## Occupation and cutaneous melanoma: a 60-year cohort study of 22.8 million people in five Nordic countries

**Jose Hernán Alfonso**
Department of Dermatology & Venereology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

**Authors:** Jose Hernán Alfonso, Jan Ivar Martinsen, Sanna Heikkinen, Johnni Hansen, Elsebeth Lynge, Jóhanna Eyrún Torfadóttir, Ingrid Sivesind Mehlum, Jenny Selander, Marcin W. Wojewodzic, Eero Pukkala

**Background:** The Nordic countries have among the highest global incidence rates of cutaneous melanoma (CM), with steadily increasing trends over the past five decades. Ultraviolet radiation is the main established risk factor, but the contribution of occupational determinants is insufficiently understood. Nordic population-based registries provide a unique opportunity to study occupational risk patterns using high-quality cancer register data.
**Objective:** To identify occupational categories with increased risk of CM in the Nordic countries.
**Material and Methods:** We conducted a historical prospective cohort study with a 60-year follow-up (1961–2020) using the updated Nordic Occupational Cancer Study (NOCCA). The cohort included residents aged 30–64 years in Denmark, Finland, Iceland, Norway, and Sweden, based on record linkages between national censuses and cancer registries. Occupational codes were harmonized into 60 categories. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected CM cases, with expected numbers derived from stratum-specific person-years and national incidence rates.
**Results:** During 557 million person-years of follow-up, 176,000 incident cases of CM were identified (92,000 in men and 84,000 in women). For all Nordic countries combined, the statistically significantly elevated SIRs ranged from 1.08 among female communication workers to 1.66 among male dentists. Elevated risks were observed:
•For both women and men: technical, chemical, physical and biological workers; physicians; dentists; other health and medical workers; teachers; juridical workers; religious and social science–related workers; administrators and managers; clerical workers; sales and agents; transport workers; other public safety and protection workers; hairdressers.
•For men only: firefighters; policemen; military personnel; journalists; shop managers/assistants; postmen/sorters; printers.
•For women only: nurses; laboratory assistants.
**Conclusion:** This large, population-based study confirms and extends previous evidence that cutaneous melanoma risk varies across occupational groups in the Nordic countries, underscoring the importance of considering both occupational and non-occupational factors in prevention strategies.

## Recent melanoma incidence trend in Sweden and the effect of immigration

**Yodit Girmay**
Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden

**Authors:** Yodit Girmay, Rasmus Mikiver, Karolin Isaksson, Hildur Helgadottir

**Background:** Cutaneous melanoma is primarily caused by ultraviolet (UV) radiation, with fair-skinned individuals at greatest risk. Globally, over 75% of melanoma cases are UV-related. Sweden has the sixth highest melanoma incidence, though recent data show a decline among young people, potentially linked to increased immigration from populations with darker skin tones. Since 2000, Sweden's foreign-born population has grown substantially, now accounting for 20% of the total population. This study investigates whether demographic changes have influenced melanoma incidence and subtype distribution.
**Methods:** This population-based cohort study used data from the Swedish Melanoma Registry and Cancer Registry, which cover over 99% of primary invasive cutaneous melanoma diagnosed in Sweden. All patients diagnosed between 2000 and 2022 were included, excluding those born in Africa or Asia. Incidence rates per 100,000 inhabitants were calculated shown as average annual rates for every 3-year period from 2000 to 2022. Incidence data with the addition of the years 2023-2024 will also be presented. Joinpoint regression was used to evaluate statistical significance of temporal trends and change points.
**Results:** Among individuals aged 50–59 years, melanoma incidence increased steadily from 2000 to 2022. In age groups 20–49, incidence peaked in 2014, followed by declining trends until 2022. These trends remained after excluding individuals born in Africa or Asia, though the decline was less pronounced. Superficial spreading melanoma, the most common subtype, was the primary contributor to the declining incidence in individuals aged 20–49 and the increasing rates in those aged 50–59.
**Conclusion:** This study confirms the significant downward trend in melanoma incidence among 20–49-year-olds in Sweden, even when excluding individuals born in Asia or Africa. This suggests that the observed trend is not primarily driven by demographic shifts and may reflect other contributing factors such as behavioral changes in the population.

# Recurrence After Diagnosis of Primary Cutaneous Melanoma; Population-based Risk Prediction

**Anastasia Giorcelli**
Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway

**Authors:** Anastasia Giorcelli, Morten Valberg, Adele C. Green, Marit B. Veierød, Denise R. Costa, Jon Michael Gran, Henrik L. Svendsen, Henrik Jespersen, Bettina K. Andreassen, Trude E. Robsaham, Reza Ghiasvand

**Introduction:** The incidence of melanoma and number of melanoma survivors are increasing, highlighting a growing population that requires long-term care. Regular follow-up is crucial for early detection of recurrence. However, the risk of recurrence varies significantly between individuals. The factors predicting this variability have not yet been extensively studied, presenting a critical gap in understanding and clinical management.
**Aims:** To investigate patient and tumor characteristics predicting melanoma recurrence, and to develop a prediction model using data from national registries.
**Methods:** The study included 24,095 patients diagnosed with primary melanoma with TNM stages I-III, in Norway from 2008 to 2021. We used data from the Cancer Registry of Norway, Norwegian Melanoma Registry, and Norwegian Patient Registry. The cumulative probability and recurrence rate up to 10 years post-diagnosis were estimated using competing risk model. A model for predicting recurrence up to 5 years post-diagnosis was developed and internally validated using the Fine and Gray method, incorporating patient and tumor characteristics.
**Results:** Recurrence rate was highest during the first three years after the diagnosis. The characteristics associated with a higher recurrence rate were male sex, age over 70, TNM stage III, thickness greater than 4.00 mm, ulceration, nodular subtype, and a melanoma on the head/neck. For a patient with this combination of characteristics, the predicted probabilities of recurrence at 1, 3, and 5 years after diagnosis were 34%, 58%, and 75%, respectively. The 5-year prediction model demonstrated strong calibration and discrimination (optimal Brier scores range: 0.04-0.12; optimal area under the curve range: 0.77-0.81).
**Conclusions:** Our findings highlight the high-risk period and patient and tumor characteristics that are strong predictors of recurrence. The prediction model offers a valuable prognostic tool to help identify high-risk patients and to guide more personalized follow-up strategies.

## Teledermoscopic triage of melanoma-suspicious lesions with multiple assessors: Safe but impractical?

**Gustav Gede Nervil**
Department of Plastic Surgery, Copenhagen University Hospital Herlev and Gentofte, Denmark

**Authors:** Gustav Gede Nervil, Niels Kvorning Ternov, Henrik Lorentzen, Charles Kromann, Åsa Ingvar, Kari Nielsen, Martin Tolsgaard, Tine Vestergaard, Lisbet Rosenkrantz Hölmich

**Background:** The rising incidence of melanoma has significantly increased pathology work-load and surgical interventions, with many benign lesions unnecessarily excised. This study assessed teledermoscopic triage as a potential solution to optimize the melanoma care pathway by reducing unnecessary histopathological examinations while maintaining diagnostic safety.
**Methods:** We conducted a retrospective comparative diagnostic accuracy study of 250 patients referred through the expedited Cancer Pathway for suspected melanoma. Five board-certified dermatologists independently reviewed clinical and dermoscopic images, assigning diagnoses and management recommendations. We simulated teledermoscopic triage panels of 1, 2, 3, and 5 assessors using two consensus strategies: Caution Protocol (prioritizing highest-severity recommendations) and Majority Vote. Bootstrap analyses with 2000 iterations were performed for all unique combinations of teledermatologists in each panel configuration.
**Results:** Single teledermatologist triage demonstrated a sensitivity of 92.3% (95% CI 90.1-94.8) with a 58.7% reduction in unnecessary excisions (95% CI 54.2-63.5). Only a single melanoma, 0.4% (95% CI 0-0.6%), was missed. Implementation of safety procedures for cases with poor image quality or high diagnostic complexity further reduced the rate of incorrect management. Using the Majority Vote strategy, 3-assessor panels achieved 96.7% sensitivity (95% CI 93.2-100) and 51.9% specificity (95% CI 38.7-63.8).
**Conclusion:** Expert teledermoscopic triage is highly sensitive and could reduce excision procedures and histopathological examinations of benign lesions by half, while dismissing very few melanomas, even in high-prevalence pre-triaged populations.
It addresses the burden on pathology departments and surgical resources, optimizes resource allocation to where it is most needed, and improves the efficiency of the diagnostic process from clinical suspicion to pathological confirmation.
Multiple teledermatologists enhance sensitivity, but this comes at the expense of specificity unless a Majority Vote consensus strategy is implemented. Future teledermoscopy guidelines should include safety procedures and protocols for resolving disagreements between assessors.

# Real-World Evaluation of Two Dosing Regimens, NIVO3+IPI1 or NIVO1+IPI3 in Patients with Advanced Melanoma

**Hildur Helgadottir**
Karolinska University Hospital, Karolinska Institutet, Sweden

**Authors:** Hildur Helgadottir, Karl Björkström, Cissi Liu, Anna Fager, Lisa Liu Burström, Lars Ny

**Background:** Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1+IPI3) was approved for advanced melanoma in 2016. After the publication of the CheckMate 511 trial in 2019, the NIVO3+IPI1 regimen was also introduced as a therapeutic option in Sweden. However, the NIVO3+IPI1 regimen has not been approved in melanoma by regulatory authorities. In this study the efficacy and safety of the two dosing regimens was compared.
**Patients and methods:** Patients with advanced unresectable melanoma treated in routine clinical care with NIVO3+IPI1 or NIVO1+IPI3 at the Karolinska and Sahlgrenska university hospitals were included. Objective response rate (ORR), Overall survival (OS), progression-free survival (PFS), and immune-related adverse events (AEs) were compared between the two treatment groups.
**Results:** In total, 399 patients with advanced unresectable melanoma (stage III/M1a:n=69; M1b:n=53; M1c:n=138; M1d:n=139) were included, 209 had NIVO3+IPI1 and 190 NIVO1+IPI3. Median follow-up in the two cohorts was 41 (range 20-86) and 53 months (range 19-130), respectively. The ORR was 48.8% in NIVO3+IPI1 and 36.9% in NIVO1+IPI3 treated (P = 0.016). Adjusted hazard ratio (aHR) was 0.72 (95% CI 0.56-0.93, P = 0.011) for PFS and 0.65 (95% CI 0.48-0.86, P = 0.003) for OS. In the studied subgroups aHR for OS was also <1, in favor of the NIVO3+IPI1 regimen. The incidence of irAEs grade 3-5 was 30.6% with NIVO3+IPI1 vs. 51.1% with NIVO1+IPI3 (P<0.001). Of the patients treated with NIVO3+IPI1, 57.4% received all four doses, compared to 33.7% with NIVO1+IPI3 (P<0.001).
**Conclusion:** The present study shows in a real-world setting, that the NIVO3+IPI1 regimen demonstrated superior efficacy compared to NIVO1+IPI3, possibly related to a beneficial safety and tolerability profile allowing for more received doses. The findings raise concerns regarding possible overtreatment with the higher dose of ipilimumab in the traditional NIVO1+IPI3 regimen and warrants continued evaluation of the flipped dose NIVO3+IPI1 regimen in advanced melanoma.

# Grand SLAM: A Prospective Randomised Multicentre Study of Shortened versus Standard Duration Adjuvant Immune Checkpoint Inhibition (ICI) for Stage IIB-C, III and IV Cutaneous Melanoma (CM)

**Gustav Ullenhag**
Department of Oncology, Uppsala University Hospital, Sweden

**Authors:** Patric Ejder, Henrik Jespersen, Micaela Hernberg, Lars Ny, Ana Carneiro, Sander Ellegård, Kalle Mattila, Roger Olofsson Bagge, Georgios Fountoukidis, Yvonne Brandberg, Mario Mandala, Brent O´Carrigan, Bastian Schilling, Ana Arance, Omid Hamid, Anders Berglund, Hildur Helgadottir and Gustav Ullenhag

**Background:** Adjuvant treatment with PD-1 inhibitors for 12 months has been the established standard of care for resected stage IIB-IV cutaneous melanoma patients. In other solid tumours (e.g. breast and colorectal), a shorter duration of chemotherapy (no data with immunotherapy) has been shown to be non-inferior with improved toxicity profile. More recently, neoadjuvant immunotherapy for clinically detectable stage III and stage IV disease has been introduced. There is no clear biological rationale for the chosen duration, and no studies have investigated duration of adjuvant treatment with ICI. A reduced duration of adjuvant therapy could lead to less toxicity from reduced drug exposure, patients returning to their lifes sooner, significantly lower drug costs and better healthcare resource utilization. There remains significant interest from patients and clinicians to address this important question.
**Methods:** Grand SLAM is a prospective phase III randomised, controlled international multi-centre non-inferiority study. The primary objective is to investigate if short (6 months) has equal efficacy as long (12 months) duration of (neo-)adjuvant ICI in relation to distant metastasis-free survival and relapse-free survival at landmark analysis at 2 years. After radical surgery of stage IIB-C, III or IV cutaneous melanoma, patients are randomly assigned 1:1 to short or long adjuvant treatment with either nivolumab or pembrolizumab. Patients who have received neoadjuvant treatment with major pathological response are excluded. The sample size of 1,880 patients was determined based on a non-inferiority margin of 4%, a significance level of 0.045 and 80% statistical power. An interim analysis will be conducted when 2/3 of patients are accrued. Biomarkers and the role of food supplements for relapse (MelKo) will be investigated in prespecified substudies.
**Discussion:** This is the first randomised study to assess a shorter duration of (neo-) adjuvant standard single agent ICI in cutaneous melanoma. As of August 2025, the study is recruiting patients in the Nordic countries. Centres in other countries will open shortly.

# Predictive markers of response to immunotherapy in melanoma using clinical trial data

**Kjersti Tefre Davidsen**
Department of Oncology, Haukeland University Hospital, Bergen, Norway

**Authors:** Kjersti T Davidsen, Sura Aziz, Austin J Rayford, Franziska SM Görtler, Muntequa Siraji, James B Lorens, Lars A Akslen, Cornelia Schuster, Oddbjørn Straume

**Background:** The treatment of malignant melanoma has been revolutionized by immunotherapy with checkpoint inhibitors. A disease that is inherently chemo- resistant range among the best responders to immunotherapy, with the possibility for long- lasting responses. However, half of all melanoma patients will not respond to immunotherapy and there is an urgent need for predictive biomarkers. Harmful side effects of immunotherapy are common and can have severe and even life-threatening consequences. Identifying predictive biomarkers for response is necessary for achieving tailored cancer medicine where expensive and potentially toxic treatments are reserved for those most likely to benefit from them.
A successful predictive biomarker for response to immunotherapy should identify the tumors that are dominated by an immunosuppressive mechanism that will be targeted and hence effectively shut down by the checkpoint inhibitor. We propose that FOXP3+ regulatory T cells (Tregs) represents such a target. Tregs are crucial regulators of immune tolerance and are key players in suppressing anti-tumor immunity and preventing autoimmunity, and Tregs are abundantly present in melanoma.
**Methods:** Pretreatment biopsies from melanoma patients from a national, multicenter, randomized Phase Ib/II study (A randomized phase Ib/II study of the selective small molecule AXL inhibitor bemcentinib (BGB324) in combination with either dabrafenib/trametinib or pembrolizumab in patients with metastatic melanoma) have been analyzed by immunohistochemistry, whole exome sequencing and RNA sequencing. Spatial phenotyping with imaging mass cytometry is currently under way.
**Results:** Quantification of Tregs by FOXP3 staining is a powerful positive predictive marker of response to PD-1 inhibitors in this study. These and other preliminary results will be presented.

# Neoadjuvant LTX-315 in combination with pembrolizumab in resectable stage III/IV melanoma (NeoLIPA trial): Rationale, protocol and preliminary results.

**Astrid Berild**
Oslo University Hospital, Department of Oncology, Oslo, Norway

**Authors:** Astrid Berild, Anna Katharina Winge-Main, Marta Sølvi Nyakas, Sverre Edvard Truls Ryder, Robert Hermann, Lars Inge Frich, Audun Elnæs Berstad, Marianne Fretheim, Marike Feenstra, Katrine Høeg Liland, Assia Vassileva Bassarova, Gunhild Mari Mælandsmo, Henrik Jespersen

**Background:** Clinically detectable, resectable stage III or oligometastatic IV melanoma can be surgically cured, though it carries a high risk of recurrence. Neoadjuvant pembrolizumab is now the standard of care, but the rate of pathologic complete response (pCR), a surrogate for longterm benefit, is only modest (20%). Combined checkpoint inhibition has been shown to increase the rate of pCR, but at the cost of a high risk of severe adverse events. Consequently, new neoadjuvant treatment regimens are needed. We hypothesize that intratumoral administration of the oncolytic peptide LTX-315 will enhance the effect of pembrolizumab as neoadjuvant treatment prior to surgery for stage III or IV melanoma.
**Methods:** NeoLIPA is a phase II open label clinical trial of neoadjuvant LTX-315 in combination with pembrolizumab in patients with clinically detectable and resectable stage III-IV melanoma. Patients will receive pembrolizumab 200 mg IV every three weeks for a total of three doses, while LTX-315 will be given as five weekly intratumoral injections. After 9 weeks, patients will undergo surgery. The primary endpoint is the rate of pCR.
**Results:** To date, 9 of 27 patients have been enrolled. Preliminary results will be presented.

## Uveal, mucosal and acral melanomas: Long-term trends in incidence, survival and treatment in Norway

**Nils Leitzinger**
Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Norway

**Authors:** Nils Leitzinger, Ragnhild S Falk, Anna Winge-Main, Henrik Jespersen, Nils A Eide, Adele C Green, Anna Skog, Trude E Robsahm, Marit B Veierød

**Background:** Uveal melanoma (UM), mucosal melanoma (MM) and acral melanoma (AM) are rare, non-UV-related melanoma subtypes with poorer prognosis than non-acral cutaneous melanoma. Population level trends remain understudied. We investigated long-term trends in incidence and survival for UM, MM and AM as well as treatment for MM and AM in the Norwegian population.
**Methods:** We analysed data from the Cancer Registry of Norway for all patients diagnosed with primary UM (1993–2021), MM (1955–2021) and AM (1993–2021). Age-standardized incidence rates (European standard population), net survival (Pohar-Perme estimator) for survival trends, and overall survival by treatment modality were calculated.
**Results:** We identified 1,497 patients with UM (50% men), 998 with MM (30% men) and 378 with AM (42% men). Age-standardized UM incidence rates increased by about 50% over 29 years, primarily driven by localized, T1 and T2 choroidal melanoma. The MM incidence doubled over 67 years, while AM exhibited a U-shaped pattern over 29 years. Ten-year net survival for UM remained stable, with notable improvement for choroidal melanoma. Ten-year net survival was substantially lower for patients with MM compared to UM and AM. For MM, purely surgical approaches have declined, while multimodal treatments, including immunotherapy have increased. The shift toward immunotherapy has been accompanied by an improvement in net and overall survival for MM patients. For AM, surgical approaches, net survival over time, and overall survival by treatment modality remained largely constant.
**Conclusions:** Improved detection of choroidal melanoma likely contributed to increased UM incidence and choroidal melanoma survival. The MM incidence has doubled, with recent treatment advances accompanied by improved survival. A U-shaped incidence pattern was observed for AM, with largely stable treatment trends and survival.

## A nationwide study on Pediatric Melanoma in Denmark: Outcomes, Tumor Characteristics, and Follow-Up Practices Since 2000

**Ida Kirkeskov Wulff**
Department of Plastic Surgery, Copenhagen University Hospital, Herlev and Gentofte, Herlev, Denmark

**Authors:** Ida K. Wulff, Grethe Schmidt, Mette Bybjerg-Grauholm, Lisbet R Hölmich, Louise Mahncke Guldbrandt, Mathias Ørholt, Linnea Langhans

**Background:** Melanoma in children is rare. It often presents and behaves differently from adult melanoma. This makes diagnosis and treatment difficult. The aim of this study was to analyze pediatric melanomas diagnosed since 2000 in Denmark in terms of clinicopathological features, prognosis and follow-up.
**Methods:** In this retrospective cohort study, we reviewed medical charts and pathology reports for all patients up to 15 years diagnosed with cutaneous melanoma in Denmark from 2000–2023. Surgical treatment and follow-up programs were analyzed to assess treatment regiments and prognosis. Information on local recurrence and metastasis was obtained from clinical assessments and pathology findings. We evaluated tumor characteristics (mitosis, ulceration, thickness and tumor subtype) together with surgery characteristics (excision margins, sentinel node biopsy, and additional surgeries).
**Results:** The study included 45 patients with a median age of 12 years, with a median follow-up time of 14 years. All patients underwent re-excision and 82% had sentinel node biopsy performed, of whom 50% were positive. Seventeen patients underwent completion lymph node dissection, which was standard at the time in patients with positive sentinel node. Local recurrence was seen in three patients and distant metastasis in one patient, who died. This patient was the only one to receive oncological treatment. Most patients were followed as adult high-risk melanoma, including clinical visits every three months the first two years, then every six months for the following three years, including PET/CT scans at 6, 12, 24 and 36 months.
**Interpretation:** Pediatric melanomas are rare and often present with aggressive histopathological features; however, outcomes were generally favorable, with only one melanoma-related death observed over the 25-year study period. The favorable outcome profile could indicate that pediatric melanoma may be considered a low-grade neoplasm.

## Path towards Uveal Melanoma transcriptomic Atlas

**Vojtech Hanicinec**
Oslo University Hospital, Department of Ophthalmology, EYETEC, Oslo, Norway

**Authors:** Vojtech Hanicinec, Xavier Tekpli, Marie Fongaard, Sunniva Bøstrand, Michael Frisk, Giang H. Nguyen, Thomas P. Bærland, Huy Bao Ngo, Nils A. Eide, Øystein Garred, Morten C. Moe, Jürgen Geisler, Henrik Jespersen/Agate Noer

**Aims/Purpose:** Uveal melanoma (UM) is the most common intraocular malignancy in adults and frequently leads to metastatic disease with limited treatment options. While bulk transcriptomic studies have identified molecular subtypes and prognostic markers, the spatial and cellular heterogeneity of UM remains poorly understood. Our aim is to construct a high-resolution transcriptomic atlas of UM by integrating single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics, to better characterize the tumor microenvironment and its role in disease progression.
**Methods:** We analyzed 24 UM samples (11 from patients without metastasis, 9 from patients with metastasis, and 4 metastatic samples paired with primary tumors) using the 10x Genomics Visium platform. Formalin Fixed Paraffin-Embedded (FFPE) tissues underwent spatially barcoded RNA capture and sequencing. Data were processed with Space Ranger and Scanpy. To complement spatial data, we integrate publicly available scRNA-seq datasets from UM as well as our own in-house single-cell transcriptomic data.
**Results:** Data generation and analysis are ongoing. Preliminary observations highlight regional immune and stromal heterogeneity across samples. Integration of spatial and single-cell modalities is expected to uncover diverse cellular states and tumor–immune interactions. Publicly accessible atlas will be developed to facilitate community exploration of UM biology.
**Conclusions:** By combining spatial and single-cell transcriptomic data, this study aims to generate a comprehensive transcriptomic atlas of UM. This resource will advance our understanding of tumor architecture and cell-cell interactions, ultimately informing prognostic biomarkers and therapeutic strategies.

## Head and Neck Mucosal Melanoma: Prognostic Factors and Survival in a Single-Center Experience

**Marcus Nyberg**
Department of Otorhinolaryngology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

**Authors:** Marcus Nyberg, Malin Berg, Roger Olofsson Bagge

**Background:** Head and neck mucosal melanoma (MM) is a rare and aggressive malignancy with high recurrence rates and poor prognosis. Evidence regarding clinical outcomes remains limited, and treatment strategies are heterogeneous.
**Methods:** We retrospectively analyzed 40 consecutive head and neck MM patients treated at Sahlgrenska University Hospital 2008–2025.
**Results:** Median age was 71 years, 50% females. Tumor sites included sinonasal tract in 36 patients (90%) and oral cavity in 4 patients (10%). Tumor stage distribution was Stage III in 11 patients (28%), IVA in 20 (55%), IVB in 4 (15%) and IVC in 5 (13%). Mean tumor size was 39 mm (IQR 30-59.5 mm). Nodal metastases were present in 8 patients (20%), with level I or II involvement in all cases.
Curative intent treatment was administered to 32 patients (80%), frequently combining surgery and adjuvant radiotherapy (63%). Surgery was performed in 28 patients (88%), with negative margins in 8 (29%) and uncertain in 13 (46%). Neck dissection was carried out in 3 patients (11%). Neoadjuvant chemotherapy was administered to 7 patients (22%). Surgical morbidity was low, with Clavien–Dindo complication grade I in 7%, grade II in 14% and grade IIIb in 7%.
Median overall survival (OS) was 35 months for the entire cohort, significantly shorter for patients treated with non-curative compared to curative intent (9 vs 44 months, $p<0.001$). Among the 32 patients treated with curative intent, there was no significant correlation between tumor stage and OS. Patients with oral tumors, compared to sinonasal, had numerically but non-significantly better outcomes (5-year OS 75% vs 36%, $p=0.527$)
**Conclusions:** Head and neck MM remains a therapeutically challenging disease with poor long-term survival. Multimodal treatment offers improved outcomes, although surgical margins are often uncertain. Consistent with earlier reports, patients with oral cavity primaries appear to have better prognosis.

## Magnetic seed localization in patients with nodal stage III melanoma and neoadjuvant immunotherapy, a feasibility study

**Ellen Krabbe**
Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

**Authors:** Ellen Krabbe, Andrew Wong, Axel Nelson, Lars Ny, Anne Huibers, Roger Olofsson Bagge

**Introduction:** Current guidelines for resectable macroscopic stage III melanoma recommend neoadjuvant immunotherapy and therapeutic lymph node dissection (TLND), followed by adjuvant treatment. However, the PRADO trial showed that TLND and adjuvant treatment could be omitted in patients with a major pathological response (MPR) in the index node after neoadjuvant immunotherapy. This questions whether TLND is necessary in patients with MPR after index node resection (INR). The aim of this study was to evaluate the feasibility of using a magnetic seed (Magseed®) to localize the index node for selective removal in patients with stage III melanoma receiving neoadjuvant immunotherapy.
**Method:** From November 1, 2024 to August 5, 2025, twenty patients with resectable stage III melanoma and planned TLND after neoadjuvant immunotherapy were enrolled. Prior to treatment, a Magseed® was placed in the largest metastatic node under ultrasound guidance. INR was performed concurrently with TLND, 6–8 weeks after therapy initiation. Before skin incision, a handheld magnetometer (Sentimag®) was used to localise the marker before incision. The index node was analysed separately for pathological response and seed presence.
**Result:** Eighteen of the planned 20 patients have undergone surgery so far. Preliminary data show successful transcutaneous localization and retrieval of the marked node in 17 of 17 patients (100%) with femoral or axillary lymph node metastases. The study is is fully recruited but two patients are still under neoadjuvant treatment.
Discussion: In this first feasibility trial evaluating Magseed® as a marker for INR in patients with stage III melanoma, preliminary data supports the feasibility of this approach.

## Peri-operative treatment with tranexamic acid (TXA); prognostic and treatment related impact of the plasmin(ogen) pathway in melanoma

**Marie Øbo**
Dept. of Plastic Surgery, Aarhus University Hospital, Denmark

**Authors:** Louise Bønnelykke-Behrndtz, Christian Lodberg Hvas, Julie Brogaard Larsen and Martin Roelsgaard Jakobsen

The PRIME trial (Perioperative treatment with tranexamic acid in melanoma) is a national randomized controlled trial, within the Danish Melanoma Group. Over an estimated period of three years (2023-2026), we include adults (n=1204) diagnosed with cutaneous melanoma (tumor grade≥T2b) and eligible for sentinel node dissection, to receive either perioperative treatment with tranexamic acid or placebo.
In PRIME-Translational, we conduct a comprehensive analysis of a proportion of these participants (n=250) exploring how melanoma surgery affects molecular pathways of fibrinolysis, inflammation, and the gut microbiome and how perioperative treatment with tranexamic acid impacts prognostic and treatment-related outcomes, aiming to provide a rationale for novel and early targets of therapy for patients with melanoma.
Blood samples are assessed at baseline, 2 hours-, 12 days-, 3, 12, and 24 months or post-surgery or at first relapse, analyzing markers of fibrinolysis (SuPAR, fibrinogen, fibrin D-dimer, t-PA, PAI-1, and fibrinolytic capacity) and inflammation (hs-CRP, differential count, macrophage markers and a wide range and panels of inflammatory cells and cytokines). In addition, we assess fecal samples at baseline, 12 days, 3-, and 24-months post-surgery or at first relapse exploring the composition of intestinal microbiome and metabolites.
The markers are associated with known prognostic markers of melanoma (Breslow thickness, presence of ulceration, mitosis), clinical stage (presence of micrometastases), and relapse (local, regional, or systemic).

# Neoadjuvant immunotherapy for patients with resectable stage III/IV cutaneous melanoma – a Swedish retrospective real-world study (NEO-MEL)

**Axel Nelson**
Sahlgrenska University Hospital, Sweden

**Authors:** Axel Nelson, Ellen Krabbe, Karl Björkström, Anne Huibers, Braslav Jovanovic, Christian U. Blank, Ana Carneiro, Karolin Isaksson, Gustav J. Ullenhag, Hildur Helgadottir, Lars Ny and Roger Olofsson Bagge

**Background:** Randomized trials have shown that neoadjuvant PD-1 blockade, alone or in combination with CTLA-4 inhibition, yields superior outcomes compared with adjuvant PD-1 therapy in patients with resectable stage III–IV cutaneous melanoma. The applicability of these findings to unselected, real-world populations is uncertain.
**Methods:** We performed a retrospective multicenter study at four academic hospitals in Sweden. Eligible patients had macroscopic, resectable stage III–IV cutaneous melanoma and received neoadjuvant immune checkpoint inhibitor (ICI) therapy between January 2022 and September 2024. Clinical and pathological data were obtained from medical records.
**Results:** In total, 172 patients were included, with a median age of 71 years. Sites of disease were lymph node metastases (67%), in-transit lesions (19%), combined nodal and in-transit metastases (8%), and distant stage IV disease (6%). Patients received a median of two cycles of neoadjuvant ICI; 96% were treated with PD-1 monotherapy. Planned surgery was completed in 92% of cases. Reasons for not undergoing surgery included progression to stage IV disease, patient choice, or progression to locally inoperable disease.
Pathological evaluation showed major response (MPR) in 42%, partial response (pPR) in 7%, and no response (pNR) in 31%. Radiological response (CT) correlated poorly with pathological findings. Following surgery, 64% of patients received adjuvant PD-1 therapy (median 5 cycles), while 25% received no adjuvant treatment. With a median follow-up of 12 months, the estimated 12-month relapse-free survival (RFS) was 73% (95% CI, 66–82). RFS rates were 95% in patients with MPR, 92% in pPR, and 58% in pNR.
**Conclusions:** This Swedish real-world cohort demonstrates that neoadjuvant ICI is feasible in real-world patients with resectable stage III–IV cutaneous melanoma, with efficacy outcomes comparable to those reported in clinical trials.

## Nevoid and desmoplastic melanoma – two important diagnostic pitfalls

**Assia Bassarova**
Department of pathology, Oslo University Hospital, Norway

**Authors:** Assia Bassarova, Alec Thompson

Nevoid melanoma (NM) is a rare subtype of melanoma which is considered as one of the most difficult to diagnose. Clinically and histopathologically it resembles a benign nevus, often resulting in misdiagnosis and allowing the tumor to progress.
Desmoplastic melanoma (DM) is another rare variant of melanoma with distinct histopathologic features and immunophenotypes. Its recognition is relevant because it represents a diagnostic pitfall for both clinicians and pathologists.
The two entities differ substantially both as clinical presentation and morphologically. The immunohistochemical profile, molecular findings and prognosis are different as well.
Here we present routine diagnostic cases from the Department of Pathology, Oslo University Hospital, diagnosed between 2019 and 2025. The focus is on the main morphological characteristics of both entities, as well as on some minor histological clues which can be used in the pathology practice. The immunohistochemical profile is discussed in detail, emphasising on the importance of some markers as Melan A, HMB-45, p16 and Ki67. Data from molecular profile are integrated to support the diagnosis of melanoma.
We discuss the list of differential diagnostic entities. Both the morphological clues and specific immunohistochemical markers, as well as useful genetic alterations will be summarized in a helpful diagnostic algoritm.
Finally, we will focus on the current classification of these lesions and the importance of correct diagnosis, particularly given the substantial prognostic differences and divergent treatment options.

# Cumulative Cost Analysis of Skin Surveillance versus Cancer Treatment in CDKN2A- or CDK4-related Familial Melanoma: Insights from the EU PREVENTABLE Project

**Birte B. Lundhaug**
Western Norway Familial Cancer Center, Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway

**Authors:** Birte B. Lundhaug, Cathrine Bjorvatn, Ingeborg M. Bachmann, Rita Grude Ladstein, Oddbjørn Straume, Jurgita Januleviciüte Gangstøe, Marianne Tveit Haavind, Ricardo Amorim, Sara P. Pereira, Liliana Sousa, Janneke Schuurs-Hoeijmakers, Katja Verbeek, Laura Duran-Lozano, Judith Balmaña, Nuria Dueñas, Joan Brunet, Mia Quante, Amalia Nanciu, Stefan Aretz, Veronica Höiom, Svetlana Bajalica-Lagercrantz, Marbélia Fernandes, António Moreira, Rui Sousa, Carla Oliveira, Hildegunn H. Vetti

**Background and objective:** Familial melanoma (FM), caused by germline pathogenic variants in CDKN2A or CDK4 predispose strongly to an increased lifetime risk of cutaneous melanomas, as well as an increased risk of pancreatic cancer. While international guidelines recommend genetic testing and intensive skin surveillance for these individuals, the cumulative healthcare costs in FM management remain largely unexplored. Within the framework of the European PREVENTABLE consortium, we aim to develop a cost-model to investigate cumulative costs related to FM clinical trajectories.
**Methodology:** Based on clinical and multidisciplinary expertise, we developed an FM care matrix that maps patient trajectories across six treatment modules: genetic diagnosis, risk assessment, surveillance, treatment of early-stage and advanced-stage cancer, and post-treatment follow-up. Using diagnosis-related groups (DRGs) and public reimbursement rates, each sub-procedure was cost-estimated in NOK. An IT tool was developed for systematic clinical data registration and ethical approval was obtained. Validation of the matrix was done using retrospective real-world data from five European partner centers.
**Results:** By the end of August, 252 FM patient trajectories have been registered in the IT tool. Based on the collected data, we will be able to map the distribution of patient trajectories across the six treatment modules and calculate cumulative costs per module. This will allow for cost comparisons between modules and provide deeper insights into the costs of genetic testing and regular dermatologic surveillance for FM, compared to the costs of treating melanoma at early and advanced stages.
**Conclusion:** Gaining deeper insights into the costs associated with assessment, surveillance, and treatment for FM is essential, especially for optimal allocation of healthcare resources and ensuring sustainable care delivery. We look forward to sharing fresh results from this ongoing multinational cohort, led by the European PREVENTABLE consortium, at NMM 2025.

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## Cell state dynamics shape the immunogenicity of cutaneous melanomas

**Teitur Sævarsson**
University of Iceland, Reykjavík, Iceland

**Authors:** Teitur Sævarsson, Adrián López García de Lomana, Sólrún Melkorka Maggadóttir, Siggeir Fannar Brynjólfsson, Eiríkur Steingrímsson, Sebastien Wälchli, Else Marit Inderberg and Berglind Ósk Einarsdóttir

**Introduction:** Melanoma cells frequently dedifferentiate in response to inflammation. This process entails a loss of melanocytic antigens, a gain in neural crest markers and occurs through downregulation of MITF, the master regulator of the melanocytic lineage. While antigen loss reduces immunogenicity, dedifferentiation may have broader immune related implications. We have recently described how dedifferentiating melanoma cells increase their expression of the immune checkpoint ligand PD-L1, multiple MHC complex genes and several immune modulating cytokines in response to IFN-γ, a clinically relevant inflammatory cytokine. In this talk, I will present these findings and describe a co-culture system we have established to explore how melanoma differentiation status affects interactions with cytotoxic T cells.
**Methods:** MITF expression of the human melanoma cell line 624Mel was knocked down via siRNA transfection to induce dedifferentiation, and cells subsequently stimulated with IFN-γ. The effects of dedifferentiation on gene and protein expression were estimated via RNA-sequencing, qPCR, Luminex assay, flow cytometry and western blotting. The mechanism facilitating increased PD-L1 expression was characterized using small molecule inhibitors and siRNA against relevant signalling pathway components.
Based on relative differentiation levels, four human melanoma cell lines were chosen and retrovirally transduced to express GFP. TCR-redirected T cells were generated via retroviral transduction with MART-1 or mutant TGFβR2-specific receptors. Co-cultures were performed in an Incucyte S3 live-imaging system.
**Results:** Increased PD-L1 expression in dedifferentiated melanoma cells appears mediated through the JAK-STAT1-IRF1 axis, indicating enhanced canonical IFN-γ signaling following dedifferentiation.
Preliminary results indicate that as expected, dedifferentiation impairs T cell recognition through loss of antigen. In addition, dedifferentiated melanoma cells may have impaired antigen-processing abilities.
**Conclusions:** In addition to antigen loss, dedifferentiated melanoma cells develop a distinct immunological gene expression profile. However, the functional relevance of this mechanism remains to be fully determined.

## Polygenic risk scores for melanoma in the Swedish population

**Veronica Höiom**
Karolinska Institutet, Sweden

**Authors:** Veronica Höiom, Muyi Yang, Ivette Raices Cruz, Jane Yan, Hildur Helgadottir

**Background:** The incidence of malignant melanoma has steadily increased over the years, with a growing number of patients being diagnosed with multiple tumours. Enhanced preventive strategies are needed to help reverse this concerning trend. There is substantial evidence supporting a hereditary component in the aetiology of melanoma and around 10% of the patients belong to a melanoma family. However, pathogenic variants in high-penetrance genes have been identified in only a small subset of these families, suggesting that polygenic inheritance may play a significant role in melanoma susceptibility.
The aim with this study is to calculate polygenic risk scores (PRS) for melanoma in Sweden. The PRS combines the risk of numerous genetic variants, each conferring a small effect on melanoma risk, but when combined the risk could be substantial.
**Methods:** We genotyped 68 genetic variants, previously associated with melanoma susceptibility, and calculated the PRS for 602 melanoma patients, both familial and sporadic cases (single or multiple primary) and 180 control individuals. In addition, we extracted genotypes from the SweGen variant frequency dataset (1000 Swedish population-based controls) and calculated their corresponding PRS.
**Results:** The PRS was significantly higher in melanoma patients compared to controls and had an area under the receiver operating characteristic curve of 0.723. Highest scores were observed in familial cases followed by patients with multiple melanomas. The risk for melanoma was four times higher in individuals with a PRS above the 90th percentile compared to individuals with a PRS in the 40–60th percentile. Significant predictors of PRS were skin type, hair color and number of melanomas.
**Conclusion:** PRS may be a useful tool for better risk classification of individuals beyond that identified from traditional risk factors. We hope this study will improve future preventive and screening guidelines, which subsequently can halt the concerning trend of increasing melanoma incidence.

## Gene expression signature and cell populations predict progression in stage III melanoma patients

**Eivind Valen Egeland**
Department of Tumor Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital Oslo, Norway

**Authors:** Eivind Valen Egeland, Ieva Ailte, Assia Bassarova, Marta Nyakas, Anke MJ Kuijpers, James Wilmott, Alexander CJ van Akooi, Vivi Ann Flørenes, Jon Amund Kyte, Henrik Jespersen, Gunhild M. Mælandsmo

Melanoma incidence is rising rapidly, and Norway has one of the highest incidence and mortality rates globally. Biomarkers and improved treatment selection are urgently needed to improve outcomes for the patients, who are often young and risk losing many years to the disease. When detected early, melanoma has a good prognosis, in contrast, metastatic melanoma (stage IV) is highly aggressive. The last decade has brought dramatically improved treatments with immune checkpoint inhibitors (CPI), notably PD-1 blockade, leading to long-term survival in a significant proportion of patients. Patients with regional lymphatic metastases (stage III), can be cured by surgery, but have a high risk of metastatic relapse. There is currently no reliable biomarker for identifying patients who will benefit from adjuvant treatment.
In this study, regional lymph nodes were collected from stage III melanoma patients at surgery in two distinct cohorts. In the first cohort, bulk gene expression data were generated by NanoString from patients receiving surgery without adjuvant therapy (n=125). Using Lasso regression with leave-one-out cross validation, we defined a gene signature (MEL7) with corresponding weights predicting poor prognosis in this patient group. This was further evaluated in both internal (n = 36; $p<0.001$; HR = 9.7[1.7-56.6]) and external (n = 57; $p<0.0005$; HR = 3.2[1.3-8.0]) datasets from untreated patients, as well as in patients treated with adjuvant anti-PD-1 at Melanoma Institute Australia (MIA; n = 43; p=0.012; HR = 2.7[1.1-6.8])).
The second cohort was collected for utilizing CyTOF to determine cellular composition in pre-treatment surgical specimens (n=29) from patients treated with adjuvant anti-PD-1. This allowed us to identify a subset of plasma like cells strongly linked to better outcome (n = 29; $p<0.001$; HR = 0.16[0.03-0.76]) in patients treated adjuvant with anti-PD-1.
Altogether these results highlight the potential for further improving patient stratification in stage III melanoma and suggest that utilizing gene expression and/or cell subset populations as prognostic biomarkers can help us define poor outcome groups after treatment with adjuvant anti-PD-1.

## Can immunological phenotype predict response after isolated limb perfusion for patients with in-transit metastasis of melanoma?

**Anne Huibers**
Sahlgrenska Centre for Cancer Research, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

**Authors:** Anne Huibers, Anna Constantinescu and Roger Olofsson Bagge

**Background**: Isolated limb perfusion (ILP) is a regional treatment for patients with melanoma in-transit metastases (ITM) confined to extremities, using a high dose of melphalan. ILP has a high response rate, with approximately 60% having a complete response (CR). This study aimed to validate if pre-operative immunological phenotype could be a predictive factor for CR after ILP.
**Methods:** A total of 132 patients undergoing ILP as a first treatment for melanoma ITM between January 2012 and March 2023 were included in this study. The number and percentage of naïve and memory T and B cell subtypes, as well as natural killer (NK) cells were characterized by analyzing pre-operative blood samples using fluorescence activated cell sorting (FACS). Predictive clinical and immunological factors for CR after ILP were analyzed using univariable and multivariable analysis.
**Results:** Out of the 132 patients, response was evaluable in 119 (90%) and 53% achieved a CR. After adjustment of age, sex, number of metastases and largest metastases, immunological factors significantly and independently associated with an CR after ILP, were percentage of CD3+8+ cells (OR 1.07, CI 95% 1.02-1.13, p=0.012) and percentage of CD3+8+45RA+ cells (OR 1.11, CI 95% 1.01-1.22, p=0.029).
**Conclusion:** Immunological phenotype described as percentage of cytotoxic T-cells and naïve cytotoxic T-cells are together with tumor burden important predictive factors for response after ILP for patients with melanoma ITM. These findings may support improved patient selection and individualized treatment algorithms, but might also be a foundation for future novel treatment combinations, where an ongoing trial is currently combining ILP with a PD-1 inhibitor (ClinicalTrials.gov NCT03685890).

# Analysis of ctDNA for early detection of relapse in patients with stage III-IV cutaneous melanoma receiving adjuvant PD-1 inhibitor therapy

**Anna Fager**
Department of Oncology, Sahlgrenska Academy, University of Gothenburg, Sweden

**Authors:** Anna Fager, Kerryn Elliot, Henrik Jespersen, Peter Micallef, Kina Höglund, Roger Olofsson Bagge, Erik Lekholm Larsson, Anders Ståhlberg, Lars Ny

**Background:** Patients with stage III-IV cutaneous melanoma (CM) given adjuvant immunotherapy can be monitored by biomarkers, including S100B and LDH, or radiological examinations to detect relapse of disease. The present study evaluated circulating tumor DNA (ctDNA) as a potential biomarker for detection of relapses in patients receiving adjuvant immunotherapy.
**Method:** Patients at the Sahlgrenska University Hospital diagnosed with stage III-IV CM receiving adjuvant PD-1 inhibitor therapy were enrolled in the study between May 2021 and July 2023. Blood samples were collected on 13 occasions, at treatment visits and at the first follow-up visit after treatment termination. The level of ctDNA was analyzed using SiMSen-Seq, which enables ultrasensitive mutation detection. Clinical data were collected from medical records. Correlation between ctDNA, other biomarkers and results of radiological examinations were analyzed to identify relapse.
**Results:** Forty-six patients were screened for inclusion, a specific mutation was identified in 89% (BRAF 59%, NRAS 28%, KRAS 2%) that were included in the analysis. Median age was 65 years, 41% were men, median Breslow thickness was 3.4 mm with ulceration present in 46%, 39% were stage IIIB, 56% stage IIIC and 2% stage IV. All patients received nivolumab up to 12 doses. Twelve patients (29%) terminated treatment early due to immune related adverse events. Five patients relapsed during therapy; one had a local relapse and four had a distant relapse. At relapse, one had detectable ctDNA in blood and elevated levels of S100B. The other relapses were detected by radiological examination only, with normal LDH, S100B and ctDNA. Data analysis and interpretation of the ctDNA results are ongoing.
**Conclusion:** The present study suggests that monitoring of disease activity in melanoma during adjuvant PD-1 inhibitor therapy is technically feasible. However, preliminary results do not support the clinical use of ctDNA analysis to detect early relapses ahead of radiology.

## Gender Difference in sidE eFfects of ImmuNotherapy: a possible clue to optimize cancEr tReatment (G-Definer) - Metagenomic characterization

**Szabolcs Hetey**
Department of Oncology-Pathology, Karolinska Institute, Sweden

**Authors:** Szabolcs Hetey, Nele Brusselaers, Frederico Rossignoli, Johan Franzén, Loris De Cecco, Rosalba Miceli, Åslaug Helland, Alex J Eustace, Hanna Eriksson

Cancer immunotherapies have transformed the landscape of cancer treatment over the past few decades. However, their increasing use is associated with immune-related adverse events (irAEs) caused by non-specific activation of the immune system. These effects are often low grade, treatable, and reversible; yet some irAEs can be severe and lead to permanent disorders. Accumulating evidence suggests that sex influences adaptive immunity and may affect the types, frequency, and severity of irAEs. Another important aspect of immunotherapy responses is that certain bacterial species and metabolic pathways related to the intestinal microbiome may be associated with the occurrence of irAEs. Thus, the gut microbiome and its metabolites may play key roles in the underlying mechanisms. The G-Definer study aimed to examine different cancer types—including melanoma, lung, colorectal, and head and neck cancer—to shed light on sex-based differences in the development of irAEs following immune checkpoint inhibition, as well as variations in microbiome profiles between patients with and without adverse events. We performed robust shotgun sequencing followed by metagenomic profiling on stool samples from more than 200 patients and carried out an in-depth exploratory analysis to identify components associated with the development of irAEs, as well as species showing sex-specific differential abundances consistent with adverse events. The expected outcome of this project is to identify predictive factors of irAEs and to determine whether these factors differ according to biological sex and gender-related characteristics.

# Improved stratification of risk for progression by incorporating TILs in AJCC staging of stage II cutaneous ulcerated melanomas

**Francesca Portelli**
Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden

**Authors:** Francesca Portelli, Johan Falkenius, Muyi Yang, Hildur Helgadottir, Suzanne Egyhazi Brage

**Background:** AJCC melanoma staging is based on ulceration and Breslow thickness. However, improved stratification of stage II patients could help identify those at higher risk of progression who might benefit from adjuvant immunotherapy.
Objective: To investigate whether the tumor infiltrating lymphocyte (TILs) assessment can predict relapse free survival (RFS) and melanoma specific survival (MSS).
**Methods:** Retrospective study of 109 stage IB-IIA/IIC patients diagnosed during 2004-2006 and followed-up at Karolinska University Hospital. Sentinel node biopsy was not performed as it was not a routine procedure at the time of diagnosis.
**Results:** The median age at diagnosis was 70 years. Three patients were staged as T1b-IB, twenty as T2b-IIA, thirty-eight as T3b-IIB and forty-eight as T4b-IIC. Local or distant recurrence occurred in 61 patients. BRAF status was available for 64 patients (analysis ongoing), 31 were mutated. TILs were classified as brisk in 24 cases, non-brisk in 79 and absent in 6. Patients with T3b-T4b had shorter RFS, with median values of 64.3 and 21.7 months, respectively ($p<0.0001$). T1b-T4b patients with TILs brisk had longer RFS and MSS compared to those in the same stage with TILs non-brisk ($p<0.0001$). In univariate analysis, lower Breslow thickness, lower mitotic rate/mm2, TILs brisk and Ki-67 <=10% were significantly associated with longer RFS. In multivariable analysis, only Breslow thickness and TILs remained statistically significant ($p=0.002$ and 0.018), while ki-67 showed a trend towards significance ($p=0.057$). Furthermore, Breslow thickness, TILs and gender were significantly independent prognostic factors associated with MSS ($p=0.001$; $p=0.037$; $p=0.038$).
**Conclusions:** Incorporating TILs assessment into melanoma staging may provide additional prognostic information, potentially aiding in the identification of patients at higher risk of progression.

## Exploring the effect of SAMHD1 on tumor suppression in cutaneous melanoma

**Silvia Angori**
Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

**Authors:** Silvia Angori, Alessandra Muni, Sofi Vikström, Andreas Lundqvist, Stina Wickström, Georgios Rassidakis, Nikolas Herold and Hanna Eriksson

**Background:** SAMHD1 regulates innate immunity and DNA repair, acting as a tumor suppressor in several cancers. We hypothesize that SAMHD1 expression confers a survival advantage by enhancing the anti-tumor immune response in cutaneous melanoma (CM). Loss of SAMHD1 may promote tumor progression via two mechanisms: dysregulation of dNTP pools causing replication stress, and hyperactivation of the STING pathway, which upregulates immune-suppressive molecules like PD-L1, thereby contributing to immune evasion. This project investigates the impact of SAMHD1 in inhibiting the STING-TBK1 axis, potentially improving response to immunotherapy in melanoma.
**Methods:** We generated commercially available and patient-derived SAMHD1 knock-out (KO) cells by CRISPR/Cas9 technology. Tumor infiltrating lymphocytes (TILs) and NK cells were co-cultured with SAMHD1-wt and -KO melanoma cells to evaluate how the presence of SAMHD1 can influence the immune response.
**Results:** Our data showed that higher SAMHD1 expression is significantly associated with better overall survival (458 CM patients, TCGA data) with a proportion of high-expressers as long-term survivors after adjustment for lymphocyte infiltration. This result supports the hypothesis that the expression of SAMHD1 positively affects survival in CM. Next, loss of SAMHD1 was linked to STING pathway hyperactivation, shown by increased expression of downstream targets of the STING pathway such as ISG15, IFI16, and CXCL10 in SAMHD1-KO cells. We also evaluated whether SAMHD1 status can influence the immune response. Co-cultures of SAMHD1-wt and -KO cells with NK cells from healthy donor revealed higher IFNγ secretion with SAMHD1-wt cells. Interestingly, SAMHD1-KO cells were also more resistant to NK killing. Lastly, SAMHD1 loss can impair DNA damage response following treatment with double-strand break-inducing agents.
**Conclusion:** By elucidating SAMHD1's role in CM and its effects on immune modulation and genomic stability, this work supports the development of new therapeutic strategies to improve patient outcomes.

# The effect of uveal melanoma derived extracellular vesicles on hepatocytes in 3D culture

**Emma Symonds**
Sahlgrenska Center for Cancer Research, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

**Authors:** Emma Symonds, Måns Kadefors, Karin Ekström, Rossella Crescitelli, Roger Olofsson Bagge

**Introduction:** Uveal melanoma is a rare form of melanoma that arises from melanocytes in the eye. Approximately half of patients develop metastases, primarily in the liver (approximately 90%), with a poor prognosis. Somatic mutations in the BAP1 gene encoding BRCA1-associated protein 1 are associated with increased metastatic risk. Tumour secreted extracellular vesicles (EVs) have been proposed as drivers of pre-metastatic niche formation. We investigated if EVs from uveal melanoma cells, with or without BAP1 mutation, would increase the ability of cancer cells to co-locate with hepatocyte spheroids in vitro.
**Methods:** Hepatocyte spheroids were developed by culturing THLE2 cells, stained with Calcein-AM, in ultra-low attachment culture plates (1500 cells/well) for five days. EVs were isolated from a BAP1 mutated uveal melanoma cell line (UM22), transfected either with a vector control (BAP1-mt) or wild-type BAP1 (BAP1-wt). Spheroids (n=3 per group) were treated with EVs for 24hrs (1.5x107 EVs/well). UM22 BAP1-mt or UM22 BAP1-wt cells were stained with Cell Tracker Deep Red were added to spheroid cultures (1000 cells/well) for 24, 48, 72, or 120hrs. Spheroids were fixed and imaged on a Zeiss Celldiscoverer 7 microscope and analysed using ImageJ.
**Results:** After 24, 48, and 72hrs, no cancer cells were observed to interact with spheroids. After 120hrs, when treated with BAP1mut EVs, there was a numerical increase in number of cancer cells invading spheroids compared to BAP1wt EVs (261±155 cells vs 73±8 cells p=0.10). There was no statistically significant difference in how deep into the spheres the cancer cells invaded 3.1±2.7 vs 4.6±1.1um (p=0.28).
**Conclusion:** The ability of uveal melanoma cells to interact with spheroids is time-dependent. Treatment of spheroids with BAP1mt EVs may increase the number of uveal melanoma cells interacting with hepatocyte spheroids, but confirmatory studies are needed.

## Successful Treatment of Stage IV Melanoma with an ALK Inhibitor: A Case Report

**Cornelia Schuster**
Department of Oncology, Haukeland University Hospital, Bergen, Norway

**Authors:** Cornelia Schuster

**Case, introduction:** A 67-year-old patient was diagnosed with metastatic cutaneous melanoma in November 2023. The initial response to PD-L1 inhibition was short-lived. Early evaluation after two courses of combined immunotherapy showed disease progression, and the patient experienced reduced quality of life due to treatment-related side effects.
**Background:** The patient was considered for inclusion in the IMPRESS-Norway study, a prospective, non-randomized clinical trial designed to assess the efficacy of approved anti-cancer therapies in novel indications (NCT04817956). Within this framework, patients undergo comprehensive molecular diagnostics, including extended gene panel analysis, to identify actionable genetic alterations. If a suitable targeted therapy is available in the study's drug portfolio, treatment is offered based on the individual molecular profile.
**Case, targeted therapy intervention:** Molecular diagnostics revealed a targetable ALK mutation. The patient started treatment with an ALK inhibitor in October 2024. Due to side effects, the dose had to be reduced shortly after treatment initiation. He has excellent tolerability for the adjusted dose level and is living a very active live without restrictions. The first evaluation showed treatment response, and at the time of the most recent CT scan, the disease remained under control.
**Conclusion:** This case highlights the potential benefit of selecting therapies based on molecular diagnostics rather than the anatomical origin of the primary tumour.

## Unusual Destination: Amelanotic Metastasis of Melanoma in the Palatine Tonsil

**Valters Vegelis**
Riga Stradins University, Riga East Clinical University Hospital, Latvia

**Authors:** Valters Vegelis, Valters Viksne, Ilze Strumfa

**Introduction:** Metastasis of melanoma in palatine tonsil is extremely rare, with less than 30 cases reported in world literature. The tonsillar metastasis manifests about one year after excision of primary tumor, which may be close or distant to oral cavity. In most of the cases described in literature, tonsillar metastasis suggests late-detected widespread melanoma. We present a case of metastasis in palatine tonsil caused by primary melanoma on trunk.
**Case description:** A 53-year-old woman consulted her dermatologist after spotting a bleeding naevus on her back. Excision biopsy revealed a low CSD (chronic sun damage) type melanoma (Clark IV, Breslow 10 mm, pT4bN1cM0 L+V-Pn-). The genotype of BRAF V600E/E2/D was found, and PD-1 inhibitor therapy was initiated. One year later, right-side axillar lymphadenopathy started to progress. With levels of S-100 rising significantly, therapy was changed to BRAF/MEK inhibitor. Another year later, a recurrent right-side axillar lymphadenopathy was found on a PET/CT scan. After lymphadenectomy, histological findings showed no residual metastasis. Three months later, the patient complained about mass in the left submandibular region. Also, an unclear growth in the left palatine tonsil was discovered, and a biopsy was performed. Immunohistochemistry indicated metastasis of amelanotic melanoma with high mitotic activity. Meanwhile, MRI revealed necrotic lymph nodes on the left side of neck, and contrast enhancement in left palatine tonsil. Currently, PD-1 therapy is ongoing.
**Summary:** This case demonstrates an aggressive melanoma with delayed metastasis in palatine tonsil after successful excision and BRAF inhibitor therapy.
**Conclusion:** Amelanotic melanoma metastasis in palatine tonsil is an extremely rare condition. This type of metastasis is associated with aggressive course of the tumor, supported also by amelanotic conversion, high mitotic rate and recurrent metastatic spread despite treatment with BRAF and PD-1 inhibitor.

## Defying the Odds: A Case Report of Complete Regression of Untreated Metastatic Melanoma

**Hanna Strømholt Bremnes**
Department of Oncology, University Hospital of North Norway, Tromsø, Norway

**Authors**: Hanna Strømholt Bremnes, Knut Lien, Øyvind H. Hald, Jarle Jakobsen, Anita Amundsen

**Introduction:** Spontaneous remission of metastatic melanoma, while rare, has been described in the literature. Various mechanisms involved in this phenomenon have been proposed, primarily involving immunological pathways, but the underlying processes remain largely unknown.
**Case report:** Our patient was a 78-year-old male with a history of malignancy, including previously resected thyroid cancer and metastatic, hormone-sensitive prostate cancer. He was diagnosed with metastatic melanoma with extensive liver involvement. Following rapid deterioration and clinical and biochemical signs suggestive of fulminant hepatic failure, the patient was considered unfit for melanoma-directed treatment. Due to short life expectancy, most of the patient's medications were discontinued and he was transferred to a municipal palliative care unit for end-of-life support. Unexpectedly, over the following weeks, the patient's condition improved, ultimately leading to his discharge from the palliative care unit without the oncology team's knowledge.
Approximately one year later, a referral from the patient's general practitioner prompted re-evaluation. The patient presented with peripheral oedema related to congestive heart failure, symptoms of severe hypothyroidism and increasing pelvic pain with rising PSA. However, his liver function had normalized, and CT imaging revealed complete regression of his liver metastases. Following this discovery, androgen deprivation therapy was resumed for prostate cancer, and management of heart failure and hypothyroidism was optimized. The patient remains in good general condition and is still in remission from metastatic melanoma.
**Conclusion:** This case illustrates an unexpected clinical course with complete and spontaneous regression of metastatic melanoma. While similar instances have been reported, this phenomenon remains uncommon and inadequately understood. Further investigation into the mechanisms driving these recoveries could pave the way for drug development and lead to new treatment options for patients with metastatic melanoma.

# Real-World Patient Selection for Sentinel Lymph Node Biopsy and Associated Survival in Melanoma: Evidence from a Danish Nationwide Cohort

**Marie Brinch-Møller Weitemeyer**
Department of Plastic Surgery, Copenhagen University Hospital – Herlev and Gentofte, Herlev, Denmark

**Authors:** Marie Brinch-Møller Weitemeyer, Neel Maria Helvind, Caroline A. Gjørup, Frank Eriksson, Pernille Envold Bidstrup, Karina Dahl Steffensen, Eva Ellebaek, Lisbet Rosenkrantz Hölmich

**Background:** Sentinel lymph node biopsy (SNB) refines prognosis in melanoma, but its survival impact remains debated. The randomized trial, MSLT-1, showed no survival benefit while exploratory analyses suggested a possible benefit in selected subgroups. Real-world studies have been inconsistent and vulnerable to treatment selection bias. Here, we describe baseline differences and crude outcomes between SNB and non-SNB patients within a nationwide cohort eligible for SNB according to the national guideline in effect at the time of diagnosis.
**Method:** We identified patients diagnosed with clinical stage IB–IIIC cutaneous melanoma in Denmark between 2010 and 2017 through the Danish Melanoma Database. Baseline characteristics were summarized by SNB status. Crude survival outcomes were estimated from a 60-day landmark using Kaplan–Meier methods for overall survival (OS) and cumulative incidence functions for melanoma-specific mortality (MSM), other-cause mortality (OCM), and recurrence in a competing-risk framework. To evaluate the impact of SNB on survival, average risk differences estimated by augmented inverse probability of treatment weighting (AIPTW) will be presented at the conference.
**Results:** We included 6,972 patients eligible for SNB by the guideline in effect at the time of diagnosis, of whom 5,703 (81.8%) underwent SNB, with a sentinel node positivity rate of 19%. Median follow-up was 10.7 years [IQR 9.1-12.6]. Substantial baseline differences were evident: patients who underwent an SNB were more frequently male (49.6% vs. 45.5%), younger (median age 61 vs. 81 years), and had fewer comorbidities (Charlson Comorbidity Index 0: 71.1% vs. 42.9%). Tumor characteristics were more favorable in the SNB group, with lower median Breslow thickness (1.42 mm [IQR 1.05–2.30] vs 1.92 mm [IQR 0.93–4.00]) and less frequent ulceration (20.6% vs 35.7%). Moreover, a lower proportion of tumours in the SNB group were located in the head and neck region (10.4% vs 28.5%). Crude 10-year outcomes favored SNB; OS: 75.2% vs. 34.8%, MSM: 12.5% vs. 19.2%, OCM: 12.3% vs. 46.0%, and recurrence risk: 22.3% vs. 27.3% (all $p<0.001$). Average risk differences estimated by AIPTW are ongoing.
**Conclusion:** This large nationwide cohort demonstrates substantial real-world selection into SNB, with marked differences in crude survival outcomes between groups that are likely carried by baseline differences in prognostic factors rather than treatment effects. These findings highlight the need for rigorous causal inference to assess the survival impact of SNB. Planned AIPTW analyses will address this selection bias and are expected to provide more accurate estimates than previous real-world studies.

## Survival after diagnosis of melanoma brain metastases in patients treated with PD-1 inhibitors in Finland

**Saana Virtanen**
Department of Oncology and Radiotherapy and FICAN West Cancer Center, University of Turku and Turku University Hospital, Finland

**Authors:** Saana Virtanen, Pia Vihinen, Tiia Kettunen, Aino Rönkä, Leena Tiainen, Tanja Skyttä, Nesna Wahid, Laura Kohtamäki, Sanni Tulokas, Micaela Hernberg, Kalle Mattila

**Introduction:** Despite significant advances in immune checkpoint inhibitors (ICI), BRAF and MEK-targeted therapies (TT), and stereotactic radiosurgery (SRS), the prognosis for patients with melanoma brain metastases remains poor.
**Patients and Methods:** A nationwide cohort of metastatic melanoma patients treated with PD-1 inhibitors at five Finnish hospitals between 2014 and 2020 was analyzed to evaluate brain metastasis incidence and overall survival with the median follow-up of 2.6 (IQR 1.1–5.4) years from ICI initiation.
**Results:** Of 215 melanoma patients treated with ICI, 69 (32.1%) developed intracranial disease progression (PD) during or after ICI with the median time of 15.3 months (IQR 5.0–32.2). Intracranial PD was more common in patients with higher baseline stages (19.3% in patients with M1a, 31.5% in M1b, 33.3% in M1c, and 57.7% in M1d (p=0.007)). After intracranial PD, median overall survival (mOS) was 6.6 months (95% CI 4.0–9.1) for all patients, 9.4 months (95% CI 6.0–12.9) for patients with 1–3 brain metastases, and 4.6 months (95% CI 1.5–7.7) for patients with > 3 brain metastases or leptomeningeal metastases. 17 (24.6%) of patients who developed brain metastases had only intracranial PD with mOS of 7.0 months (95% CI 2.5–11.5) and 52 (75.4%) intra- and extracranial PD with mOS of 6.0 months (95% CI 2.9–9.1). After intracranial PD, 22% received further systemic treatment, 42% SRS, 23% whole brain radiotherapy, 6% surgery, 10% only palliative care and 9% received combination of different treatments.
**Conclusions:** This observational study confirms that intracranial PD is not uncommon during or after immunotherapy, and OS after intracranial PD remains short. As patients with only 1–3 brain metastases had longer survival, annual brain imaging could be considered on a patient-by-patient basis e.g., for patients with higher stages to detect asymptomatic brain metastases during follow-up.

# Employing skin self-examination and fear of cancer recurrence management in early-stage melanoma follow-up: Evaluation of the MELACARE intervention in a randomised controlled trial

**Sara Mølgaard Hansen**
Department of Plastic Surgery, Copenhagen University Hospital, Herlev and Gentofte, Herlev, Denmark

**Authors:** Sara Mølgaard Hansen, Christoffer Johansen, Nadine A. Kasparian, Mia Klinten Grand, Pernille Envold Bidstrud, and Lisbet Rosenkrantz Hölmich

**Purpose:** The MELACARE intervention aimed to evaluate a nurse-led follow-up program incorporating skin self-examination (SSE) education and psychosocial support to address fear of cancer recurrence (FCR) in early-stage melanoma survivors. This study assessed the MELACARE intervention's impact on FCR, psychological well-being, SSE performance, and healthcare usage compared to standard physician-led follow-up.
**Methods:** A two-group randomised controlled trial was conducted at the Department of Plastic Surgery, Herlev and Gentofte Hospital, Denmark. Participants included 153 patients with surgically treated melanoma (stages IA–IIA). Patients were randomised to either the MELACARE intervention (n=78) or a control group provided treatment as usual (n=75). The intervention involved nurse-led sessions focusing on SSE techniques and metacognitive strategies. Outcomes included FCR (primary), distress, anxiety, depression, health-related quality of life (HRQoL), patient activation, and SSE frequency and confidence (secondary) at six months. Trial registration: ClinicalTrials.gov (NCT05253872).
**Results:** At six months, the mean of the primary outcome FCR was lower in the intervention compared to the control groups, but the difference was not statistically significant (-0.86 [-3.34;1.62]). Intervention patients reported higher HRQoL (18% [3;32]) and patient activation (0.43 [0.15;0.71]) as the only significant secondary outcomes. Confidence in SSE was higher in the intervention group, with most performing SSE at recommended intervals.
**Conclusions:** The MELACARE intervention may improve HRQoL and patient activation but did not reduce FCR. High fidelity of delivery and patient adherence highlight its potential utility. The MELACARE approach empowers melanoma survivors through structured SSE education and psychosocial support. Future analyses will investigate long-term safety and efficacy.

# Real-world data on late progression in patients on BRAF/MEK inhibitor therapy for advanced melanoma

**Katja Schabet**
Heidelberg University, Medical Faculty Heidelberg, Department of Dermatology and National Center for Tumor Diseases (NCT), NCT Heidelberg, a partnership between DKFZ and University Hospital Heidelberg, Heidelberg, Germany

**Authors:** Katja Schabet and Jessica C. Hassel

**Background:** BRAF/MEK inhibitor (BRAF/MEKi) therapy improves progression-free and overall survival in patients with advanced BRAF-V600E/K-mutant melanoma. In patients achieving a durable remission it is still unclear if therapy should be continued or can be safely stopped.
**Methods:** We retrospectively analyzed data from patients with advanced BRAF-V600E/K-mutant melanoma receiving BRAF/MEKi therapy who started treatment at least 2 years ago. Patients with BRAF/MEKi therapy for ≥ 3 years were identified and assessed more closely.
**Results:** 163 patients (95 (58.3%) male, median age 58 years) were identified. 101 patients (62.0%) received dabrafenib/trametinib, 39 (23.9 %) encorafenib/binimetinib and 23 (14.1%) vemurafenib/cobimetinib. Median treatment duration was 5 months.
17 patients (10.4%) received BRAF/MEKi for ≥ 3 years, 3 (17.6%) of them received the treatment firstline, 15 (88.2%) with normal LDH at treatment start. After a median follow-up of 3 years treatment is ongoing in ten patients. In four patients BRAF/MEKi therapy was discontinued due to progression after 3 to 6 years of therapy, in one patient therapy was discontinued due to deterioration of the patient's general condition and two patients wished to discontinue. From these 2 patients one patient with PR progressed five months later, one with CR is still without recurrence 6 years after treatment cessation. However, one patient with CR and continuous BRAF/MEKi therapy progressed rapidly after more than 6 years.
**Conclusion:** In addition to existing data our real-world-data confirm that there is a risk for progression also under long-term BRAF/MEKi therapy. Patients should be monitored closely. Treatment discontinuation should be considered thoughtfully.

## Smoking cessation at melanoma diagnosis associated with longer survival – a real-world data study

**Veera Sivonen**
Turku University Hospital and University of Turku, Department of Oncology, Turku, Finland

**Authors:** Veera Sivonen, Kalle Mattila, Toni Mikkola, Antti Karlsson, Tarja Laitinen, Maarit Bärlund, Pia Österlund, Pia Vihinen, Eetu Heervä

**Introduction:** Previous studies have shown that tobacco smoking impairs cancer-specific and overall survival in patients with cutaneous melanoma. The effects of quitting smoking after melanoma diagnosis are sparsely described.
**Patients and Methods:** Unselected cohort of all patients diagnosed with cutaneous melanoma between 2009–2019 were obtained from the electronic medical records of Turku and Tampere University Hospitals, Finland. Smoking status was determined with a validated natural language processing algorithm. Diagnostic and treatment data were combined at secure data-analysis platform. Hazard ratios (HR) with 95% confidence intervals (HR 95% CI) were calculated using Cox regression.
**Results:** From 2395 melanoma patients smoking status was available for 1584 (66%). 5-year overall survival rate was 77% for never (reference, n=994), 67% for former (HR 1.32 (1.07–1.62), n= 272), 69% for current smokers (1.46 (1.18–1.79), n=273), and 79% for those who quit at melanoma diagnosis (0.78 (0.42–1.47), n=33). Median overall survival was 14, 13.6, 12.1 years and not reached, respectively. HR for melanoma mortality was 1.43 (1.09–1.88) for former smokers, 1.55 (1.18–2.03) for current smokers and 0.87 (0.39–1.95) for quitters.
Non-significant trends for baseline differences between current smokers and recent quitters were observed: quitters were more commonly female (49% vs 38%) and younger (median 55 vs 61 years), but melanoma stage (I-II 66% vs 61%, III 16% vs 23%, and IV 19% vs 16%), comorbidity index (CCI 2 or more 18% vs 16 %) and performance status (ECOG 2-4 0% vs 17%) were similar.
**Conclusions:** The current study suggests that smoking cessation at melanoma diagnosis was associated with favorable outcomes, with the caveat of younger patients managing to quit smoking more often. Although the number of recent quitters is small in this study, it shows a rationale to ask smoking status and support quitting smoking after melanoma diagnosis.

## Validation of data quality in the national population-based Swedish Melanoma Registry

**Karolin Isaksson**
Department of Clinical Sciences, Surgery, Lund University, Lund, Sweden
Department of Surgery, Skåne University Hospital, Kristianstad, Sweden

**Authors:** Magdalena Claeson, Rasmus Mikiver, Omta Moushe Ashak, Hanna Eriksson, Hildur Helgadottir, Iva Johansson, Kari Nielsen, Roger Olofsson Bagge, Karolin Isaksson

**Introduction:** National population-based cancer registries are well established in the Nordic countries. Reporting to these registries is key for evaluating outcomes and improving care. In addition, the registries are valuable sources for epidemiologic research. The Swedish national quality registry for cutaneous melanoma (SweMR) was established in 1990 and currently includes data on nearly 100,000 primary cutaneous invasive melanomas. This formal validation aimed to assess the data quality in SweMR.
**Methods:** Data from the SweMR for the time period 2016–2020 were comprehensively evaluated using international guidelines for cancer registry validation, focusing on the four key quality dimensions: completeness, timeliness, comparability and validity. Completeness was analysed through cross-referencing with the Swedish Cancer Registry. Timeliness was defined as the interval from diagnosis or histopathology availability to registry entry, assessed at 3, 6, and 12 months. Comparability was evaluated by reviewing coding, criteria, and reporting forms. Validity was assessed through re-abstraction of the original medical records of 488 randomly selected melanomas in eleven hospitals, representing all Swedish healthcare regions, using measures of exact agreement and concordance.
**Results:** SweMR demonstrated near-complete (99%) coverage of all incident melanoma cases during the period 2016-2020. Differences between time periods and healthcare regions were small. Timeliness was moderate to high, with room for improvement: 48% of cases were reported within 3 months, 73% within 6 months, and 91% within 12 months. Coding practices were compliant with international standards. Overall, the agreement between registry and re-abstracted data was strong, with 41 of 48 variables showing high agreement, for example, ‘Breslow thickness’ (exact agreement 95%) and ‘Ulceration’ (96%).
**Conclusions:** This comprehensive national validation confirms that SweMR provides overall robust, high-quality data, demonstrated by its completeness, timeliness, comparability, and validity. Action plans are initiated to enhance timeliness as well as variables identified with less strong validity to even further strengthen the registry.

# Development of locoregional cell therapy using tumor infiltrating lymphocytes for patients with metastatic uveal melanoma

**Lars Ny**
Department of Oncology, Sahlgrenska Comprehensive Cancer Centre and Sahlgrenska Center for Cancer Research, Sahlgrenska University Hospital and University of Gothenburg, Gothenburg, Sweden

**Authors:** Lars Ny, Axel Nelson, Rebecca Riise, Samuel Alsén, Andrew Wong, Per Carlsson, Iva Johansson, Sebastian Edman, Jan Holgersson, Roger Olofsson Bagge, Lisa M Nilsson and Jonas A Nilsson

**Background:** Cell therapy using autologous tumor infiltrating lymphocytes (TIL) has emerged as an important treatment option in refractory metastatic cutaneous melanoma. Also, in uveal melanoma (UM) TIL therapy has shown clinical efficacy using conventional systemic administration of cells. Based on the prominent liver tropism for UM, we investigated whether local administration of TIL directly into the liver circulation is feasible, safe and an effective option to increase clinical efficacy while maintaining acceptable toxicity.
**Methods:** An exploratory phase 1 trial was designed with six patients with treatment refractory metastatic UM. Key criteria for participation included histologically confirmed diagnosis of UM, performance status of ECOG 0-2, liver dominant disease and acceptable cardiovascular and pulmonary comorbidity, if any. The cells were manufactured using the Miltenyi Biotec CliniMACS Prodigy bioreactor at the GMP facility, Sahlgrenska University Hospital. A dose-escalation regimen of cells was applied, 10X8-10X9, and the cells were infused by hepatic artery infusion (HAI). Lymphodepletion was achieved by melphalan and following HAI the patients received low dose IL-2 for up to 14 days. Safety was assessed by observation of incidence and severity of adverse events according to CTCAE criteria. Efficacy was evaluated by PET-CT using RECIST 1.1 criteria.
**Results:** Manufacturing of TILs was carried out in all six patients from liver metastases according to protocol. In the last patient the planned dose of 10X9 cells was not reached. No major unexpected safety issues of clinical relevance were observed. Hematological toxicities was the major AEs observed. Anti-tumoral activity was demonstrated in radiological examinations.
**Conclusion:** Locoregional administration of TILs using HAI to patients with liver metastases of UM is a unique method that is feasible and safe and demonstrate anti-tumoral activity. The hospital-based manufacturing process for TILs is under evaluation for use in subsequent clinical trials.

# Defining the Role of Radiotherapy in Advanced Melanoma Patients Failing Targeted Therapy

**Ellen Heurlin**
Karolinska University Hospital, Karolinska Institutet, Sweden

**Authors:** Ellen Heurlin and Hildur Helgadottir

**Background:** Approximately 50% of patients with metastatic melanoma harbor mutations in the BRAF gene, making them eligible for targeted therapy with BRAF and MEK inhibitors (BRAF/MEKi). However, treatment options become limited once resistance develops, particularly in patients who have also failed immune checkpoint inhibitors (ICI). The role of radiotherapy (RT) in this context remains unclear, and concerns exist regarding toxicity when RT is delivered concurrently with targeted therapy.
**Method:** This retrospective study included all patients with metastatic melanoma treated with RT during progression on targeted therapy in Stockholm, Sweden, between 2015 and 2023. Clinical characteristics, treatment details, dosimetry data, and outcomes were collected. Patients were stratified into three groups: RT-STOP, discontinued systemic therapy after RT; RT-TT, continued targeted therapy after RT; and RT-ICI, switched from targeted therapy to ICI following RT. Study endpoints were overall survival (OS), progression-free survival (PFS), and toxicity.
**Results:** Sixty-three patients received RT while progressing on targeted therapy. Patients were followed up to 5 years after RT. Median PFS and OS were 1.9 and 3.1 months, respectively. The 6- and 12-month OS in RT-STOP was 13.6% and 4.9%, in RT-TT 34.6% and 7.6%, and in RT-ICI 46.8% and 33.4% ($p = 0.001$). One-year OS was 0% for CNS irradiation, 10.2% for visceral, and 24.9% for skin, soft tissue and lymph nodes ($p = 0.114$). RT was well tolerated, with no grade ≥3 adverse events observed.
**Conclusion:** RT in patients progressing on targeted therapy with BRAF/MEKi was safe, with no high-grade toxicity observed. While survival outcomes remained poor, patients who transitioned to ICI following RT demonstrated improved survival compared with those continuing or discontinuing targeted therapy. These findings suggest that RT may serve as a safe bridging strategy, particularly when followed by ICI, and warrant further prospective evaluation.

# A retrospective study on treatment experiences of stage IIIB-D/IVM1a melanoma with talimogene laherparepvec (T-VEC) at the Comprehensive Cancer Center, Helsinki University Hospital, Finland

**Lina Snickars**
Department of Oncology, Comprehensive Cancer Centre, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

**Authors:** Lina Snickars, Juho Halme, Sanni Tulokas, Hanna Laurén, Siru Mäkelä, Micaela Hernberg

**Background:** Talimogene laherparepvec (T-VEC) is a genetically modified herpes simplex virus type 1 (HSV-1) used in the treatment of unresectable melanoma metastases in stages IIIB–D/IVM1a. For T-VEC therapy to be applicable, the metastases must be injectable, i.e. superficially located in the skin, subcutaneous tissue, or lymph nodes. In Finland, T-VEC therapy is centralized to the University hospitals of Helsinki and Kuopio.
**Materials and Methods:** This retrospective study evaluated the treatment outcomes of patients who received T-VEC therapy at the Helsinki University Cancer Center between 2019 and 2025.
A total of 36 patients were included, with a median follow-up time of 19.5 months. The median age at treatment initiation was 68.5 years, and the most common AJCC8 stage was IV M1a, present in 77.8% (n=28) of patients.
**Results:** T-VEC was used as first-line therapy in 14 patients (38.9%). The planned course of treatment was completed in 19 patients (52.8%). Due to disease progression, treatment was discontinued in 13 patients (36.1%), while treatment was discontinued due to adverse events in four patients (11.1%).
Most patients experienced adverse events related to T-VEC injections. The most common were local reactions, reported in 50% (n=18) of patients, and fever or febrile symptoms, reported in 47.2% (n=17). Two patients developed HSV infection as an adverse effect of T-VEC injections, leading to premature discontinuation of treatment.
The overall response rate to treatment was 47.2% (n=17), with a complete response achieved in two patients (5.6%) and partial responses in 15 patients (41.2%). The median progression-free survival was 11.0 months. One-, two- and three-year overall survival was 94%, 85% and 76%, respectively.
**Conclusions:** T-VEC treatment was well tolerated. Patients who received T-VEC as a first- or second-line treatment had better overall survival and progression-free survival compared to those who received it as a third- to sixth-line treatment.

# Pre-treatment immune profiles in patients with metastatic uveal melanoma undergoing isolated hepatic perfusion

**Måns Kadefors**
Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

**Authors:** Måns Kadefors, Axel Nelson, Tobias Österlund, Anders Ståhlberg, Lars Ny, Jonas Nilsson, Roger Olofsson Bagge

**Background:** The SCANDIUM trial investigated the efficacy of isolated hepatic perfusion (IHP) with high-dose melphalan in patients with metastatic uveal melanoma. In addition to direct cytotoxicity, IHP may trigger immunogenic cell death, suggesting that baseline tumor immune status could influence treatment response and survival.
**Methods:** We retrospectively analyzed baseline transcriptomes of liver metastases from 27 IHP-treated patients, with 22 samples passing quality control. Response was assessed by RECIST 1.1 (responders: CR/PR; non-responders: SD/PD). Immune signatures, including interferon gamma (IFNG), tumor immune dysfunction and exclusion (TIDE), and related stromal markers, were calculated using TIDEpy. Median scores stratified patients for survival analysis. Wilcoxon rank-sum and log-rank tests were used to compared signatures and survival.
**Results:** Non-responders exhibited significantly higher TIDE scores than responders ($p<0.001$), whereas IFNG did not differ. Patients with low TIDE scores had longer progression-free survival (PFS: 10.3 vs 5.6 months, $p=0.014$) and overall survival (OS: 32.5 vs 11.5 months, $p=0.011$), capturing all long-term survivors. Higher IFNG scores showed nonsignificant PFS benefit (11.6 vs 5.6 months, $p=0.076$) but significantly improved OS (23.7 vs 8.8 months, $p=0.01$).
**Conclusions:** Pre-treatment immunological signatures IFNG and TIDE are associated with IHP response and survival in metastatic UM, highlighting their potential as predictive biomarkers for patient stratification and warranting further validation.