the usual treatment, especially when it is erosive, budding and painful. The main etiological feature of the tumour is continuous maceration. Maceration can be maintained by a number of factors, including cultural factors found in our context: ritual ablutions performed 5 times a day, without drying the inter-toe spaces, and domestic cleaning involving large amounts of water several times a week.

Conclusion: Localization of squamous cell carcinoma in the inter-toe space is rare, with an intertrigo appearance resistant to antifungal treatment.

Supporting Document 1



Supporting Document 2



Successes and failures during Libtayo treatment

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Introduction and Objectives: Non-melanocytic malignant dermal tumors are among the most common malignancies, one of them, the squamous cell carcinoma is second behind basal cell carcinoma. Recently, in metastatic or locally advanced forms of squamous cell carcinoma, systemic cemiplimab (anti-PD-1) immunotherapy is promising beyond chemotherapy.

Materials and Methods: Authors, during the last 18 months used anti-PD-1 treatment in 6 cases with advanced, inoperable squamous cell carcinomas. Four of these patients are presented, with different treatment protocols, efficiency and side effect profiles.

Results: 1. 82-year-old female with right facial squamous cell carcinoma with relapses and cervical lymph node metastases. Following treatment in 4 cycles with cemiplimab, patient was tumor free. Already, after first cycle fever appeared and temporary pseudo-progression was observed.

Second case: 92-year-old female with peri-ocular squamous cell carcinoma with relapses following multiple surgical and radiotherapy. After 5 cycles of cemiplimab therapy, complete regression was observed. As side effect, hypothyroidism was found.

Third case: 74-year-old male with myelofibrosis, and relapsing squamous cell carcinoma on the back of nose. He received simultaneously cemiplimab and radiotherapy because of rapid progression of the tumor. During the therapy further progression occurred and the patient deceased regardless of treatment.

Fourth case: 80-year-old male with CLL without symptoms, as well as, inoperable progressive periocular squamous cell carcinoma. Cemiplimab therapy was combined with radiotherapy. During treatment, CLL relapsed and needed systemic therapy. Squamous cell carcinoma progressed further and he deceased due to brain metastasis.

Conclusions: Treatment of locally progressive and metastatic carcinomas is a challenge. The anti PD1 treatment proved to be significant, showing 50% response in clinical investigations. The side effect profiles are similar than in other anti-PD therapies. The tumor location, incidental hematological diseases can affect the efficiency, without contraindication. Known that some discrepancies are common in hemograms of non-reacting cases, which can explain the therapeutic failures of patients with hematological diseases. Combinability with radiotherapy is also discussed.

Surgical excision versus topical 5% 5-fluorouracil and photodynamic therapy in treatment of Bowen's disease: a multicenter randomized controlled trial

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Background: Large randomized controlled trials with head-to-head comparison of the effectiveness of 5-fluorouracil cream and methylaminolevulinate photodynamic therapy (MAL-PDT) with that of surgical excision in patients with Bowen's disease are currently lacking.

Methods: In this multicenter non-inferiority trial, patients with a histologically proven Bowen's disease of 4-40 mm were randomly assigned to excision with 5 mm margin, 5-fluorouracil cream twice daily for four weeks or MAL-PDT two sessions with one week interval. The primary outcome was the proportion of patients with sustained clearance at 12 months after treatment. A non-inferiority margin of 22% was used. This trial is registered with ClinicalTrials.gov number, NCT03909646.

Findings: Between May 2019 and January 2021, 250 patients were randomized. The proportion of patients with sustained clearance at 12 months was 97.4% (75/77) after excision, 85.7% (66/77) after 5-fluorouracil and 82.1% (64/78) after MAL-PDT. Absolute differences were -11.7% (95% CI -18.9 to -4.5; $P=0.0049$) for 5-fluorouracil versus excision and -15.4% (95% CI -23.1 to -7.6, $P=0.00078$) for MAL-PDT versus excision. Cost-effectiveness results showed that 77% of the ICERs of 5-fluorouracil compared to excision were in the south-east quadrant of the CE-plane which represents more QALYs and lower costs. For MAL-PDT versus surgical excision 52% of the ICERs were in the north-east quadrant indicating more QALYs but higher costs. Both non-invasive treatments significantly more often lead to good or excellent cosmetic outcome.

Interpretation: The results indicate that compared with excision an increase of treatment failure by 18.9% (after 5-fluorouracil) and 23.1% (after MAL-PDT) cannot be excluded. When an increase by less than 22% is considered acceptable, 5-fluorouracil is non-inferior to excision. Treatment with 5-fluorouracil cream and MAL-PDT resulted in a better cosmetic outcome and 5-fluorouracil is in contrast to MAL-PDT cost-effective compared to excision. Therefore, 5-fluorouracil is preferred over excision and MAL-PDT in treatment of Bowen's disease.

The 40-gene expression profile (40-GEP) continues to demonstrate independent metastatic risk stratification and improved accuracy in risk assessment in a novel cohort of cutaneous squamous cell carcinoma (cSCC) patients with one or more risk factors

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Introduction and Objectives: Staging and traditional clinicopathological risk factors are used for risk factor assessment of cSCC, yet lack accuracy for prognostication of poor outcomes. Therefore, the 40-GEP test was developed and validated as an independent predictor of regional/distant metastasis based on the biology of the patient's tumor. The 40-GEP test stratifies patients diagnosed with primary cSCC having one or more risk factors into three statistically significant risk groups: Class 1 (Low- with <7% metastasis rate), Class 2A (Moderate- with 20-25% metastasis rate), or Class 2B (High- with >50% metastasis rate).^{1,2} The current study evaluates the performance of the 40-GEP in a novel cohort and its ability to improve metastatic risk prediction when combined with staging systems.

Materials and Methods: The 40-GEP test was conducted on archival, primary cSCC tumors with known patient outcomes that met clinical testing criteria (n=534) from 45 different clinical sites. Risk stratification was assessed using Kaplan-Meier analysis and log-rank test. Cox models were used to compare Class 1 vs. Class 2 and risk prognostication of clinicopathologic staging vs. staging+40-GEP.

Results: This cohort had an overall metastasis rate of 14.6%. Kaplan-Meier analysis demonstrated a statistically significant separation in metastasis-free survival rates between Class 1 (n=309; 93.2%), Class 2A (n=200; 76.5%), and Class 2B (n=25; 60%) (p<0.001). Univariate Cox models demonstrated Class 2A and 2B had 3.8 and 7.0-fold increase in metastasis compared to Class 1 (p<0.001), respectively. Multivariate models for both American Joint Committee on Cancer (AJCC8) and Brigham and Women's Hospital (BWH) staging systems were significantly improved when 40-GEP was included in risk prediction (p<0.005). Importantly, when interaction terms were assessed, none were significant (p>0.05), indicating that the 40-GEP makes an independent contribution to risk assessment over staging alone.

Conclusions: In a novel cohort, the 40-GEP demonstrates consistent significant risk stratification in high-risk cSCC patients. The test provides independent value in predicting regional/distant metastasis and significantly enhances risk assessment accuracy over clinicopathologic staging alone.

Therapeutic effect of S-1 on locally advanced cutaneous squamous cell carcinoma of the head and neck

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Introduction and Objectives: Most cases of cutaneous squamous cell carcinoma (CSCC) are treated surgically; however, cases of locally advanced CSCC (LACSCC) that cannot undergo complete resection exist. Although recent National Comprehensive Cancer Network (NCCN) Guidelines have recommended the use of cisplatin-based regimens, epidermal growth factor receptor inhibitors, and anti-PD-1 antibodies, including cemiplimab and pembrolizumab, those regimens require intravenous administrations. S-1 is an oral drug with a low incidence of severe adverse events, which is indicated for head and neck cancer, including head and neck CSCC, in Japan. The aim of the present study was to evaluate the therapeutic effect of S-1 on LACSCC.

Materials and Methods: We included 14 consecutive patients with LACSCC treated with S-1 between 2008 and 2022 from two Japanese institutions. The clinical response was assessed based on the Response Evaluation Criteria in Solid Tumors. Progression-free survival (PFS) and overall survival (OS) were estimated with the Kaplan–Meier analysis. Toxicity was assessed according to Common Terminology Criteria for Adverse Events 5.0.

Results: The objective response rate was 78% (complete response [CR] rate, 64.3% [nine patients]). Of the nine patients who achieved complete response, six showed no evidence of recurrence during the follow-up (median follow-up, 13 months; range: 1–79 months). Three patients showed relapse after the achievement of CR and cessation of the S-1 treatment, two of whom resumed S-1 and underwent salvage surgery, leading to no recurrence subsequently. One patient developed lung metastasis and died, although S-1 therapy was resumed. The median PFS was 12 months (1-year PFS, 50%; 2-year PFS, 40%), and the median OS was not reached (1-year OS, 82.2%, 2-year OS, 70.7%). The three patients who had bone spread/destruction at baseline did not show response. No cases of grade 4 adverse events occurred, and only one (7.1%) patient developed grade 3 anemia. All cases of toxicity were reversible after dose reduction or cessation of S-1.

Conclusions: The S-1 therapy showed effectiveness and ease of administration in patients with LACSCC of the head and neck, with a low toxicity rate. Therefore, it can potentially be used for LACSCC, together with other recommended regimens.

Utility of surveillance ultrasound for the detection of nodal metastatic disease in high-risk cutaneous squamous cell carcinoma

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Introduction/Objectives: High-risk cutaneous squamous cell carcinomas (cSCC) have an 11-37% risk of developing nodal metastases. However, there are no standardized recommendations on the use of imaging in disease management. We conducted this study to assess ultrasound (US) for the detection of metastatic nodal disease in high-risk cSCC.

Methods: Single-center retrospective study of subjects with high-risk cSCC (BWH stage T2b/T3, with perineural invasion, and/or recurrent) who underwent a dermatologist-performed lymph node US and computed tomography (CT) at diagnosis and in follow-up.

Results: Forty-four tumors were included, of which 5 (11.4%), 36 (81.8%), and 3 (6.8%) were BWH stage T2a, T2b, and T3, respectively. One (2.3%), 3 (6.8%), 39 (88.6%), and 1 (2.3%) were AJCC8 stage T1, T2, T3, and T4a, respectively. Five (11.4%) presented with recurrent tumors. Thirty-seven (84.1%) presented with cSCC on the head/neck. The tumors were treated with Mohs surgery only (16, 36.4%), Mohs with adjuvant radiation (ART) (23, 52.3%), excision only (2, 4.5%), or excision with ART (3, 6.8%). The median (range) follow-up time was 13.0 (0.03-35.1) months.

One-hundred eleven US and 141 CT scans were performed. The median (range) of US performed per subject was 2 (1-6). The median (range) of CT performed per subject was 3 (1-13). Metastatic cSCC and incidental metastatic melanoma were detected by both modalities and histologically confirmed in 2 (4.5%) and 1 (2.3%) subject, respectively. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of US were 100% (95% CI, 29.2%-100%), 93.5% (95% CI, 87.1%-97.4%), 30% (95% CI, 17.3%-46.7%) and 100%, respectively. This was **similar to CT, which had a sensitivity, specificity, PPV and NPV of 100% (95% CI, 31.0%-100%), 95.7% (95% CI, 90.4%-98.2%), 33.3% (95% CI, 9.0%-69.1%) and 100%, respectively.** The number needed to screen to identify one nodal metastasis by US and CT was 15 and 14 subjects, respectively.

Conclusions: US may be a reliable screening modality for metastases in high-risk cSCC. This data shows superior performance to prior reports, likely due to its application in a higher-risk population. While performing similarly to CT, US can be conducted in-office, lacks radiation exposure, and is cost-effective.

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