Intratumoral immunostimulatory LOAd703 gene therapy combined with atezolizumab in advanced malignant melanoma patients; early results from the LOKON003 study

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Background: LOAd703 (delolimogene mupadenorepvec) is an immunostimulatory gene therapy based on a tumor-selective replication competent adenovirus that encodes for trimerized, membrane-bound (TMZ)-CD40L and 4-1BBL. CD40L is involved in the initiation of antitumor immune responses through several mechanisms, including activation of antigen presenting cells, such as dendritic cells (DCs) that results in activation of CD4+ and CD8+ T-cells, as well as natural killer (NK) cells and M1 macrophages. Further, CD40/CD40L interactions on tumor cells facilitates tumor cell apoptosis. 4-1BB is a co-stimulatory molecule expressed on both T-cells and DCs and its activation by 4-1BBL is involved in cytokine production (DCs, T and NK), proliferation (T and NK), and memory formation (T-cells).

LOAd703 infects cells via the CD46 receptor. Its oncolytic property is restricted to malignant cells due to dependency on a dysfunctional retinoblastoma pathway, however, transgenes can be expressed in all infected cells through the CMV promoter. Treatment with LOAd703 is currently evaluated regarding safety in patients with pancreatic-, colorectal-, and ovarian cancer as well as in cholangiocarcinoma.

Material and methods: This phase I/II clinical trial enrolled patients with unresectable stage III or IV malignant melanoma, after treatment failure with at least one immune checkpoint inhibitor (and for Swedish patients BRAF/MEK-inhibitors in case of BRAF-mutated melanoma). Patients were enrolled at three sites, starting 2020, and were treated every third week with an image guided intra-tumoral injection of LOAd703, together with concomitant intravenous atezolizumab. Two dose levels of LOAd703 were evaluated. Treatment was repeated up to 12 three-week cycles, after which atezolizumab monotherapy could proceed for another 7 cycles. The same tumor lesion was injected, commonly a lymph node or another superficial metastasis. In the case of clinical or radiological disease progression, treatment was withdrawn.

Results: Currently, data is being evaluated and a preliminary report will be presented at the conference.

Radiotherapy for ICI-resistant melanoma: The PROMMEL study

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Despite the success of immune checkpoint inhibitors (ICIs), there are still ~50% of melanoma patients that within one year progress on e.g. anti-PD-1 therapy. This group of patients warrants other treatment options. Irradiation has been shown to exert immunomodulatory effects on irradiated tumors and at times also on the non-irradiated lesions. This is largely attributed to a radiotherapy (RT) induced systemic immune activation, a phenomenon called "abscopal effect".

We have conducted retrospective analyses on 88 melanoma patients receiving RT in combination with ICIs. In the group of patients receiving RT when they have progressed on ICIs (n=41), we have observed a best response rate of 68% in irradiated metastases and 15% in non-irradiated metastasis. As a next step we are conducting a phase II multi-center prospective trial, studying Precision Radiation (SBRT) of Immune checkpoint therapy Resistant Melanoma Metastasis (PROMMEL-study). Here, we are currently enrolling melanoma patients that have progressed upon anti-PD-1 treatment and have at least two progressing metastases, one of which is amendable for SBRT and at least one lesion not to be irradiated. So far 11 patients have been included. We will perform interim analysis on the first 13 patients. If an abscopal effect has been seen in at least one patient, inclusion will resume with the goal to include in total 27 patients.

For the translational analyses, we simultaneously profile the DNA and RNA of single cells from sequential tumor biopsies. We have observed frequent copy number aberrations across the genomes of melanoma cells. In one non-responder, we have observed vast intra-tumoral heterogeneities and enrichment of a specific melanoma subclone with up-regulation of the NGFR gene, known to induce a phenotypic switch to a de-differentiated "immune-cold" state. In one responder, we have observed the up-regulation of JUNB from a population of NK cells and CD4+ T cells, and achieved therapy response of non-irradiated tumor which carries NRAS Q61K mutation. Our prospective analyses hence seek to evaluate the benefits of combining RT with ICIs and the mechanisms behind a potential systemic response triggered by RT.

Neoadjuvant LTX-315 in combination with pembrolizumab in resectable stage III/IV melanoma (NeoLIPA trial): Protocol for a single center phase II open label study

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Clinically detectable, resectable stage III or oligometastatic IV melanoma can be cured with surgery, but has a very high risk of local or systemic recurrence. The risk of recurrence can be significantly reduced by adjuvant treatment with the PD-1 inhibitor pembrolizumab, and it was recently shown that the effect is improved further by giving three doses prior to surgery, ie neoadjuvant. Neoadjuvant pembrolizumab is now becoming standard of care, but the rate of pathologic complete response (pCR), a surrogate for long-term 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, there is a need for novel, more efficient neoadjuvant treatment regimens. In parallel, it is necessary to identify new biomarkers that predict response and resistance to therapy, to ultimately allow for personalized, biomarker driven treatment. 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. The proposed mechanisms include local lytic effects and induction of strong immunogenic cell death.

NeoLIPA is a phase II open label clinical trial of neoadjuvant LTX-315 in combination with pembrolizumab in 27 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 repeated intratumoral injections. After 9 weeks, patients will undergo surgery. Primary endpoint is the rate of pCR. Secondary endpoints include frequency and severity of adverse events, recurrence free survival and objective response rate. In addition we will collect serial tissue biopsies and blood for extensive exploratory analyses using mRNA sequencing, imaging mass cytometry, multiplex flow cytometry and quantification of circulating tumor DNA.

Overall Survival After the Introduction of Adjuvant Treatment in Stage III Melanoma: A Nationwide Registry Based Study

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Background: Adjuvant treatments with PD-1 and BRAF+MEK inhibitors significantly prolong recurrence-free survival in stage III cutaneous melanoma. However, the effect on overall survival is still unclear. After the approval of adjuvant treatments with PD-1 inhibitors and BRAF+MEK inhibitors, based on recurrence-free survival data, these treatments have been widely implemented. However, there are significant side effects and costs of the treatment, and the overall survival effect remains a highly anticipated outcome.

Methods: The Swedish Melanoma Registry and the Cause of Death Registry were used to gather data on clinical and histopathological parameters and outcomes. Patients diagnosed with stage III primary melanoma between 2016 and 2020 were included and divided depending on if they were diagnosed before or from July 2018, the timepoint when adjuvant treatment was introduced in Sweden (pre- and post-cohorts). Patients were followed until the end of 2021.

Results: There were 1371 patients diagnosed with stage III melanoma in Sweden in 2016-2020. The 2-year overall survival rates, comparing the 634 patients in the pre-cohort and the 737 in the post-cohort, were 84.3% (95% CI 81.4-87.3) and 86.1% (95% CI 83.4-89.0), respectively, with an adjusted HR 0.91 (95% CI 0.70-1.19, P= 0.51). Further, no significant overall or melanoma-specific survival differences were seen when comparing the pre- and the post-cohort in different subgroups depending on the age, sex or tumor characteristics.

Conclusions: To our knowledge, this study is the first to assess the impact on overall survival from a national introduction of adjuvant treatment in stage III melanoma. In this nationwide, population and registry-based study, no survival benefit was detected at a median follow-up of 2 years in the cohort receiving adjuvant therapy. At the NMM meeting an additional year of follow-up, including 2022, will be presented.

Minimal Invasive Limb Perfusion (MI-ILP)

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Introduction: In patients diagnosed with malignant melanoma, approximately 4-10% will develop in transit metastasis (ITM). Surgical resection is an option if the number of tumors is limited, but if this is not feasible or the tumors are rapidly recurring, isolated limb perfusion (ILP) or isolated limb infusion (ILI) are established treatment options. This study presents the feasibility of a technique that combines the benefits of both methods: minimally-invasive ILP (MI-ILP).

Methods: Data on 17 patients undergoing MI-ILP were included in the study. Fourteen patients were diagnosed with melanoma ITM, one with squamous cell carcinoma, one with sarcoma and one with merkelcel carcinoma. Percutaneous vascular access of the extremity vessels was performed and the inserted catheters were then connected to a perfusion system.

Results: The median age of patients was 69 years (range, 64 -76). Patients had on average 3 ITMs (range, 1 – 8) and the average size of their largest tumor was 15 mm (range, 4 -250). None of the patients had evidence of recurrent lymph node metastasis, but one patient had systemic metastases. All patients underwent the procedure without the need for conversion to an open procedure. In one of 17 patients perfusion was not possible due to a too high leakage rate. Data on response rates were therefore available in 16 of 17 patients. Nine of 16 patients (56%) showed a complete response, 5 of 16 (31%) a partial response and 2 of 16 (13%) showed progressive disease. Toxicities, using Wieberdink classification, were grade I (1 patient, 6%), grade II (9 patients, 56%), grade III (5 patients, 32%), and grade IV (1 patient, 6%).

Conclusion: This series of 17 patients shows the feasibility of MI-ILP. MI-ILP is feasible and gives the same treatment characteristics as open ILP, but with the advantage of a minimal invasive vascular access.

A role for pelvic sentinel lymph nodes in lower extremity melanoma

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Background and objective: Consensus on management of pelvic sentinel lymph nodes (PSLNs) has not been reached and thus the extent of sentinel lymph node biopsy (SLNB) of the groin in melanoma patients varies among centers and surgeons. Lymphatic drainage to PSLNs is often identified in, but the diagnostic and clinical relevance of PSLNs has been debated. Our aim was to determine if the presence of PSLNs affected recurrence or survival rates in patients with melanoma in the lower extremities.

Methods: This retrospective study consisted of 702 patients with cutaneous melanoma operated between 2005 and 2018. Of these, 134 patients with melanoma in the lower extremities were included in the study. Images of lymphoscintigraphy and SPECT-CT studies were thoroughly observed together with surgery reports to define the status of SLNs.

Results: Overall, 85 of 134 patients went through SLNB and 28 of them had PSLN identified. Two had their PSLN removed, which led 26 patients with PSLN to be compared to the 57 who did not have PSLN identified. We did not find statistically significant differences in overall recurrence (26.9% versus 28.0%, $p = 1.00$), regional nodal recurrence (11.5% versus 15.8%, $p = 0.67$), local or in-transit recurrence (19.2% versus 8.8%, $p = 0.17$), or distant recurrence rates (15.4% versus 19.3%, $p = 0.66$). Disease-free survival did not differ between the groups (median 23.0 (IQR 15.0–39.0) versus 19.0 (IQR 10.3–61.8) months, $p = 0.82$). Likewise, there was no statistically significant difference in melanoma-specific 5-year survival (78.6% versus 87.2%, $p = 0.42$).

Conclusions: We did not find more frequent recurrence, shorter disease-free survival, or poorer melanoma-specific survival in patients with drainage to PSLN. Our findings strengthen the evidence that PSLNs should not be routinely biopsied if they are not the first-tier nodes.

Survival in cutaneous head and neck melanoma is affected by a non-radical primary diagnostic biopsy

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BACKGROUND: It is still unclear if a non-radical diagnostic biopsy results in higher risk for metastasis and poorer survival for patients with cutaneous head and neck melanoma (cHNM).

METHODS: Histopathological radicality of initial diagnostic biopsies and outcome for 368 consecutive cHNM patients, clinically asymptomatic of metastatic disease and referred to a tertiary care academic center for sentinel lymph node biopsy staging from 2004 through 2018 were analyzed.

RESULTS: Patients with positive (n=133) or narrow (0.1-0.5 mm) (n=34) histopathological margins had significantly lower overall (p=0.017) and melanoma specific survival (p=0.0002) as well as worse loco-regional and distant control (p=0.004) than those with clear margins (n=201) at the diagnostic procedure. Multivariable analysis indicated positive or narrow histopathological margins as an independent negative prognostic factor for melanoma specific survival (HR 2.16, p=0.015), as was higher Breslow with increments in mm (HR 1.17, p<0.001) and ulceration (HR 2.49, p=0.003) of the primary tumor.

CONCLUSIONS: Non-radical primary diagnostic biopsies increase the risk for metastatic disease and impairs survival in cHNM. Thus, radical diagnostic procedures should be encouraged for patients with cutaneous melanoma in the head and neck region when possible.

BRN2 acts as a guardian of melanocyte stem cells and as a non-classical tumor suppressor

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Although the causes of melanoma initiation have been identified, the role of certain transcription factors in regulating dysregulated signaling remains unclear.

The transcription factor BRN2 is associated with melanoma invasion but its function in melanocyte physiology and melanoma initiation is unknown. In mice, BRN2 inactivation leads to stable hyperpigmentation, and loss of melanocytes and McSCs in response to genotoxic insult, indicating its significance in regulating pigmentation and McSCs turnover. Moreover, BRN2 facilitates DNA damage repair and suppresses cell death in melanocytes. In the context of a BrafV600E Pten+/- background, BRN2 haploinsufficiency increases the initiation and metastasis of melanoma but reduces the efficiency of metastatic colonization. BRN2 directly induces PTEN expression and represses PI3K signaling, while MITF, a target of BRN2, represses PTEN transcription.

In the absence of BRN2, cells become more sensitive to ionizing radiation but more proliferative and aggressive due to changes in PTEN transcription.

Melanoma dedifferentiation and immune evasion

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Background: For melanomas to develop they must evade the cytotoxicity of immune cells. Tumor-infiltrated immune cells secrete cytokines (e.g. IFNg) which can change the phenotype of tumor cells, making them better equipped to survive immune surveillance. MITF is a key regulator of melanoma phenotype, and it is well-defined that its activity regulates the differentiation status of cells. However, how differentiation status affects the ability of melanoma cells to evade immune surveillance is less defined. This study aims to decipher the effect differentiation has on melanoma immune evasion.

Methods: The differentiated 624mel melanoma cells were transduced with siMITF to generate dedifferentiated cells or with siCTRL as control, and stimulated with IFNg or control. To analyze CD274 (PD-L1) expression, q-PCR was performed. PD-L1 protein expression was analyzed by flow cytometry and western blotting. The expression profile was determined by RNA sequencing. Secretion of 18 cytokines and chemokines was quantified using a Luminex instrument.

Results: Dedifferentiated cells alter their phenotype as a response to IFNg stimulation by increasing expression of PD-L1 on mRNA and protein levels, 2-3 fold compared to differentiated cells. The RNA sequencing data revealed that, as a response to IFNg the dedifferentiated cells alter in a non-additive manner, the expression of genes taking part in antigen presentation, MHC, and immune response. Additionally, the dedifferentiated cells secrete a higher level of IL-10 (465 pg/ml), and a higher level of CCL2 (4600 pg/ml) as a response to IFN stimulation, compared to the differentiated cells (184 and 550 pg/ml, respectively). The mechanism of this phenotypic change is now being elucidated in the lab and points towards a mechanism restricted to a subgroup of melanoma cells, and not a universal mechanism.

Conclusion: This project will increase our understanding of how melanoma cells evade immune surveillance during melanomagenesis and potentially during immune therapy treatment failure.

EGLN1 is a druggable dependency in neural crest-like melanoma

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Melanoma cells can adopt transcriptional cell states that resemble different stages of embryonic development of melanocytes from the neural crest. Multiple studies have implicated a neural crest-like melanoma cell state in resistance to multiple therapeutic modalities, including MAP kinase directed molecular targeted therapy, adoptive T cell transfer, and immune checkpoint blockade. Identification of therapeutic targets in neural crest-like melanoma cells could provide new strategies for limiting tumor cell state-related treatment resistance in melanoma. Here, we leveraged genome-wide CRISPR screen data from the Cancer Dependency Map (DepMap) to identify genetic dependencies unique to neural crest-like melanoma cell lines.

DepMap analysis identified EGLN1, a key cellular oxygen sensor and key regulator of the hypoxia response, as a novel dependency in neural crest-like melanoma cells. In vitro studies confirmed loss of fitness following EGLN1 deletion in neural crest-like melanoma cells, which was phenocopied with a small molecule pan-EGLN inhibitor (FG4592). Consistent with the known cellular function of EGLN1, both HIF1a and HIF2a are stabilized following either EGLN1 knockout or pharmacological inhibition, although the growth inhibitory effect of FG4592 was rescued with deletion of HIF1a, but not HIF2a.

In summary, we have identified EGLN1 as a novel vulnerability in neural crest-like melanoma and confirmed loss of melanoma viability following inhibition/deletion of EGLN1 in a HIF1a-dependent manner. These findings suggest that targeting EGLN1 may represent a novel therapeutic strategy for neural crest-like melanoma cells to counteract the development of dedifferentiation-related treatment resistance.

Mechanistic basis of atypical TERT promoter mutations in melanoma

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Non-coding mutations in the TERT promoter (TERTp), typically at one of two bases -124 and -146 bp upstream of the start codon, are among the most prevalent driver mutations in human cancer. Several additional recurrent TERTp mutations have been reported specifically in skin cancers, but their functions and origins remain unexplained. Here, we show that atypical TERTp mutations are secondary to canonical TERT promoter mutations. Canonical TERTp mutations create de novo binding sites for ETS family transcription factors, known to induce favorable structural conditions for DNA damage formation by UV light, thus creating a hotspot effect only after a first mutational hit. In agreement, we find that atypical TERTp occur in tandem with the canonical mutations in large cancer cohorts, and that they arise subclonally specifically on the TERTp mutant chromosome homolog of melanoma cells treated with UV light in vitro.

Our study gives and in-depth view of TERTp mutations in human cancers and provides a mechanistic explanation for non-canonical TERTp mutations.

MITF represses the expression of the receptor-ligand pair VEGFA and FLT1

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Melanoma is the deadliest form of skin cancer and originates from melanocytes. The Microphthalmia-associated transcription factor (MITF) is known as the master regulator of melanocytes and has been shown to play an important role in melanoma. The rheostat model proposes that high MITF activity leads to proliferation and differentiation of the cells whereas low activity leads to quiescence and migratory properties; very low levels result in senescence. The receptor tyrosine kinase FLT1 and its ligand VEGFA are overexpressed in the absence of MITF and can trigger downstream signalling pathways.

This study aims to find the link between this receptor-ligand pair and MITF and determine if VEGFA-FLT1 can mediate the effects of MITF-loss in melanoma cells. Based on previous ChIP-seq data from our lab, there are several binding sites (E and M box) for MITF on the FLT1 and VEGFA genes. RNA seq data show a negative correlation between MITF and both FLT1 and VEGFA genes.

Our preliminary results show that both proliferation and migration are increased in FLT1-KD cells compared to controls transfected with scrambled shRNA. Together, this suggests that MITF can suppress the expression of VEGFA and FLT1 and that this signaling pathway affects cell proliferation and migration in melanoma cells.

Teledermatoscopy in the Stockholm region, Sweden: Improved Lead Times for Melanoma Care

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Background: The Swedish National Board of Health and Welfare has recommended teledermatoscopy to increase access to specialist care for patients with suspected melanoma. In Region Stockholm, with a population of 2.4 million, the method was recently implemented in all 240 primary care units, preceded by a successful pilot project during 2015-2021. Around 1,500 referrals for suspected skin lesions are now assessed monthly at the Dermatology Unit at Karolinska University Hospital, which is financially reimbursed by the health system.

Objective: To study the lead time from initial consultation in primary care to diagnostic excision of suspected malignant melanoma by comparing mobile teledermatoscopy and traditional referrals to a dermatology clinic at a tertiary hospital.

Methods: A retrospective cohort study was conducted from January 2016 to March 2019. Patients managed by traditional referral (n=53) were compared with patients managed in primary care units using teledermatoscopy (n=128) regarding lead time from first visit to diagnostic excision.

Results: Patients with suspected melanoma identified in primary care units, regardless of referral route, had a median lead time of 12 days (IQR 6-19; mean 15.8) from first visit to diagnostic excision, but significantly faster for teledermatoscopy performed at the patient's first visit and excision in primary care. In the teledermatoscopy group, the median lead time for patients excised in a primary care unit (n=40) was significantly shorter (p=0.013) than for patients excised in other units (n=87): 7.5 days (IQR 3-19.5, mean 13.2) compared to 13 days (IQR 8-19, mean 15.2).

Conclusions: The lead time to diagnostic excision for patients with suspected malignant melanoma managed by teledermatoscopy was comparable and not inferior to the traditional referral pathway. Teledermatoscopy is more efficient than traditional referral if used at the first consultation in primary care. Lead times are even shorter if the excision is also performed in primary care units.

The use of RCM in detection of local recurrence of Lentigo maligna melanom (LMM)

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Lentigo maligna melanom (LMM) is a subtype of melanoma that is strongly associated with chronically sun-exposed skin, predominantly on the face of elderly patients. It has a slow growth pattern combined with high local recurrence. Reflectance confocal microscopy (RCM) provides real-time noninvasive imaging of cell structure and may be useful in diagnosing LMM recurrences after treatment, minimizing the need of control biopsies. One side effect of the radiation therapy with Grentz ray is post inflammatory hyperpigmentation that sometimes can be difficult to distinguish from recurrence and necessitates biopsies. Few studies have compared performance of RCM with histopathology in diagnosing LM, and specific features are not well described.

Objective: We are planning to determine concordance rate between RCM and histopathology in the evaluation of suspected local recurrence / hyperpigmentation after Grentz ray treatment for LMM and to identify factors that may obscure diagnosis.
Methods: We designed a pilot study involvi
ng patients treated for LMM with Grenz ray in our unit during 2020-2022. During the planned follow up if suspicious pigment was seen in the previously treated area clinically or /dermatoscopy the patients underwent RCM examination followed by biopsy.

Preliminary results: RCM and histopathology interpretations were concordant in most cases. So far none was false negative using RCM and 1 case was false positive using RCM (LMM recurrence on RCM that was not confirmed by histology). Features suggestive of LMM in the false-positive case included the presence of numerous hyperreflective large cells at the dermo-epidermal junction and follicular localization of those cells, however without fully developed "Medusa" image.

Conclusion: RCM can be used for detecting LMM recurrence after treatment and minimize the need of biopsies in the area, although features of benign hyperpigmentation can obscure diagnosis and limit its specificity especially if inflammation is still present after the radiation treatment.

Trial to assess the Role of Imaging during follow up after radical surgery of stage IIb-c and III cutaneous malignant Melanoma (TRIM) – an interim analysis

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Aim/background: Imaging is part of the routine follow-up program after surgery for high-risk cutaneous malignant melanoma (CMM) in several countries, although no randomized study has yet been conducted to show patient benefit. The Swedish national guidelines stipulate clinical examination only every 6 to 12 months for 3 years. The main aim of the TRIM study is to investigate if scheduled whole-body imaging leads to improved patient outcome by earlier detection of recurrence compared to clinical examination only in patients operated for high-risk CMM. The TRIM study is supported by the Swedish Melanoma Study Group (SMSG) and is recommended in the national guidelines.

Materials and Methods: The primary endpoint is overall survival at 5 years. Secondary endpoints are disease-free survival and health related quality of life (HRQoL). Main inclusion criterion is radical surgery of stage IIb - stage III CMM. The goal is to include 1300 patients. Randomization is performed 1:1, stratified for tumor stage, between follow up according to Swedish national guidelines +/-whole-body imaging with CT or FDG-PET/CT at baseline, 6, 12, 24 and 36 months plus biochemistry including S-100B. HRQoL assessments are carried out for participants at oncology sites. An interim analysis will be conducted at the point of 1000 included patients with the main aim to assess possible differences in the number of relapses detected and time to relapse between the study arms.

Results: The TRIM study started in 2017 and it is expected that 1000 patients have been recruited at 19 sites in July 2023. The results of the interim analyses regarding number of relapses and time to relapse will be presented.

Recurrence and mortality in melanoma Stage-specific risks and the role of routine FDG PET-CT in surveillance

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Background: In 2016, Denmark added routine whole-body Fluorodeoxyglucose positron emission tomography-computed tomography scans (PET-CT) to the surveillance of stage IIB-IIID patients. However, evidence of the diagnostic value of routine PET-CT was limited and the impact on recurrence detection unknown. Furthermore, AJCC8 stage-specific risk of recurrence and recurrence patterns in melanoma had never been described.

This project aimed to determine the diagnostic value, yield and clinical consequences of routine PET-CT in surveillance (Study I), stage-specific risks of recurrence, MS mortality and recurrence-patterns (Study II), and the impact of surveillance with routine PET-CT on recurrence detection (Study III).

Methods: Study I was a retrospective population-based study of patients from two large centers, detailing the results of surveillance scans in 138 stage IIB-III patients. Study II was a nationwide, population-based cohort study of 25,720 Danish patients diagnosed in the years 2008-2019. Stage-specific risk of recurrence, MS recurrence-free survival and MS mortality was estimated using the Aalen-Johansen estimator. In Study III, the same cohort dataset was used to compare recurrence hazards and patterns in patients diagnosed in 2016-2017 and 2008-2010 (followed with and without routine PET-CT, respectively).

Results: Study I showed a high diagnostic value of routine PET-CT. Study II showed that the risk of recurrence and mortality increased with increasing AJCC8 stage, except in stages IIIA and IIIB, who had a better prognosis than stages IIB-IIC and that 56.8% of first recurrences were distant. Finally, Study III, showed improved and earlier recurrence detection, with a 51% increase in hazard of distant recurrence within the first two years, in patients followed with routine PET-CT.

Conclusion: Our results support risk-stratified surveillance in melanoma. A high proportion of initial distant recurrence and a higher hazard of recurrence detection within the first two years of surveillance with PET-CT suggests a diagnostic gain of routine PET-CT in surveillance.

Population-based prognostic instrument (SweMR 2.0) for melanoma-specific survival - a tool for individualised treatment decisions

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Introduction: The prognosis for patients with cutaneous malignant melanoma has improved due to better treatments in recent years and updated tools to accurately predict an individual's risk are warranted. A prognostic instrument is available online in Sweden since 2016. This study aims to describe an updated version of the instrument for patients with cutaneous invasive melanoma and its potential as a clinical device.

Methods: Patients with localised invasive cutaneous melanoma diagnosed in 1990-2021 were identified from the population-based Swedish Melanoma Registry, SweMR. The parametric Royston-Parmar (RP) method was used to estimate melanoma-specific survival (MSS) probabilities. Separate models were constructed for patients with thin melanoma, ≤1 mm, and patients with tumor thickness, >1 mm, and prognostic groups were created based on all combinations of age, sex, tumour site, tumour thickness, absence/presence of ulceration, histopathologic subtype, Clark's level of invasion, mitoses and sentinel lymph node (SLN) status.
Results: In total, 72 616 patients were identified, 41 764 with melanoma ≤1 mm and 30 852 with melanoma >1 mm. The most important variable was tumour thickness for both groups, that explained more than 50 percent of the survival. The second most important variable were mitoses for the "≤1 mm" group and SLN status for the ">1 mm" group. The prognostic instrument successfully created probabilities for > 30 000 different prognostic groups.

Conclusions: The Swedish updated population-based prognostic instrument (SweMR2.0), predicts MSS survival up to 10 years after diagnosis. The prognostic instrument gives more representative and up-to-date prognostic information for Nordic patients with primary melanoma than the present AJCC staging. Additional to clinical use for decision making of follow up and individualized treatment, the information retrieved could also be used in the planning of future trials. The instrument will be available online and also launched as a smart phone application.

Loss in life expectancy in patients with stage II-III cutaneous melanoma in Sweden

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Background: Survival in cutaneous melanoma (CM) is heterogeneous. Life expectancy (LE) is the expected remaining years of life for an individual or population and Loss in LE (LLE) quantifies the reduction in LE following a cancer diagnosis. This study aimed to investigate the LLE in stage II-III CM patients, to identify CM patients with the highest LLE.

Methods: We included 9,261 patients aged 40-80 years diagnosed with stage II–III CM in Sweden between 2005-2019 by using the Swedish Melanoma Register (SweMR). A flexible parametric method was applied to estimate LE and LLE.

Results: In 2019, it was estimated that stage II and III CM patients lost 2164 and 2286 life years, respectively. LLE was higher in stage III; eg a 60-year-old female with stage II CM had an LLE of 5.0 years, while for stage III it was 8.3 years. As expected, younger patients had higher LLE; e.g. a 40-year-old male with stage II CM had an LLE of 10.3 years, while a 70-year-old male had an LLE of 3.9 years. Females had lower LLE than males.; eg a 50-year-old female with CM stage II had an LLE of 6.8 years compared to a 50-year-old male with CM stage II, with an LLE of 7.8. LLE increased with higher substages with stage IIB resembling IIIB and IIC resembling IIIC-D.

Conclusions: Overall, this study demonstrated significant losses in LLE for patients diagnosed with stage II-III CM, compared to the general population, with higher losses in patients with stage III CM. LLE patterns differed between substages and between men and women. This highlights to consider other measures, such as LE and LLE, than established survival analyses for evaluation and prognostication of CM patients in relation to the general population.

Perioperative examination of inflammatory markers in relation to sentinel lymph node biopsy in patients with melanoma; a pilot study

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Introduction and objectives: Sentinel lymph node biopsy (SLBN) is essential in staging melanoma and selecting patients for adjuvant immunotherapy. 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. 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 inflammation and established prognostic factor in serval malignancies. Supplementary markers for inflammation will also be assessed.

Methods: We conducted a prospective uncontrolled longitudinal pilot study. In total, 20 patients diagnosed with melanoma and undergoing SLBN 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-g) 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 ($p<0.0001$). NLR increases further 6 hours postoperatively to 16.04 (95% CI:9.89:22.19) ($p=0.0151$). Remaining granulocytes decrease postoperatively. No changes in acute phase reactants are found. Among 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-g ($p=0.0003$) ($p=0.0125$) decrease 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.

Treatment strategies and outcome for a nationwide cohort of real-world patients with melanoma brain metastases and meningeal carcinosis, and benefit of postoperative stereotactic radiotherapy

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Introduction: Modern therapies have significantly improved outcome for patients with melanoma brain metastases (MBM). Still, the prognosis is poor, and the optimal treatment strategy for patients not fulfilling inclusion criteria for clinical trials is not clearly defined. In this nationwide study of real-world patients with MBM, we describe systemic and locoregional treatment strategies and survival outcome for improved decision-making in this challenging patient group.

Methods: All patients diagnosed with MBM in Denmark between 2015-2022 were included in the study. Patients were identified using the Danish Melanoma Database (DAMMED) and local records of surgery and radiotherapy. Data was collected from electronic patient records.

Results: A total of 838 patients were included. Median overall survival (mOS) was 9.0 months, and 112 patients were alive >3 years after diagnosis of MBM. Treatment with immune checkpoint inhibitors (ICI), ipilimumab + nivolumab, showed an intracranial overall response rate (icORR) of 46%, and a 2-year OS of 49% whereas BRAF/MEK-inhibitors resulted in an icORR of 56% and 2-year OS of 20%.

Patients with meningeal carcinosis at baseline (n=67) had a mOS of 8.4 months. Systemic therapy significantly improved OS for these patients, but no survival benefit was observed for patients receiving ICI compared to BRAF/MEK-inhibitors. In total, 230 patients underwent surgery for MBM; of these, 30 received postoperative stereotactic radiosurgery (SRS). Baseline characteristics were balanced between the two groups but no difference in OS or intracranial progression-free survival was observed.

Conclusion: Modern systemic therapies have improved survival for real-world patients with MBM but where BRAF/MEK-inhibitors have the highest icORR, ICIs are able to generate durable responses. However, ICI does not seem to result in long-term responses for patients with meningeal carcinosis. As an interesting finding, postoperative SRS did not affect outcome for patients undergoing surgery for MBM questioning this as a standard procedure.

Patient Perspectives on Diagnosing and Treatment of Stage III and IV Melanoma — A Nordic Patient Survey

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Background: We conducted a survey to hear patients' perspectives on various aspects of melanoma treatment in the Nordics.

Methods: This patient survey was done in a collaboration between Novartis, treating physicians, and patient associations in Sweden (SE), Norway (NO), Denmark (DK), and Finland (FI). The Nordic countries have similar health care systems, however, national guidelines and early availability of new treatments differ between the countries. A semi-structured web-questionnaire was developed by Novartis and the results were analyzed by NordiMED. Patients with stage III and IV melanoma were invited through the local patient associations to participate in the survey in 2020 (FI) or 2021 (DK, NO,SE).

Results: The survey had 146 respondents: 51 (35%;SE), 45 (31%;NO), 41 (28%;DK), and 9 (6%;FI). Of these, 62 (42%) had stage III and 84 (58%) stage IV melanoma. Of the respondents, 41% were satisfied and 31% dissatisfied with how their diagnosis of melanoma was presented (similar ratio in stage III and IV). Of stage III patients, 54% did not know their substage (3A–D); and 58% of stage III and 37% of stage IV patients did not know the BRAF-status. Of stage III and IV patients, 27% and 20% respectively, felt they were not presented with different treatment options, and 12% and 13%, respectively, reported not getting sufficient information on side effects. Most stage III (92%) and stage IV (84%) patients were generally concerned about side effects, whereas 77% of stage III and 59% of stage IV patients were concerned about long-term side effects.

Conclusions: These results show there is room for further improving patient experience. It is also worth noting that as information about BRAF status is important in determining the course of therapy, this information and other knowledge related to the disease should be communicated effectively to the patients.

Investigation of predictive markers in melanoma patients treated with Ipilimumab

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Background: Immune checkpoint blockade has revolutionized treatment options in patients with metastatic melanoma. The CTLA-4 antibody Ipilimumab was the first to show survival benefit in patients whose median survival time was historically less than one year. Up to date, there are no clinically validated predictive markers to optimize the benefit of immune checkpoint blockade. Recent research supports the impact of beta-adrenergic signalling on tumour progression. Its role in supporting immunosuppression is of special interest in the era of immune checkpoint blockade. Our project focuses on assessing the predictive value of proteins involved in stress response and the presence of immune cells in melanoma patients treated with Ipilimumab.

Methods: Our present work is based on a national, multicentre, single arm phase IV study with the primary objective to estimate incidence and severity of adverse reactions to Ipilimumab in a post-approval real-world setting in metastatic melanoma patients. Explorative objective is to identify predictive markers of response. Patients were enrolled at multiple centres in Norway between January 2014 and March 2015. The present analysis is based on the landmark analysis after five-year follow up. Immunohistochemistry was used to investigate the expression of immune related markers and markers of stress response in archived tissue samples taken prior to treatment with Ipilimumab. The focus is on the intratumoural expression of β2-adrenergic receptor, COX2 and VEGF-A as well as the intra or peri-tumoural presence of CD3, FoxP3, CD8.

Results: Preliminary results show a non-significant correlation between low expression of β2-adrenergic receptor in melanoma metastases and clinical benefit from Ipilimumab. Expression of COX2 in metastases and the number of CD3 positive cells were not associated to treatment outcome. Final data including the correlation of VEGF-A expression, the presence of FoxP3 and CD8 positive cells and efficacy of Ipilimumab will be presented.

The tumor microenvironment may have an influence on isolated limb perfusion treatment outcome in locally advanced melanoma

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Background and aim of the study: Our aim was to find molecular predictive factors within the tumor microenvironment (TME) that may be useful in the selection of melanoma patients that may benefit from isolated limb perfusion (ILP) in the era of new melanoma treatment options.

Materials and methods: Pre-ILP metastatic samples from 22 patients treated with ILP during 2008 to 2018 were analyzed with multiplex immunohistochemistry (mIHC) and digital data imaging. Three different antibody panels were used. We examined if treatment response (CR vs non-CR) and PFS (<6 months vs 6 months) after ILP correlated with immune cell subtypes or immune checkpoint molecules/markers.

Results: Lower distribution of CD45+ cells inside the tumour correlated with longer PFS (A Mann-Whitney U-test (p=0,001), crosstabulation (p=0,016) and Kaplan-Meier analysis (p=0,018)). Lower number of CD45+CD3+ cells inside the tumour were related to longer PFS (Mann-Whitney U-test (p=0,005), crosstabulation (p=0,016) and Kaplan-Meier (p=0,032)). Longer PFS was also seen in patients with lower CD45+CD3+CD4+ cell count inside the tumour (Mann-Whitney U-test (p=0,002), crosstabulation (p=0,016), and Kaplan-Meier (p=0,032)). A significant correlation was also found regarding a lower distribution of CD45+CD3+CD8+ cells within the tumour and longer PFS (Mann-Whitney U-test (p=0,008), crosstabulation (p=0,016) and Kaplan-Meier analysis (p=0,032)).

A correlation between longer PFS, treatment response and a lower number of CD45+CD3-CD4+ within the tumour was also observed (Mann-Whitney U-test (p= 0,036 and p=0,003, respectively)) and crosstabulation revealed better treatment response (p=0,005).

More CRs (crosstabulation, p=0,01) and longer PFS (Kaplan-Meyer, p=0,048) were seen patients with higher distribution of CD3+CD8-PD1+PDL1- cells outside the tumour. Smaller proportions of PDL1+PD1- cells related to total amount of PDL1 positive cells within the tumour correlated with a longer PFS (Kaplan-Meier, p=0,009).

Conclusions: We found that some cell subtypes correlated with a better and longer treatment response to ILP.

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% in thin melanoma: a multicentre Danish cohort study

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Background: Sentinel lymph node biopsy (SLNB) is used to staging and guide subsequent management of melanoma. However, proper patient selection for SLNB is challenging; 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 model (CP-GEP) was developed to identify low risk melanoma patients who may safely forgo SLNB. The CP-GEP 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 in a multicentre Danish cohort.

Material and Method: Archived formalin-fixed paraffin-embedded primary cutaneous melanoma tissue from 537 T1-T3 melanoma patients was collected and analysed with CP-GEP. 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 (IQR 44-70) and median Breslow thickness was 1.3 mm (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 negative predictive value (NPV) of 91.3%. When analysing the T1 subgroup (n=176) the CP-GEP low risk rate was 72.7% with a NPV of 94.5%.
Conclusion: The CP-GEP identifies most patients at low risk for SN metastasis, especially in patients with T1 melanoma. Results are in line with previous retrospective validation studies on European and US cohorts. This study, however, contains the largest T1 subgroup validation with a potentially very high SLNB reduction rate.

Inflammation-related proteins associated with worse clinical outcome in melanoma patients treated with immune checkpoint inhibitors

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Background. Although treatment with immune checkpoint inhibitors (ICIs) has been very successful in metastatic cutaneous melanoma, only a subset has long-term benefit from the treatment. There is thus a great need to identify biomarkers that can predict long-term benefit of ICIs and avoid unnecessary immune-related adverse events. We have recently suggested a panel of high-abundant inflammation-related plasma proteins as having the potential of being used as prognostic and predictive biomarkers for stratification of melanoma patients for ICIs. The aim of this study is to search for and validate potential predictive biomarkers among low-abundant inflammation-related proteins in plasma from patients with metastatic melanoma receiving ICIs.

Methods. Fifty-eigth patients with metastatic disease receiving anti-PD1 were included in the study between 2015 and 2019, 20 females and 38 males. The median age was 70 years old (range 31 – 84). Inflammation-related proteins were assessed in pretreatment plasma samples utilizing the OLINK target 96 inflammation platform. Further validation of potential candidates was performed utilizing ELISA or ProQuantom immunoassays. The levels of inflammation-related proteins were related to plasma thymidine kinase (TK) levels and clinical outcome.

Results. In the OLINK analysis, high baseline EN-RAGE/S100A12 and IL8 expression and low baseline DNER expression were significantly associated with shorter OS (adjusted p-value <0.05). The correlation between baseline S100A12 and IL8 levels and OS was confirmed with ELISA or ProQuantom immunoassays (HR=8.39; 95%CI 3.24–21.70; p=0.012) and (HR=3.621; 95%CI 1.371–9.560; P=0.008), respectively. We found that the proliferation marker TK, recently reported by us as associated with survival in melanoma patients treated with ICI, also correlate to several of the inflammation-related proteins.

Conclusions. Our findings suggest that a panel of inflammation-related proteins may provide prognostic value and predict worse clinical outcome for patients with metastatic melanoma receiving anti-PD1 therapy. These proteins warrant further investigation as potential prognostic biomarkers and as additional therapeutic targets.

Checkpoint inhibitor-induced adverse events in the CNS – T cell characteristics and biomarkers

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Immune checkpoint inhibitors block inhibitory receptors PD-1 (nivo) and CTLA-4 (ipi) which activates T cells to kill cancer cells. Ipi+nivo can cause inflammation in the central nervous system (CNS irAE), a rare but potentially fatal adverse event. Blood tests are used to detect most irAE but there are no blood tests to detect CNS irAE.

In addition, T cell subtypes are likely central in driving CNS irAE, but the profiles of circulating T cells during CNS irAE are not characterised beyond reports on single patients.

In my PhD thesis, I aimed to:
- Identify biomarkers for detection and monitoring CNSirAE (paper I and II)
- Define T cell characteristics associated with CNSirAE (paper I and III)
- Determine the incidence of CNS irAE in ipi+nivo treated patients (paper II)

In a patient with near fatal CNS irAE brain damage markers S-100B and NfL in blood was high (paper I). These findings were confirmed in a subsequent cohort of nine CNS irAE patients (paper II). CNS irAE was detected with a sensitivity of 100% (S100B) and 79% (NfL) and a specificity of 89% (S100B) and 74% (NfL). All patients with CNS irAE had simultaneous irAE hepatitis and elevated CRP. CNS irAE patients had high proportions of circulating inducible T cell costimulatory receptor (ICOS)-expressing CD4+ T helper cells and CD8+ cytotoxic T cells (paper I and III). The proportion of ICOS expressing T cells decreased as the patients recovered. The incidence of CNS irAE was 4.6% (9 of 197) in our cohort of ipi+nivo treated patients (paper II).

In conclusion, combined analysis of S100B and NfL in blood facilitate diagnosis and monitoring of CNS irAE. Increased CRP and irAE hepatitis during CNS irAE suggest shared immune mechanisms between CNS and hepatitis irAE. Finally, ICOS-expressing CD4+ and CD8+ cells may promote CNS irAE.

A potential role of antigen-presenting non-classical monocytes in mediating exceptional response in checkpoint inhibitor-induced sarcoidosis

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Background: Immune-checkpoint induced sarcoidosis (ICI-sarcoidosis) is a rare immune related adverse event (1-2%). Clinically it resembles primary sarcoidosis, a granulomatous autoimmune disease of unknown origin, but the underlying mechanism may differ. Interestingly, an exceptional anti-tumoral response has been reported in patients with ICI-sarcoidosis. However, the immune mechanisms behind ICI-sarcoidosis remain unknown.

Methods: ICI-sarcoidosis was diagnosed as inflammatory uptake on PET/CT followed by tissue biopsies in patients with stage III (n=6) and IV (n=4) malignant melanoma, cancer of unknown primary (n=1), colorectal cancer (n=1) and lung cancer (n=1). Overall survival (OS) was compared to patients with metastatic malignant melanoma treated with PD-1 inhibition (Nivolumab or Pembrolizumab) at the Department of Oncology, Sahlgrenska University Hospital between 2016-2023 (n=326). Single-cell RNA-sequencing was performed on peripheral blood mononuclear cells (PBMCs) during active and resolved ICI-sarcoidosis from a subset of melanoma patients (n=3). Tissue samples from organs developing ICI-sarcoidosis were stained with multiplex immunostaining to visualize the cellular components and architecture of the granulomas.

Results: Patients with ICI-sarcoidosis had better survival than patients without ICI-sarcoidosis (100% vs. 49% OS at 30 months). There was a pronounced increase in non-classical monocytes in blood during sarcoid irAE. The most highly differentially expressed genes in non-classical monocytes during sarcoid irAE included the two HLA II genes, HLA-DQA2 and HLA-DRB5. In addition, the expression of the inflammatory membrane protein IFITM2 was increased during sarcoid irAE. IFITM2 is part of the IFN signaling pathway. IFN signaling is central in response to checkpoint inhibition but the role of IFITM2 in this context is unknown. Immunostaining showed co-localization of macrophages and CD4 helper T cells in the core of sarcoid granulomas.

Conclusion: Our preliminary data suggest that ICI-sarcoidosis, a rare but clinically favorable adverse event, may be driven by non-classical monocytes that boost the peripheral immune response by activating CD4 helper cells.

Gender differences in outcomes and side effects of immune checkpoint inhibitors in Cancer

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Background: The G-DEFINER trial has evaluated immunerelated adverse events (irAEs) inequalities between female (F) and male (M) cancer patients treated with immune checkpoint inhibitors (ICIs). Clinical data and blood/fecal samples were collected.

Methods: irAEs burden (B) was estimated as the sum of the average and worst grade of irAEs. The cumulative sum of time-specific Bs was used as irAE burden index (BI). Median BI (mBI) was modelled using quantile regression models. A univariable analysis (UA), crude incidence (CCI), and event-free survival (EFS) curves were estimated trhough Kaplan-Meier method and compared with the log-rank test. Multivariable analysis (MA) of CCI and EFS was performed.

Results: This subgroup analysis included 204 patients (86 F,118 M). Patients' age, oncologic treatments, cancer type, ICI type, were balanced in the two groups. F interrupted ICI administration more than M (44 vs 29%, p=0.034) due to irAEs (27 vs 11%); 83% F vs 71% M (p=0.069) contributed with 204 vs 240 any grade irAEs (significant differences: 36 vs 21% endocrine, p=0.016; 20% vs 9% hepatic, p=0.040). F developed more irAEs. mBI was significantly higher in F both at UA (p=0.024) and MA (p=0.048). First G≥2 irAE 6 month estimates in F vs M were 55% vs 45% (p=0.073 UA and 0.140 MA). EFS between group difference was not significant both at UA (p=0.206) and MA (p=0.729). Specifically, 74 melanoma patients were analyzed. At a median follow-up of 10.20 months, 45 patients developed ≥G2 irAEs corresponding to a 6-month incidence (95% confidence interval): 51.5% (40.8-65.0%), 12-month incidence 65.7% (54.7-78.9%) without any significant differences between F and M. GI and endocrine irAEs were most frequent.

Conclusions: F experience a higher irAE burden and require monitoring to avoid ICI interruption. The results underline the need of using a measure of irAE cumulative load to gain insights between groups

Immune-related adverse events in a nationwide cohort of melanoma patients treated with adjuvant anti-PD1 – Seasonal variation and association with outcome

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Introduction: The introduction of immune checkpoint inhibitors (ICIs) has transformed the treatment of advanced melanoma. However, treatment comes with the risk of immune-related adverse events (irAEs). Especially now treatment has moved to the adjuvant setting, doctors and patients must weigh potential benefits versus risks based on as much available information as possible. Real-world data are essential for decision-making.

Methods: A nationwide study on irAEs in Danish real-world patients treated with adjuvant anti-PD1 therapy for resected stage III-IV melanoma from 2018-2022. Data were retrieved from two national clinical databases, the IMMUNOTOX database and the Danish Metastatic Melanoma Database (DAMMED).

Results: Data from 792 patients were included. The majority of patients were male (55%) with a median age of 62 (range 16-88) at time of first treatment. In total, 697 patients (88%) experienced an irAE, the most common being fatigue (44%). Low-grade irAEs (grades 1-2) were very common, whereas different subtypes of severe irAEs (grades 3-5) were observed in 0.3-4%. In total, 121 patients (15.3%) experienced severe irAEs out of which five patients (0.6%) died due to irAE. Having at least one irAE was associated with a lower risk of melanoma relapse. Seasonal variation was observed with more frequent debut of organ-specific (gastrointestinal, ocular, musculoskeletal, and thyroid) irAEs during summer, while mild skin toxicities were more frequent in the winter period.

Conclusion: In this nationwide cohort of real-world adjuvant melanoma patients, we observe that having any grade of irAEs, as well as a severe irAE, is slightly more frequent compared to clinical phase III trials and comparable to previously published real-world studies. Further, the risk of relapse from melanoma is lower among patients experiencing an irAE. Finally, significant seasonal variation in irAE incidence was observed.

Real-world data for dabrafenib and trametinib combination therapy in patients with advanced malignant melanoma: the PRODAT non-interventional prospective multicenter study

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INTRODUCTION: The aim of this prospective non-interventional study (NIS) was to investigate the real-world effectiveness, safety and tolerability of dabrafenib (Tafinlar®) and trametinib (Mekinist®) (Dab+Tram) used in patients with advanced malignant melanoma.
METHOD: Adult patients with non-resectable or metastatic melanoma, with BRAFV600 mutation and receiving treatment with the combination of Dab+Tram (in any treatment line) and for ≤12 weeks were eligible for inclusion in this multicenter study conducted in Norway (5 sites) and Sweden (4 sites). Patient data for effectiveness and adverse events were collected during regular visits for 18 months and subsequent treatment lines for additional 12 months.

RESULTS: In total 43 patients were included during the study period (July 2017 – October 2021), in which 31 patients (72%) received Dab+Tram treatment as first line (1L), 8 (19%) as second line (2L), and 4 (%) as later line. Median PFS was 5.3 months [3.7-7.0; 95%CI] in 1L group vs 3.6 months [2.0-6.4 95%CI] in 2L group (median PFS 4.8 months [3.7-6.4; 95%CI], independent of Dab+Tram treatment line). The most frequent treatment related AEs were pyrexia (58%), nausea (26%) and fatigue (19%). 33 patients (77%) experienced grade 3 (severe) AEs or worse, most commonly reportedly grade 3 pyrexia (n=4), nausea (n=3) and sepsis (n=3) events. Discontinuation from Dab+Tram treatment due to AEs in 6 patients (14%), progression in 25 patients (58%), death in 4 patients (9%) or for other reasons in 5-6 patients (11-14%). 36 patients (84%) prematurely discontinued the study, death being the main reason for discontinuation in 33 patients.

CONCLUSION: Results from this study suggest that patients with BRAFV600-mutated melanoma more commonly received Dab+Tram in 1L rather than in later lines. The shorter median PFS compared to pivotal randomized trials implies substantial differences between patients eligible to randomized trials and those treated with the combination in real-world setting.