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A retrospective analysis of the factors influencing the efficacy and side effect profile of fixed- versus body weight dependent immune checkpoint inhibition in the treatment of malignant melanoma

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List of Abbreviations

A

AJCC ..... *American Joint Committee*
ALM ..... *Acrolentiginous Melanoma*
ALT ..... *Alanine-Aminotransferase*
APC ..... *Antigen Presenting Cells*
AST ..... *Aspartate-Aminotransferase*

B

BMI ..... *Body Mass Index*

C

CKD ..... *Chronic Kidney Disease*
CMV ..... *Cytomegalovirus*
CR ..... *Complete Response*
CT ..... *Computer Tomography*
CTCAE ..... *Common Terminology Criteria for Adverse Events*
CTLA-4 ..... *Cytotoxic T-Lymphocyte Antigen*

E

EBV ..... *Epstein Barr Virus*
ECOG-PS ..... *Eastern Cooperative Oncology Group- Performance Status*

F

FDA ..... *Food and Drug Administration*
FDT ..... *Fixed Dose Therapy*

G

GFR ..... *Glomerular Filtrating Rate*

I

ICI ..... *Immune Checkpoint Inhibition Therapy*
irAE ..... *immune related Adverse Events*

L

LDH ..... *Lactat Dehydrogenase*
LMM ..... *Lentigo Maligna Melanoma*

M

MM ..... *Malignant Melanoma*
MRI ..... *Magnetic Resonance Imaging*

N

NM ..... *Nodular Melanoma*

O

ORR ..... *Overall Response Rate*
OS ..... *Overall Survival*

P

PD ..... *Progresive Disease*
PD-1 ..... *Programmed Death 1*
PD-L1 ..... *Programmed Death-Ligand 1*
PET ..... *Positron Emission Tomography*
PR ..... *Partial Response*

R

RECIST ..... *Response Evaluation Criteria In Solid Tumors*
RFS ..... *Relapse Free Survival*

S

SD ..... *Stable Disease*
SLNB ..... *Sentinel Node Lymph Biopsy*
SSM ..... *Superficial Spreading Melanoma*
SmPC ..... *Summary of Product Characteristics*

T

TRAE ..... *Therapy Related Adverse Events*
TRIM ..... *Tissue Registry In Melanoma*
TSH ..... *Thyroid Stimulating Hormone*

W

WAT ..... *Weight Adapted Therapy*

Introduction

Melanoma Biology

As one of the sixth most frequent cancer diagnoses in the European Union in 2020, it is approximated that melanoma can be taken as the reason for 4% of all new cancer diagnoses in the EU .('European Cancer Information System' 2023; 'Cancer Today') The term melanoma derives from the Greek *melas* – black or dark and *oma* – tumor.(Rebecca, Sondak, and Smalley 2012) It is a malignant tumor which originates from neural crest-derived melanocytes. Melanocytes are found throughout the entire integument given their ectodermal origin, in addition to mucous membranes. As result, melanoma can present in a wide range of tissue sites, including the choroid retina and conjunctiva.

Melanoma has a high risk of both local- and distant metastasis and is classified into several subtypes. The most common subtype is the superficial spreading melanoma (SSM) which most commonly develops on the lower limbs in females and on the trunk in males.(Friedrich and Kraywinkel 2018) Nodular melanoma (NM) has the worst prognosis given its propensity to metastasize early via the lymphatics.(Corneli et al. 2018) Lentigo-maligna-melanoma (LMM) is essentially a melanoma in situ and commonly present in elderly patients, typically on sun-exposed areas such as the face. Finally, the acrolentiginous melanoma (ALM, Fig. 1) presents on the extremities on the palmar or plantar surfaces but may also manifest itself under the nail (subungual melanoma). The initial diagnosis of an ALM is often delayed due to late presentation. In contrast to SSM, which initially spreads horizontally before the fast invasive growth , ALM quickly enters a rapid vertical growth phase which contributes to a poorer overall prognosis due to early metastasis.(Teramoto et al. 2018) Rarer forms of melanoma include ocular, meningeal and mucosal melanoma.(Sergi et al. 2023)

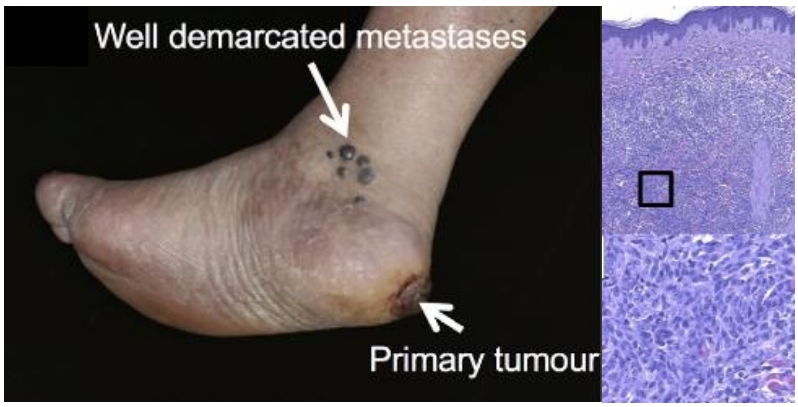

Figure 1: 61-year-old male with an ulcerated acral lentiginous melanoma on the right heel with cutaneous metastases around the right medial malleolus. The histology of a metastasis is shown on the right and at 600x magnification showing atypical melanocytes and and mitoses. Melanin pigment deposition and a lymphocytic infiltrate are also present. From Langan et. al. (Langan et al. 2019)

In line with the increasing incidence of malignant melanoma, disease-associated mortality is also on the rise. In fact, malignant melanoma has one of the highest mortality rates among skin cancer subtypes with an estimated 57000 deaths in 2020; only surpassed by non-melanoma skin cancer which encompasses both basal- and squamous cell carcinoma.(Arnold et al. 2022)

Staging

Following the histological confirmation and treatment of the primary tumor, melanoma is staged according to the TNM- and American Joint Committee of Cancer (AJCC) classification. Key diagnostic and prognostic parameters are the primary tumor thickness (Breslow thickness), the presence of ulceration, local spread (satellite and in-transit metastases), lymphatic spread and distant metastasis The Breslow classification remains the most reliable overall prognostic factor.(Gershenwald et al. 2017). It describes the tumor thickness or depth of the tumor and is measured in millimetres from tumor surface to the deepest point of infiltration.

The American Joint Commission on Cancer (AJCC), last updated in 2018, defines the different stages of malignant melanoma as follows (Keung and Gershenwald 2018):

Tumour	**Thickness**	**Ulceration**
Tis (Melanoma in situ)	N/A	N/A
Tx (Primary tumor thickness cannot be determined)	N/A	N/A
T0 (No evidence of primary tumor or completely regressed)	N/A	N/A
T1 T1a T1b T1b	≤1.0 mm <0.8 mm <0.8 mm 0.8–1.0 mm	Unknown or unspecified Without ulceration With ulceration With or without ulceration
T2 T2a T2b	>1.0–2.0 mm >1.0–2.0 mm >1.0–2.0 mm	Unknown or unspecified Without ulceration With ulceration
T3 T3a T3b	>2.0–4.0 mm >2.0–4.0 mm >2.0–4.0 mm	Unknown or unspecified Without ulceration Without ulceration
T4 T4a T4b	>4.0 mm >4.0 mm >4.0 mm	Unknown or unspecified Without ulceration With ulceration

Table 1: Tumour (T) classification

Source: (Keung and Gershenwald 2018)

Node	Number of tumor-involved regional lymph nodes	In-transit, satellite, and/or microsatellite metastases
NX	Regional nodes not assessed (e.g., sentinel lymph node [SLN] biopsy not performed, regional nodes previously removed for another reason); Exception: pathological N category is not required for T1 melanomas, use clinical N information	No
N0	No regional metastases detected	No
N1	One lymph node with tumor involvement or in-transit, satellite, and/or microsatellite metastases with one tumor affected lymph node	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	2 or 3 affected lymph nodes	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more affected lymph nodes	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Table 2: Node (N) classification

Source: (Keung and Gershenwald 2018)

Metastases	Anatomic Site	LDH Level
M0	No evidence of distant metastasis	Not applicable
M1 M1a M1a(0) M1a(1)	Evidence of distant metastasis Distant metastasis to skin, soft tissue including muscles, and/or nonregional lymph node	Not recorded or unspecific Not elevated Elevated
M1b M1b(0) M1b(1)	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified Not elevated Elevated
M1c M1c(0) M1c(1)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified Not elevated Elevated
M1d M1d(0) M1d(1)	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified Not elevated Elevated

Table 3: Metastases (M) classification

Source: (Keung and Gershenwald 2018)

Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0
III	Any T	≥N1	M0
IV	Any T	Any N	M1

Table 4: Melanoma Stage based on the T, N, M classification

Source: (Keung and Gershenwald 2018)

Modern management of melanoma

The gold standard for treatment of the primary tumor is surgical excision. The excision is a two-stage procedure; complete resection followed by re-excision of the scar, with an appropriate safety margin. In the absence of loco-regional or distant spread, and with a Breslow thickness of 1mm (0.8 mm when additional risk factors are present), a sentinel node lymph biopsy (SLNB) should be offered at the time as the scar re-excision. Whilst the SLNB traditionally only offered additional prognostic information (Stage III disease), evidence of lymph node spread now provides the possibility of specific anti-tumor therapy. Patients with distant metastases, including cerebral, pulmonary, or hepatic metastases have Stage IV disease.

Historically, the prognosis associated with Stage IV malignant melanoma was grave. Indeed, the prognosis for patients with cerebral metastases was measured in weeks rather than months. The standard treatment was with dacarbazine chemotherapy, an alkylating agent, which was associated with remarkably low response rates which were usually non-durable. Dacarbazine and was entirely ineffective in the treatment of cerebral metastases, failing to cross the blood-brain barrier.

The advent of immune checkpoint inhibition (ICI) and targeted therapies has fundamentally changed the therapeutic landscape in the management of locally advanced and/or metastatic melanoma. Both have had a dramatic impact upon overall- (OS) and progression free survival (PFS).(Jenkins and Fisher 2021) ICI, based on the Nobel prize winning work of Allison and Honjo, exploits the antagonism of naturally occurring immunological checkpoints using monoclonal antibodies. The checkpoints play an important physiological role in the prevention of autoimmune disease but can be blocked in order to promote a robust T-Cell-driven anti-tumor cytotoxic immune response. T–Cells recognise tumor antigens presented by antigen presenting cells (APCs) in the lymph nodes during the priming phase of the immune response. After tumor antigen presentation, via the Major-Histo-Compatibility (MHC) complex and T-Cell

receptor and antigen peptide, co-stimulatory molecules (B7-or CD80 and B 7-2 or CD86) signal via CD28 on T-Cell receptor. T-Cell activation is prevented by the binding of B7 (APC) to CTLA4 on T-Cells. CTLA4 is a protein which belongs to the immunoglobulin superfamily expressed on T-Cells. This co-inhibitory signal can be overcome via Ipilimumab, an anti-CTLA4 antibody. Following administration of Ipilimumab, tumor-specific cytotoxic T-Cells can expand, proliferate and infiltrate the tumor tissue in the effector phase of the immune response and result in tumor cell death. In addition, tumor cells express the programmed death ligand 1 (PD-L1), which binds PD-1 on T-Cells and prevents T-Cell mediated tumor cell death. The use of antibodies which antagonise PD-1 (Nivolumab or Pembrolizumab) or PD-L1 (avelumab) “release” this immune checkpoint break, resulting in the proliferation of tumor-specific cytotoxic T-Cell and tumor cell death. The risks of this treatment are excessive autoimmune reactions.(Willsmore et al. 2021)

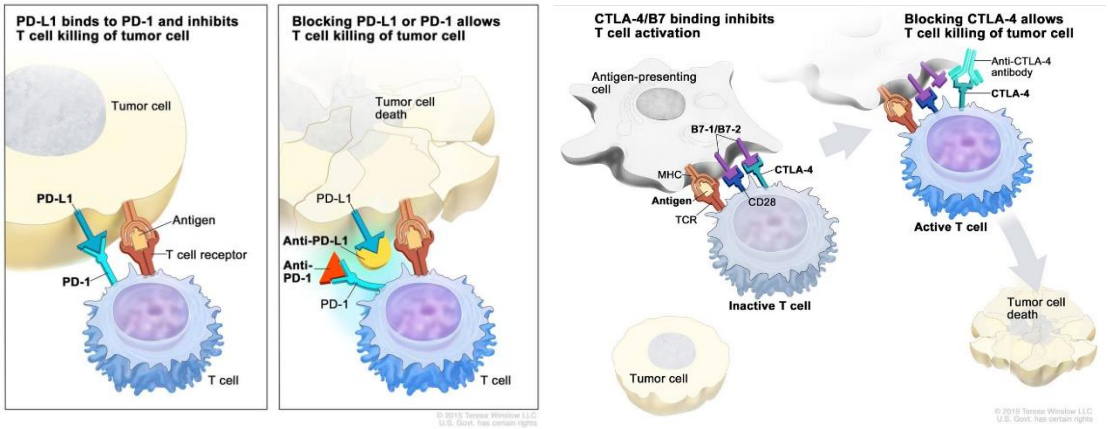

Figure 2: PD-L1/ PD-1/CTLA-4 Inhibition in T-Cells mechanism. National Cancer Institute © 2015 Terese Winslow LLC, U.S. Govt. has certain rights.

Checkpoint inhibitors licenced in cancer treatment

The following, non-exhaustive list of checkpoint inhibitors are in clinical practice in oncology in general and dermato-oncology in particular:

Drug	**Treatment (palliative/adjuvant) ***	**Mechanism of inhibition**
Pembrolizumab	Melanoma, Non–Small Cell Lung Cancer, Squamous Cell Carcinoma, Hodgkin Lymphoma, B-cell Lymphoma, Urothelial Cancer, Colorectal Cancer, oesophageal or gastroesophageal junction cancer, Cervical Cancer, Biliary Tract Cancer, Renal Cell Carcinoma, Endometrial Carcinoma, Squamous Cell Carcinoma, Breast Cancer	PD-1
Nivolumab	Melanoma, non-small cell lung cancer, malignant pleural mesothelioma, Renal cell carcinoma, Hodgkin lymphoma, Squamous cell cancer, Urothelial carcinoma, colorectal cancer, oesophageal or gastro-oesophageal junction cancer,	PD-1
Cemiplimab	cutaneous squamous cell carcinoma, basal cell carcinoma, non-small cell lung cancer, cervical cancer	PD-1
Ipilimumab	Melanoma, Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Malignant Pleural Mesothelioma, Oesophageal Cancer	CTLA-4

*(in combination with other drugs or stand-alone)

Table 5: Immune checkpoint inhibitors currently licensed according to tumour entity and mechanism of action.

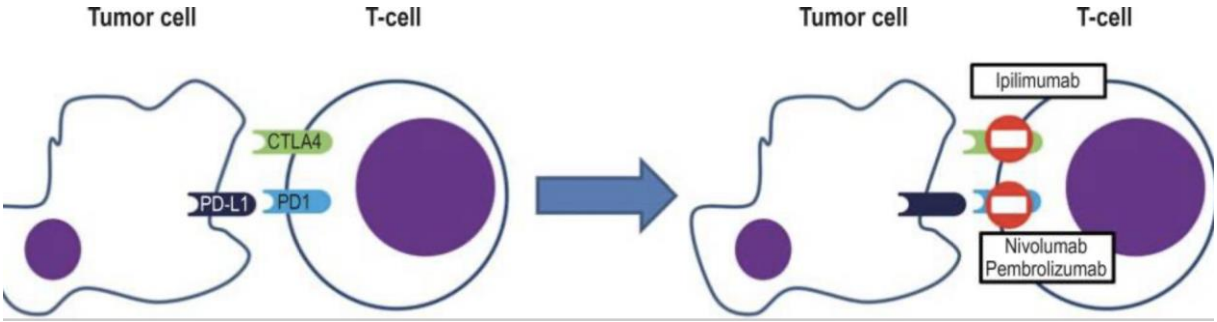

Figure 3: Immune checkpoints currently targeted in the management of melanoma. (Terheyden, Krackhardt, and Eigentler 2019)

Ipilimumab and Nivolumab

The human monoclonal IG1 κ antibody, Ipilimumab, is a CTLA-4 antibody, which was the first ICI-drug licensed for the treatment of melanoma. Ipilimumab is used for non-resectable or metastatic melanoma in stage IV and can be used in combination with Nivolumab. In the seminal study of Hodi et al., 2010, Ipilimumab resulted in improved overall survival for patients with stage III and IV metastatic melanoma treated either with Ipilimumab 3 g per kilogram body weight every four weeks alone and in combination with a glycoprotein 100 (gp100) peptide vaccine as well as only with gp100. The OS was the primary endpoint here. The patients with Ipilimumab showed improved OS (10.1 for single Ipilimumab treatment compared to 10.0 month in Ipilimumab and gp100 combination therapy compared to 6.4 months for sole use of the gp100 treatment). Also, 10-15% of the patients treated with ICI showed immune related adverse events (irAE), whereas the non-ICI patients' group had only 3% irAEs shown. Ipilimumab is often combined with Nivolumab, a PD-1 inhibitor. The dosage is 3 mg/kg administered intravenously every three weeks in combination with Nivolumab 1mg/kg.(Wolchok et al. 2022) for a maximum of 4 treatment cycles. The Checkmate 067 was a landmark study in the therapy settings of advanced melanoma.(Larkin et al. 2015; Wolchok et al. 2022) During this Phase III trial three groups of patients with metastatic melanoma grade III and IV were administered Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg once every 3 weeks (four doses) in 315 patients, Nivolumab 3 mg/kg once every 2 weeks with 314 patients or Ipilimumab 3 mg/kg once every 3 weeks for four doses in 315 patients. An elevated

progression free survival (PFS) could be seen with 11.5 month at the combination therapy vs. 6.9 month at Nivolumab vs. 2.9 months at the Ipilimumab treatment. Immune related adverse events were discontinuation reasons for the individual treatment of the patients. The combination group had higher numbers of irAE (n=18), compared to the Nivolumab group (n=8). The Ipilimumab group had the least AE with n=6.

Nivolumab

Approved for the treatment of various types of cancer, including melanoma, lung cancer, kidney cancer, and bladder cancer, the dosage for monotherapy dosage being a 60-min infusion of 3 mg/kg once every 2 weeks, can be used as well as a combination with Ipilimumab. The usage of Nivolumab is indicated for adjuvant treatment of metastatic melanoma after complete resection or lymph node involvement. The single application of Nivolumab compared to Ipilimumab showed greater progression free survival in a 5-year range, as seen in the Checkmate 238 study.(Larkin et al. 2023) Here the improvement of progression free survival(PFS) or recurrence free survival (RFS) was shown in adjuvant treatment of Nivolumab mg/kg every 2 weeks 10 mg/kg every 3 weeks compared to Ipilimumab 10 mg/kg every 3 weeks intravenously in resected melanoma Stage III B – C patients for one year. 62 months as follow-up showed superior results for Nivolumab with 5-year rates of 50% versus 39% in Ipilimumab. Overall survival rates in 5 years of the patients were 76% with Nivolumab and 72% with Ipilimumab.

Pembrolizumab

Approved for treatment of melanoma in 2014 in the United States by the FDA, Pembrolizumab has become a major player in the advanced melanoma therapy. The humanized antibody of the IgG4 isotype targets the apoptosis inducing mechanism of tumor cells (programmed death cell protein 1 – PD-1) and thus allowing the immune system to destroy the tumor cells.(Robert et al. 2014) Before the adjuvant treatment - the begin of immune checkpoint inhibition after

resection of metastatic melanoma- palliative treatment was introduced. In Europe, each drug is licensed by the European medicine agency. Being a checkpoint-inhibitor drug in a palliative setting first, newer studies showed an improvement concerning an adjuvant as well as neoadjuvant treatment approach.(Patel et al. 2023). In a phase II trial, including patients with stage III melanoma, Pembrolizumab is used as adjuvant therapy in stage IIB-IIID after complete resection.

Recent studies discuss the idea of neoadjuvant treatment with Pembrolizumab. Patel et al. 2023 assigned two groups randomly: one with Pembrolizumab 200 mg intravenously every three weeks with three doses prior and 15 doses after surgery (n=154) and one group with a Pembrolizumab therapy - 200 mg intravenously every three weeks with 18 doses after to surgery (n=159). All patients had stage IIIB to IVC melanoma. The primary endpoint was an event-free survival for two years or a therapy cancelling adverse events in the adjuvant group. Here the neoadjuvant group showed significant longer event free survival, 72%, (95% CI, 64 to 80)) compared to the adjuvant group with 49% (95% CI, 41 to 59).

Another approach happened in an adjuvant setting, with the randomized, double-blind phase-3 trials, seen in the KEYNOTE-716 study, it showed an improved OS, as well as a prolonged progression free survival. After the screening of 1182 patients in 160 academic medical centres in 16 countries, divided into a randomly chosen group who got intravenous Pembrolizumab 200 mg administered every three weeks (n=487) and a placebo group (n=489), a recurrence of the advanced melanoma had 11% of Pembrolizumab cohort and 17% of the placebo cohort.(Luke et al. 2022) Comparing reactions of the treatment, the placebo group showed in 4% adverse events compared to 78% of the Pembrolizumab group.

In the KEYNOTE 029 study Carlino et al. 2017 investigated with the KEYNOTE-029 expansion cohort a weight adapted therapeutic dosing and toxicity. Here 153 patients with advanced melanoma, no brain metastases and ICI- naive were treated with Pembrolizumab 2 mg/kg + Ipilimumab 1 mg/kg every three weeks (4 doses) and afterwards they received Pembrolizumab

2 mg/kg for two years alone during a period of eight months. Primary end point was patient safety with no treatment related death, which was successful. Secondary points were OS, PFS and ORR. Although patient safety was ensured therapy related adverse events (TRAE) occurred in all patients. The results for one year progression free survival were estimated by 69% and 89% for overall survival. They concluded, that the toxicity profile of the combination of Pembrolizumab 2mg/kg and 4 doses of Ipilimumab 1mg/kg was manageable as well as proficient anti-tumor activity.(Carlino et al. 2017)

Another result concerning the dosage of Ipilimumab was found by Long et al. 2021 in the cohort 1C of the KEYNOTE - 029 phase two study. Here, Pembrolizumab (200 mg every three weeks) was combined with Ipilimumab 50 mg or 100 mg every six weeks and compared in terms of irAE. The incidence of irAE was reduced by 13% when using lower dosage of Ipilimumab. 102 patients with unresectable, untreated stage III/IV melanoma were randomly assigned into two groups. Primary endpoint was the incidence of adverse events during a 3 – 5-year period (TRAE) and the objective response rate (ORR), The threshold was defined as the reduction of toxicity by 3–5 TRAE incidence ≤26%. Here the dosage of Pembrolizumab 200 mg + Ipilimumab 50 mg showed lower incidence concerning grade 3 - 5 adverse events which could imply a lower toxicity by dose reduction.

Palliative and Adjuvant treatment

The initial treatment setting of immune checkpoint therapy was a palliative setting and as time and studies progressed, it changed to an adjuvant setting. Here it is adamant to differentiate which level of melanoma and are metastases are present. While Stage II B - IV with or without metastases can be treated in an adjuvant setting, inoperable stage IV represents a palliative setting (Lopes et al. 2022) still includes immune checkpoint therapy, and the overall survival improves as new drugs are discovered.(Kreidieh and Tawbi 2023)

Fixed Dose (FDT) vs Adapted Weight (WAT) Therapy

Fixed weight dosage in immunotherapy refers to a standardized or predetermined dose of a medication based on the patient's body weight. Instead of adjusting the dose individually for each patient, a fixed weight dosage simplifies the administration process by using a set amount of the drug that is determined in advance. In the context of immunotherapy, these medications include Nivolumab, Pembrolizumab or Ipilimumab. Fixed weight dosages help standardize treatment protocols, making it easier for healthcare providers to administer the medication and reducing the likelihood of dosage errors. This approach is particularly useful in clinical trials and routine clinical practice where simplicity and consistency in dosing are important. It is important to note that the specific dosing regimen, including whether it is fixed weight or adapted by weight, depends on the immunotherapy drug and the clinical guidelines associated with its use.

Freshwater et al. 2017 evaluated the comparison of Pembrolizumab in fixed weight and adapted weight dosage, specifically in terms of pharmacokinetics and found no clinically relevant differences. The CHECKMATE 238 study compared a weight adapted group with monotherapy Nivolumab (administered dosage: Nivolumab 3 mg/kg every 2 weeks and Ipilimumab (administered dosage: 10 mg/kg every 3 week) and showed an improvement of Nivolumab compared to Ipilimumab in terms of recurrence free survival (RFS) 56% to 51% as well as overall survival (OS) with 76% to 72%. (Ascierto et al. 2020). In 2016 the weight adapted dosing approach (weight adapted therapy, WAT) with Nivolumab was changed to fixed dosage therapy (FDT). The modification of dosing was changed to 240 mg Nivolumab intravenous every two weeks.(Research 2018) The CHECKMATE 238 study showed significant improvements of in terms of PFS in patients treated with WAT with Nivolumab (3 mg/kg every 2 weeks intravenous) compared to patients treated with Ipilimumab 10 mg/kg every 3 weeks. 51.7% of the Nivolumab group showed a four year recurrence or progression free survival, superior to 41.2% recurrence free survival in the Ipilimumab group.(Ascierto et al. 2020) In the KEYNOTE 054 double-blind, randomized, controlled, phase 3 trial, that distant

free metastasis survival was higher in the Pembrolizumab group 65·3% vs 49·4% in the placebo group. The dosage here was Pembrolizumab 200 mg or placebo every 3 weeks for 12 months.(Eggermont et al. 2021) The different therapeutic dosage approaches remain focus of research. There is relatively sparse real-world data examining any effect of FDT versus WAT; a gap in the literature that this thesis aims to address. Of course, the effects of FDT and WAT on treatment efficacy are crucial, but any differential effects on tolerability and the development of irAE should also be critically evaluated. To this end, the incidence and evaluation of irAEs will be illustrated. This study investigates whether there is an improvement in overall survival, progression free survival and irAE comparing Ipilimumab and Nivolumab in a weight adapted dosage and fixed weight dosage as well as Pembrolizumab in both forms of dosing. The different treatment settings were examined concerning different parameters such as BMI, tumor markers and OS, as well as different laboratory parameters.

Common Terminology Criteria for Adverse Events (CTCAE)

The Common Terminology Criteria for Adverse Events (CTCAE) is a standardized system used to classify and grade the severity of adverse events (AEs) associated with medical treatments, including anticancer therapies such as immune checkpoint therapy. The current version is V 5.0. ('Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP' ; Freites-Martinez et al. 2021) Adverse events are classified from mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or death (grade 5.)

Severity/Grade	Definition
1	Asymptomatic or mild symptoms, no indication for intervention only clinical/ diagnostical observation
2	Moderate, local, or non-invasive intervention only, instrumental activities of daily life are limited
3	Significant or severe, but not life threatening, indication for hospitalization is given, ADL are limited in terms of self-care
4	Life-threatening, immediate indication for intervention
5	Death related to AE

Table 6: The Common Terminology Criteria for Adverse Events (CTCAE) Reproduced with permission from (Das and Johnson 2019) Copyright Massachusetts Medical Society.

Immune-related adverse effects

The major drawback of ICI is the development of immune-related adverse events. The most common immune-related adverse events include skin reactions (rash, pruritus, xerosis cutis, vitiligo), intestinal reactions (colitis, diarrhoea), hepatic, pulmonary or renal inflammation and endocrinopathies including hypothyroidism and/or hyperthyroidism and adrenal gland insufficiency.(Postow, Sidlow, and Hellmann 2018) More uncommon irAEs include arthritis, encephalitis and myocarditis.(Liu et al. 2019; Lamos and Hunger 2020; Kurzhals et al. 2021)

In the case of ICI, hepatitis is used for patients with liver disfunction, meaning elevated transaminases as well as elevated direct or indirect Bilirubin. It is important to differentiate between the possible side effects of ICI and reactivated viral infections, such as hepatitis A/B/C, cytomegalovirus (CMV), Epstein-Barr virus (EBV) as well as infections on the gastrointestinal tract i.e. clostridium difficile.(Kähler et al. 2020)

IrAE are likely due to T-Cell activation, leading to a direct T-Cell attack on healthy tissue as a consequence of epitope spreading.(Venkatesha, Durai, and Moudgil 2015) As a result, B-cells

are activated and generate (autoimmune) antibodies. Iatrogenic T-Cell hyperactivation, based on immune checkpoint inhibition therapy leads to the peripheral accumulation of activated B-cells, such as antibody-producing plasma blasts and CD21lo B cells.(Das et al. 2018) This and direct molecular mimicry and off-target toxicity by activating the complement system may lead to a direct reaction to. Resulting in an elevated production of cytokines, which bind to the immune cells, leading to increased, dysregulated proinflammatory reactions via intracellular signalling pathways for example PI3K-AKT-mTOR, or JAK-STAT.(Esfahani et al. 2019; O'Shea et al. 2015) Vetizou and al. highlighted the dependence of immune checkpoint therapy on the gut microbiome, which may also predispose patients to irAEs via dysbiosis and production of microbiota metabolites.(Vétizou et al. 2015)

On the other hand, the development of irAEs is associated with an improved response to immune checkpoint inhibition.(Das and Johnson 2019) Indeed a more robust immune response and consequently an increased incidence of irAEs is seen with combined immune-checkpoint therapy, particularly with combined anti- PD-1 and anti CTLA-4 antibodies. Elevated expression of CTLA-4 on pituitary gland tissue is suspected to be one of the reasons for a higher level of inflammatory cytokines in ICI with Ipilimumab, in both murine and human studies.(Iwama et al. 2014; de Moel et al. 2019; Lupi et al. 2019) The extent to which individual ICIs contribute to overall morbidity and mortality, as well as the precise mechanisms underpinning irAEs remain unclear.(Albandar et al. 2021)

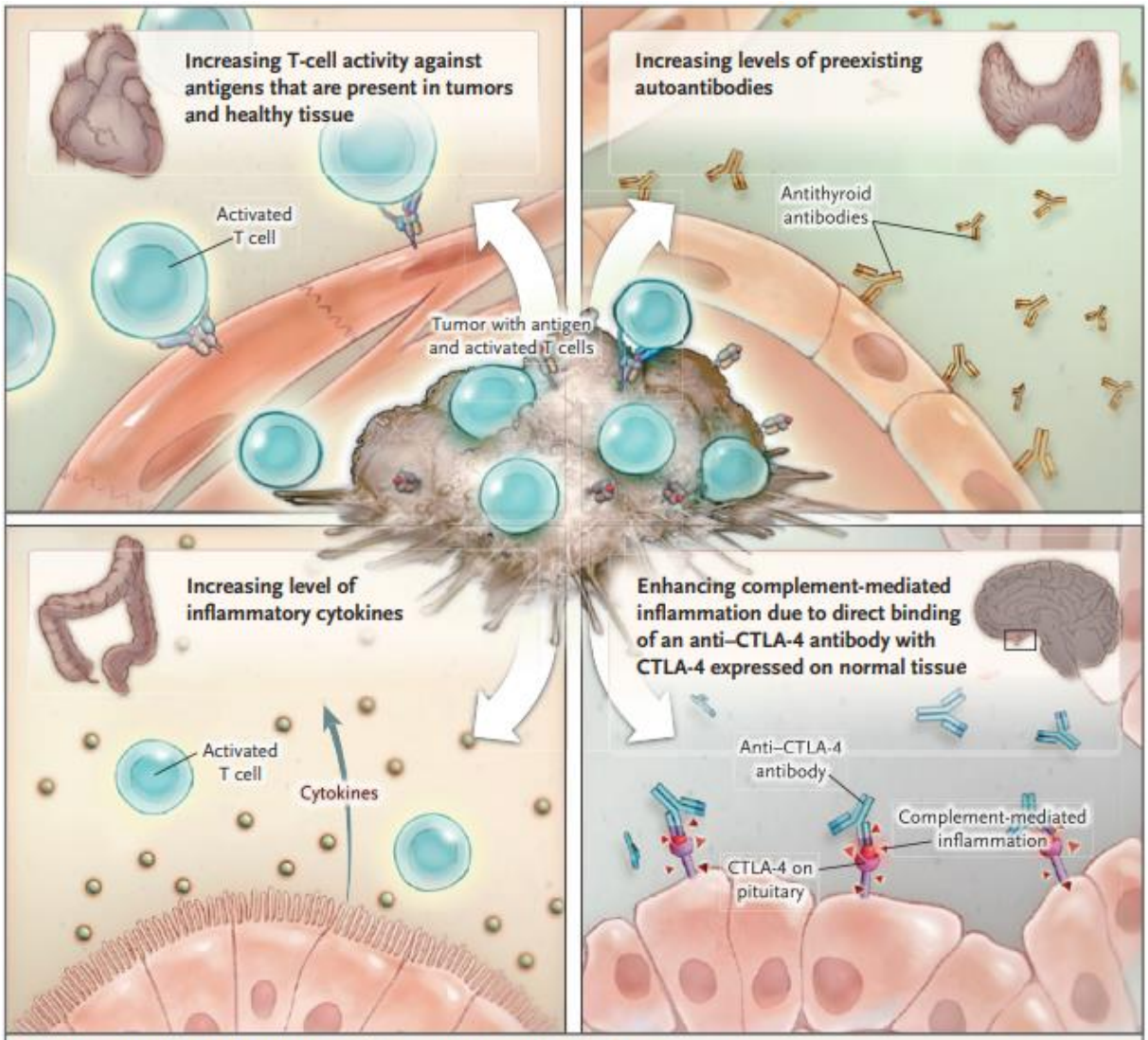

Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland.

Figure 4: The mechanisms underlying immune-related adverse events (irAEs) Postow et al. Reproduced with permission from (scientific reference citation), Copyright Massachusetts Medical Society.

Targeted Therapy

In addition to ICI therapy, targeted therapy also plays a vital role in the modern management of metastatic melanoma, both in the adjuvant and palliative setting. The most common targetable mutation is a mutation in the BRAF gene, present in up to 50% of all cutaneous melanomas.(Ugurel and Schmidberger 2023) The BRAF gene is a proto-oncogene that

encodes a protein involved in cell signaling and regulation. Mutations in the BRAF gene can lead to the activation of the MAPK/ERK signaling pathway, which plays a role in cell growth and proliferation. BRAF inhibitors (e.g., vemurafenib, dabrafenib) and MEK inhibitors (e.g., trametinib, binimetinib), have been developed and are approved for the treatment of metastatic melanoma (Figure 5).(Ascierto et al. 2021; Dummer et al. 2020) The combination of BRAF/MEK inhibition with immune checkpoint inhibition have shown promising results and is currently under further research.(Welti et al. 2022) Given that the sequence of therapy may influence overall survival, only patients treated with immune checkpoint inhibition up front were included in the analyses.(Haist et al. 2022; Trojaniello et al. 2023; Gratz et al. 2019)

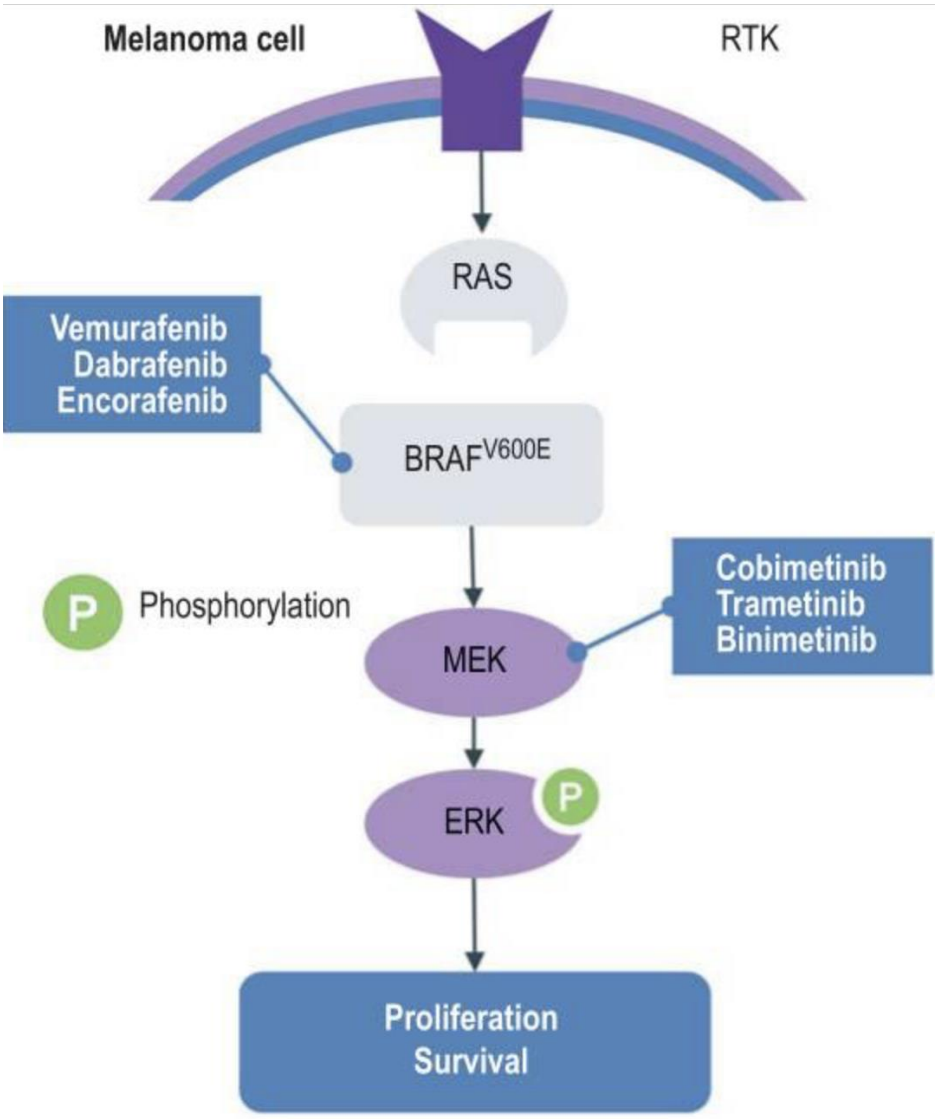

Figure 5: The BRAF signalling pathway which is targeted by combined BRAF and MEK inhibition. FromTerheyden et al.(Terheyden, Krackhardt, and Eigentler 2019)

Eastern Cooperative Oncology Group (ECOG) Status

Finally, the ECOG status of all patients was recorded from the electronic case records. ECOG performance status is a widely used system to assess the functional status of cancer patients participating in clinical trials. It ranges from 0 to 5, with lower scores indicating better functional status and higher scores indicating a decline in performance.(Simcock and Wright 2020)

Status	**Definition**
0	Fully active, able to continue all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.
2	Ambulatory and capable of all self-care but unable to conduct any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot continue any self-care. Totally confined to bed or chair.
5	Dead

Table 7: Performance Status

Aims of this Thesis

Whilst the advent immune checkpoint inhibition-based immunotherapy has revolutionized the management of locally advanced and metastatic melanoma, only 40 - 60% of patients respond to treatment in the first-line setting and 50% will develop disease progression (Zaremba et al. 2021). Therefore, there is intense interest in identifying factors which may potentially influence response to treatment. One potential factor is the dosing schedule. In 2017 the dosing schedule for Nivolumab was modified from weight-adapted dosing to a fixed-dose regimen, irrespective of body weight. In 2018 the European Medicines Agency approved fixed dosing for Pembrolizumab in the adjuvant setting, which replaced the weight-dependent dosing established in the palliative setting based on the pivotal Keynote clinical trials.(Robert, Long, et al. 2015b; Robert, Schachter, et al. 2015; Ribas et al. 2015; Schadendorf et al. 2016; Elassaiss-Schaap et al. 2017)

Despite the pharmacokinetic data supporting the use of fixed dosing of ICI therapy (Ogungbenro et al. 2018; Elassaiss-Schaap et al. 2017), “real world” data comparing fixed-dose versus weight-adapted dosing in melanoma is sparse. This is somewhat surprising given body mass index, kidney disease and the development of immune-related adverse events, have been shown to affect the response to treatment (Schadendorf et al. 2017; McQuade et al. 2018; Cheun et al. 2019).

Therefore, the aims of this thesis were threefold:

1. To determine the extent to which renal function and body mass index impact upon the efficacy of ICI treatment in patients with advanced melanoma.
2. To examine whether the use of fixed-dose therapy (FDT)- or weight-adapted therapy (WAT) with ICI treatment influenced progression-free and overall survival rates.
3. To establish which factors may affect PFS in patients treated with FDT or WAT.

Material and methods

Ethical approval for the project was obtained from the Ethics Committee of the University of Luebeck (AZ 20-386, see attachment). The electronic case notes of all patients (n=77) in whom treatment with immunotherapy was initiated in the Department of Dermatology of the University clinic Schleswig-Holstein, Campus Lübeck, for locally advanced or metastatic melanoma between the 1st of January 2017 and the 31st of December 2020 were retrospectively analysed. Thirty patients were excluded from further analyses given they did not receive treatment in the first-line setting. These patients had either undergone previous treatment with BRAF/MEK inhibitor-based targeted therapy ICI-based immunotherapy. Given that prior treatment may not only have influenced the progression-free survival, but also the incidence of irAEs, their inclusion would have been a potential source of bias (see Flowchart). All data were collated, anonymised, and analysed after institutional ethics approval and according to the Declaration of Helsinki principles.

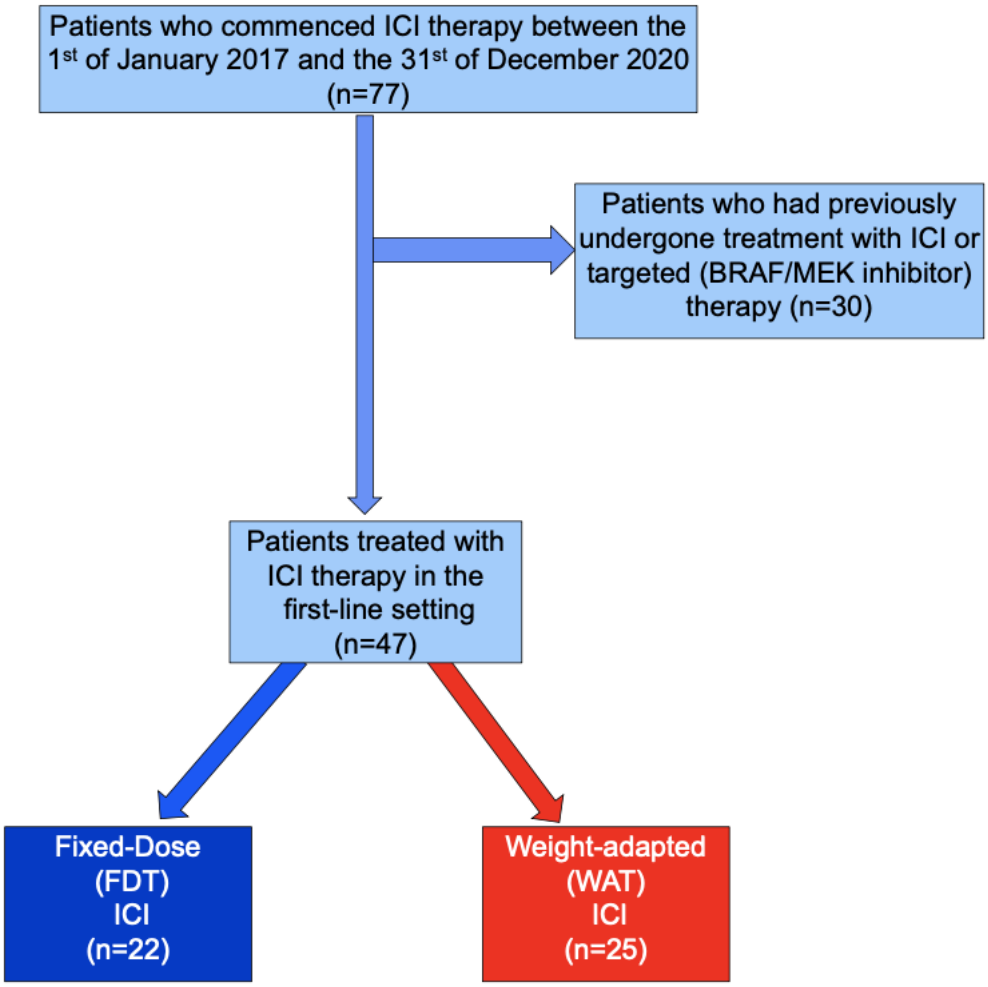

Figure 6 Cohort differentiation of all patients

Therefore, the final analyses were based on forty-seven patients who were treatment with ICI therapy according to national guidelines and the prevailing regulatory requirements at the time of treatment initiation. The changes in the Summary of product characteristics (SmPC) permitted an analysis of the clinical outcomes and adverse events in patients were treated with WAT or FDT. Treatment was administered according to the SmPC and monitored at each infusion to evaluate tolerability, efficacy, and the development of irAEs as part of routine clinical practice. When the development of severe irAEs resulted in temporary suspension or permanent discontinuation of treatment, this was noted.

In addition, standard laboratory parameters were evaluated during treatment, initially on a weekly basis, and complemented by standard radiological examination, including CT scans

(abdomen and thorax) and MRI brain imaging where appropriate. Radiological imaging was performed earlier than planned when disease progression or relapse was suspected based on clinical examination, lymph node sonography or elevated circulating S100 concentrations. All treatment decisions were reached in multi-disciplinary tumor boards and not influenced by this retrospective analysis.

To address the aims of this thesis, data on the following parameters were collated:

Age	Age at treatment initiation
Body mass index	<25, ≥25 kg/m^2
Cardiovascular Disease	Pre-existing Cardiovascular Disease/No pre-existing cardiovascular Disease
Diabetes Mellitus	Pre-existing Diabetes Mellitus/No pre-existing Diabetes Mellitus
Immune mediated adverse events (irAE)	Number and Grade (common terminology for adverse events v.5)
Immunotherapy Setting	Adjuvant/Palliative
Kidney function	Creatinine (µmol/l) and eGFR (CKD-Epi-Formula)
Melanoma Stage	Stage IIc, III or IV
Mutation Status	BRAF/NRAS/cKit
Overall survival (OS, final follow up December 31st 2020)	Days
Progression-free survival (PFS)	Days
Serum S100 concentration prior to treatment	µg/l, elevnated or not elevated
Sex	Female/Male

Table 8: Parameters documented from the electronic case records

Statistical analysis

Data was collected and integrated into Microsoft Excel (Version 16.82). All statistical analyses were performed using Microsoft Excel and survival analyses were calculated using GraphPad Prism (version 8). Statistical advice was obtained from the Institute of Biomedical Statistics in Lübeck ("Institut für Medizinische Biometrie und Statistik"). P values < 0.05 were considered statistically significant. For the descriptive analyses bar and pie charts as well as frequency tables were used. Kaplan-Meier curves were used to calculate progression-free and overall survival as well as potential influencing factors. The following test methods were used to determine statistical significance depending on the distribution of the data and whether it was nominal or ordinal:

- Chi square test
- Fisher´s exact test
- Log-rank (Mantel-Cox) test
- Mann Whitney test
- Pearson's correlation

Results

Demographics

Between the 1st of January 2017 and the 31st of December 2020, a total of 77 patients received ICI therapy for locally advanced or metastatic melanoma. All patients attended the immunotherapy out-patient unit of the Department of Dermatology and underwent regular clinical examination and laboratory investigation. 47 patients underwent treatment with ICI therapy in the first list treatment setting (figure 7).

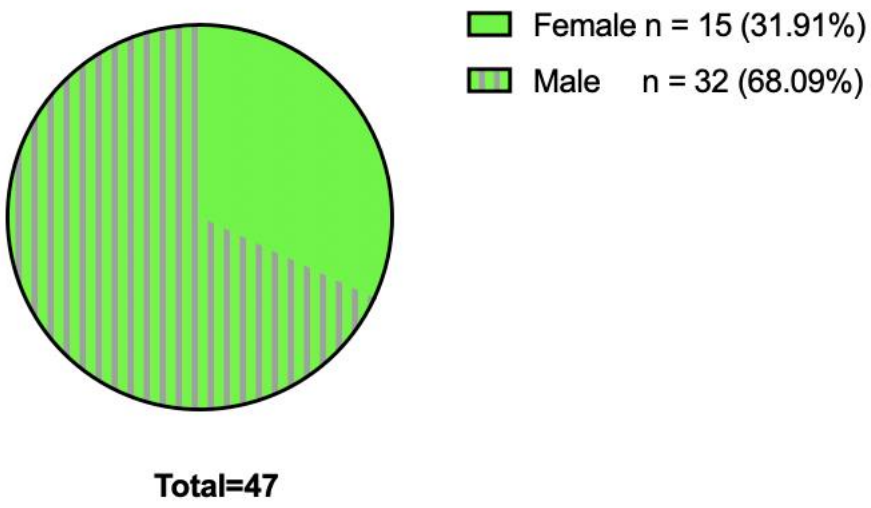

Figure 7: Ratio of females to males in both weight-adapted therapy (WAT) and FDT (fixed-dose therapy) groups combined.

The patients were categorized according to whether their initial treatment was with weight-adapted - fixed-dose ICI therapy.

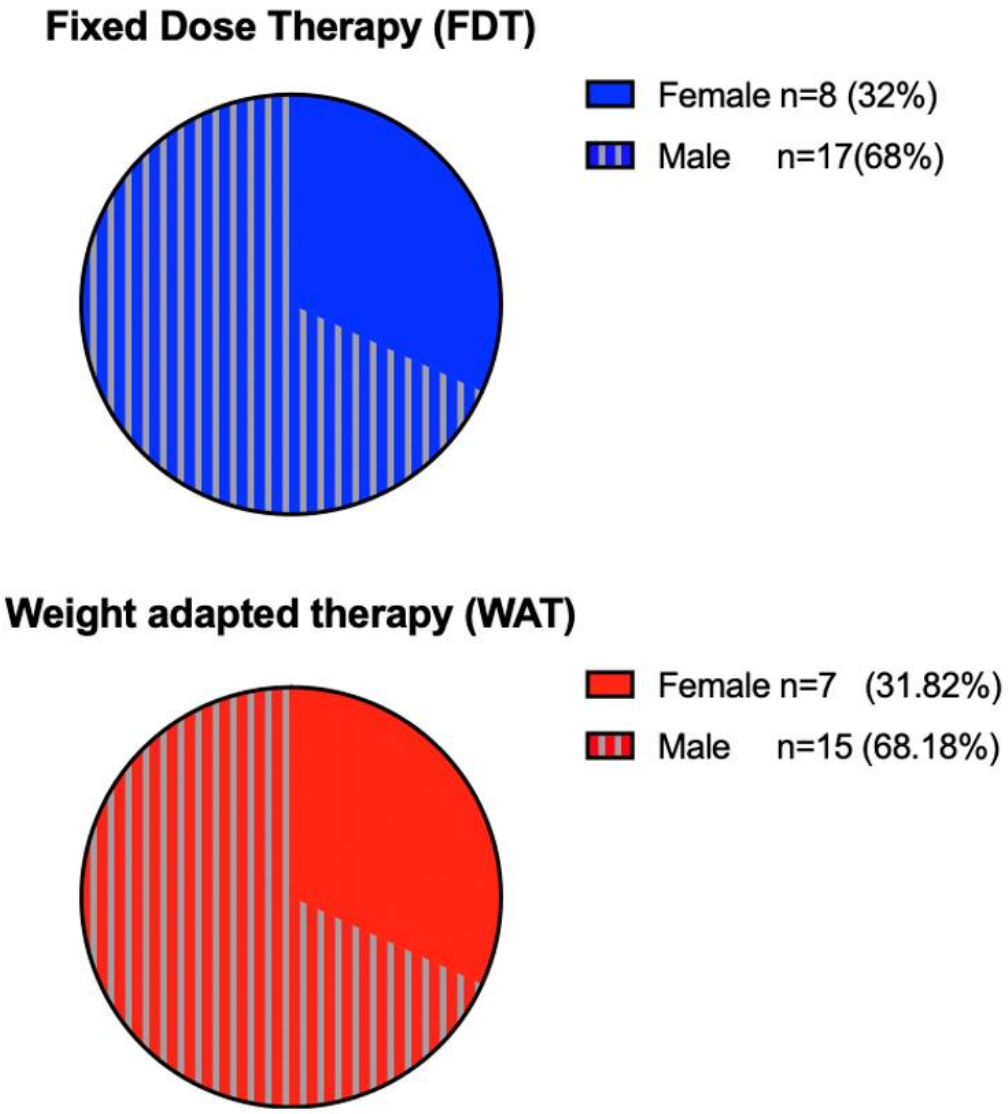

Figure 8: Sex distribution in the FDT and WAT cohorts

The mean age of the patients was 67.24 years (SD +/- 16.98) in the FDT cohort and 78.82 years (SD +/- 16.11) in the WAT cohort.

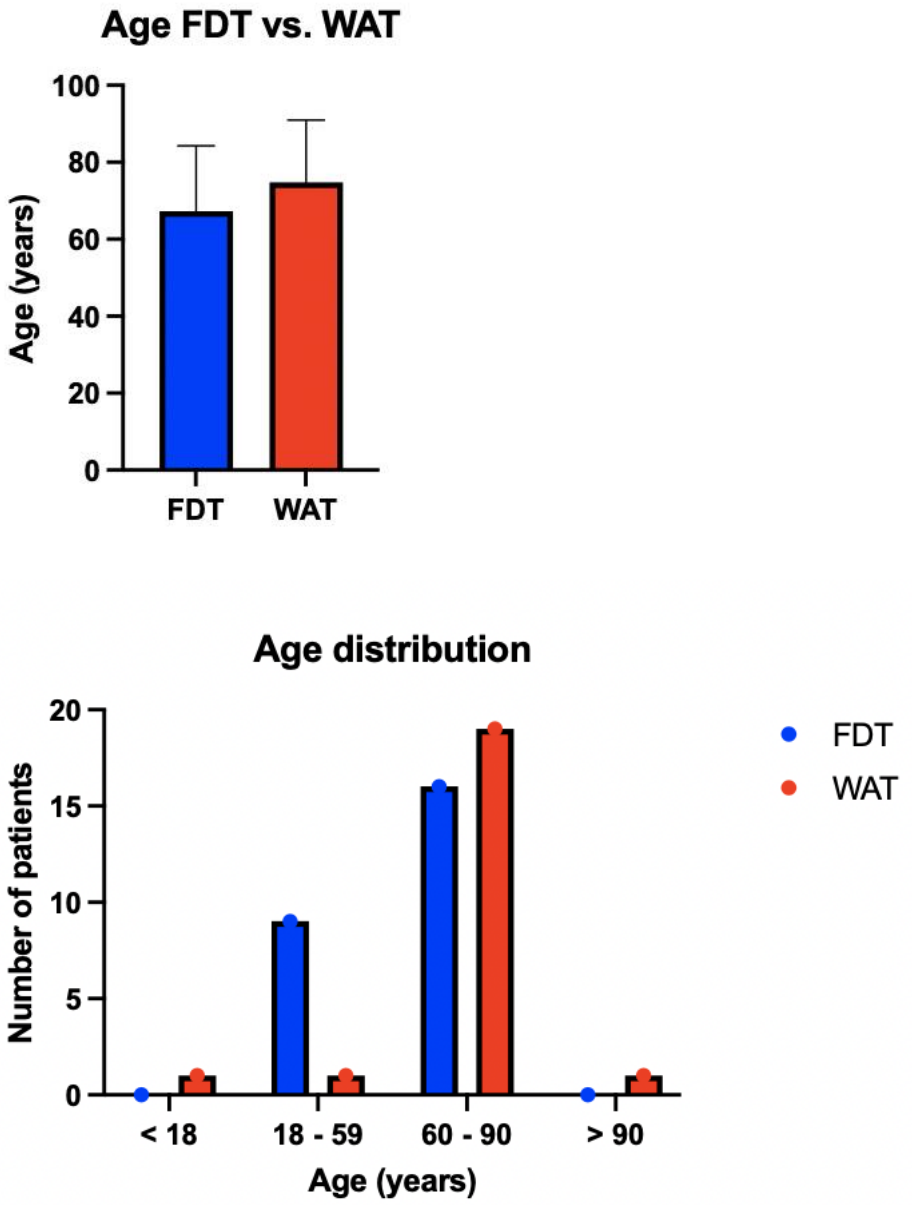

Figure 9:Age distribution in both cohorts

Overall, patients were aged between 17 and 97 at the initiation of ICI therapy. The youngest patient in the WAT cohort was 17 years old, with the oldest being 97 years of age. The equivalent figures in the FDT cohort were 22 and 89 years of age respectively. In terms of age distribution according to sex the groups were broadly similar.

The distribution of melanoma cancer types is seen in figure 10. As expected, metastatic superficial spreading melanoma was the most encountered subtype, with lentigo maligna melanoma the least frequent.

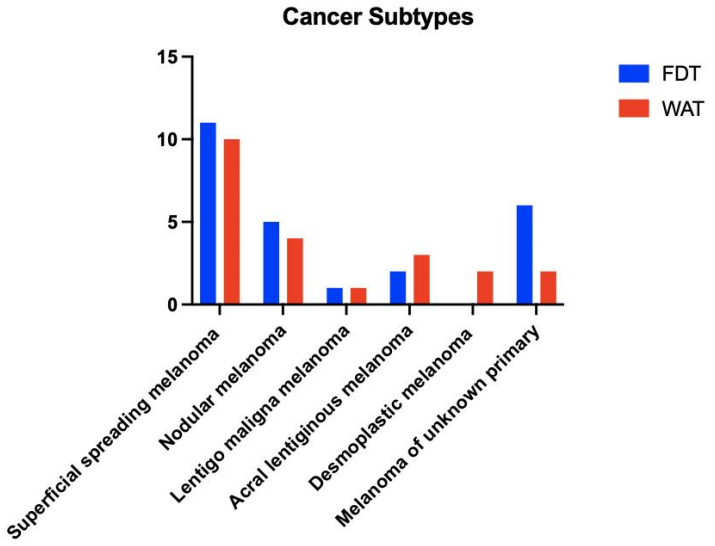

Figure 10: Melanoma subtypes in both cohorts

Cancer treatment setting

All patients underwent treatment for locally advanced or metastatic malignant melanoma. The treatment context was either in the adjuvant or palliative setting. Whilst the overall numbers in both groups were similar, a higher percentage of patients in the WAT group were treated in the palliative setting.

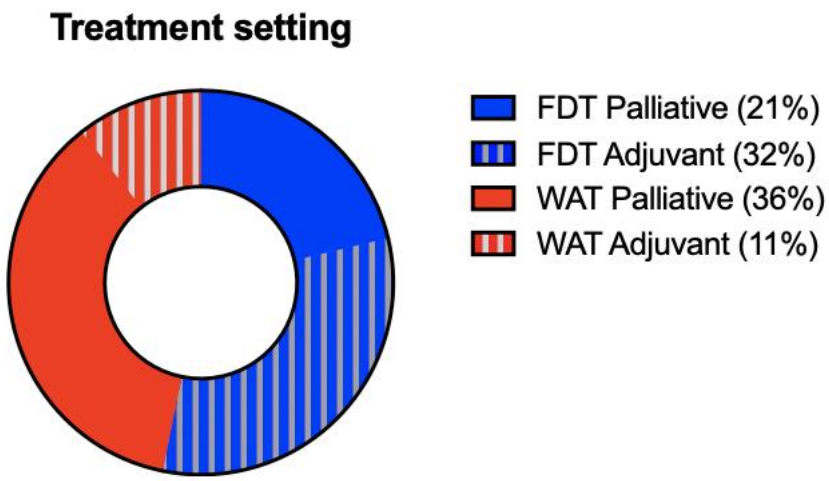

Figure 11: Treatment setting comparing palliative and adjuvant settings

However, there was no significant difference in ECOG performance status between the cohorts (Fisher's exact test, p=0.17).

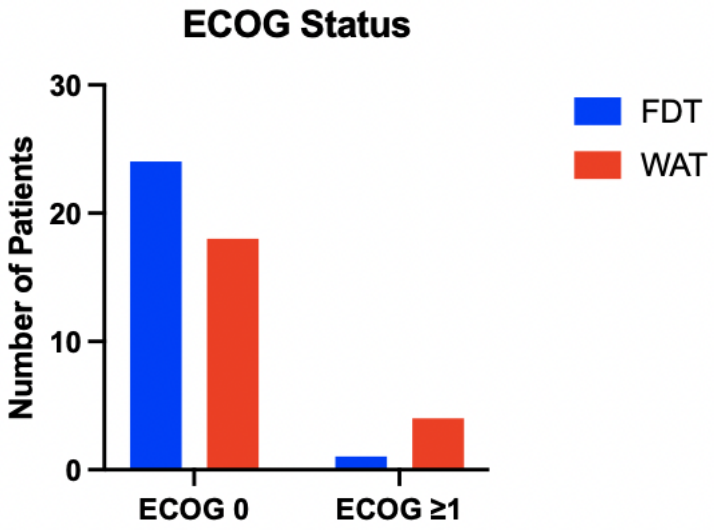

Figure 12: ECOG Performance Status in both cohorts

Of the 47 patients treated with ICI therapy there were no significant differences in the number of patients receiving treatment with Nivolumab (n=25) or Pembrolizumab (n=22).

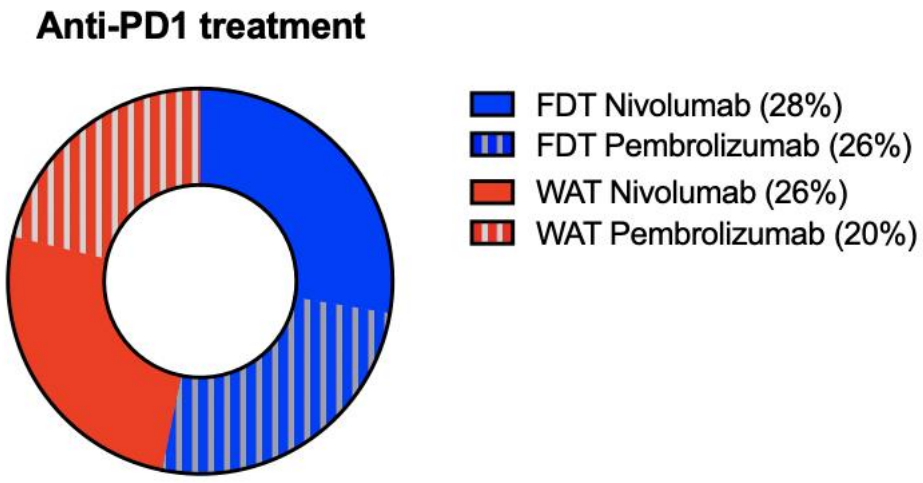

Figure 13: Anti-PD1 Therapies according to treatment cohort.

Aim number one

To determine the extent to which renal function and body mass index impact upon the efficacy of ICI treatment in patients with advanced melanoma.

In order to determine the effects of body mass index and renal function upon the efficacy of ICI in melanoma patients treated with ICI, pre-treatment weight (kg), height (cm), serum creatinine (µmol/l) and estimated glomerular filtration rate (ml/min/1.73) were extracted from the electronic patient records.

There was no significant difference between the groups in terms of serum creatinine. The mean serum creatinine (+/- SD) was 84.41 +/- 18.46 µmol/l and 101.7 +/- 30.31 µmol/l in the FDT and WAT groups respectively.

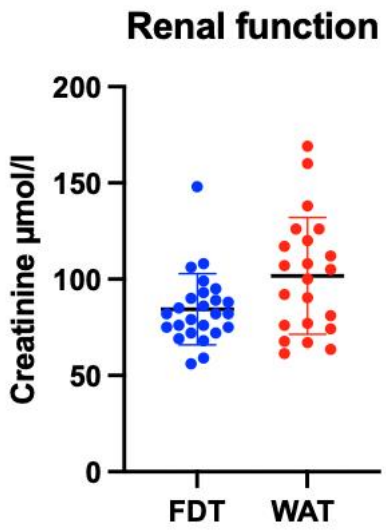

Figure 14: Renal function as measured by serum creatinine in both cohorts. There was no significant difference in renal function between the groups.

However, there was a significant difference in the estimated glomerular filtration rate between the groups. The mean eGFR (+/- SD) was 78.44 +/- 21.16 ml/min/1.73 in the FDT group compared to 63.14 +/- 23.28 ml/min/1.73 in the WAT group (p=0.02).

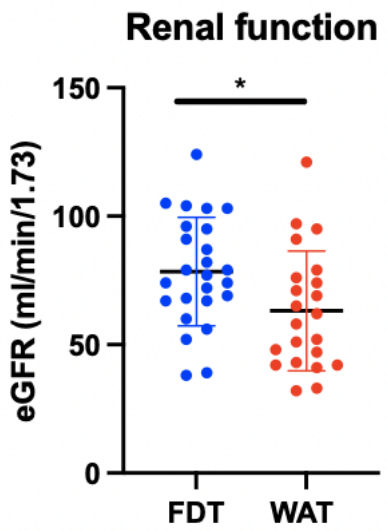

Figure 15: Renal function as measured by eGFR differed significantly between the groups at the outset of treatment (p=0.02)

Since eGFR takes muscle mass, age, sex, and race into account, it is a more accurate measure of renal function. The significantly poorer renal function in the WAT cohort likely reflects the higher proportion of patients treated in the palliative context as compared to the FDT cohort.

Although there was a significant difference in baseline eGFR between the groups, this did not translate into a significant correlation between renal function and progression free survival in either group (FDT r = 0.11 p=0.58, WAT r = 0.33 p=0.14) nor in OS in either group FDT (r = 0.09 p=0.65, WAT r = 0.33 p=0.13).

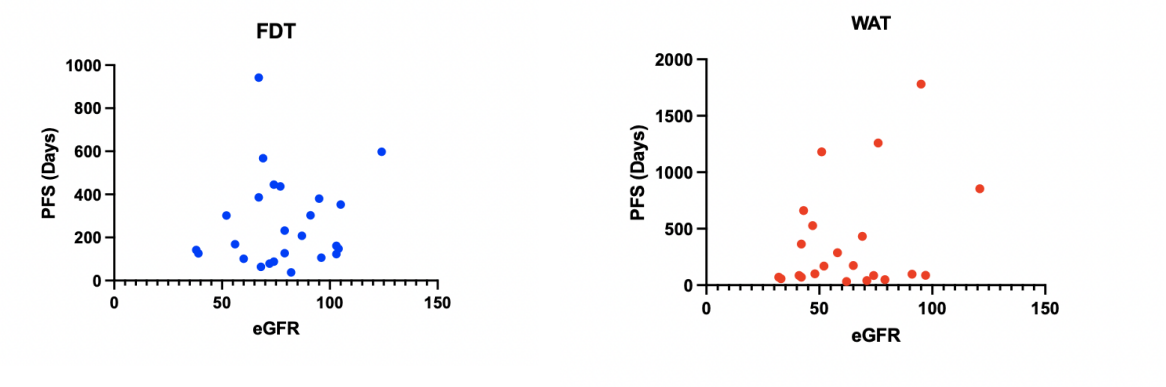

Figure 16: Correlation between eGFR and treatment response as measured in PFS (FDT r = 0.11 p=0.58, WAT r = 0.33 p=0.14)

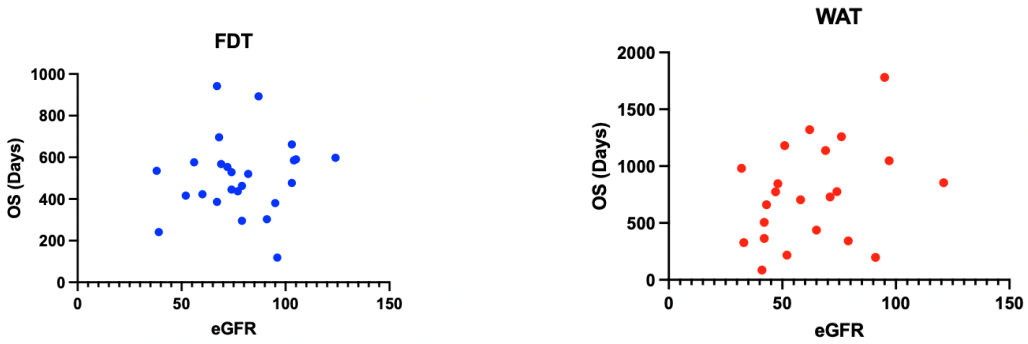

Figure 17: Correlation between eGFR and treatment response as measured in OS (r = 0.09 p=0.65, WAT r = 0.33 p=0.13)

Next, BMI was calculated prior to treatment onset. The mean BMI (+/- SD) was 26.76 +/- 4.45 and 27.47 +/- 3.93 in the FDT and WAT cohort respectively.

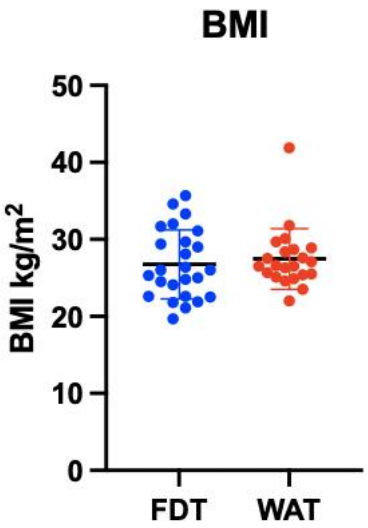

Figure 18: BMI per group. There was no significant difference in baseline BMI

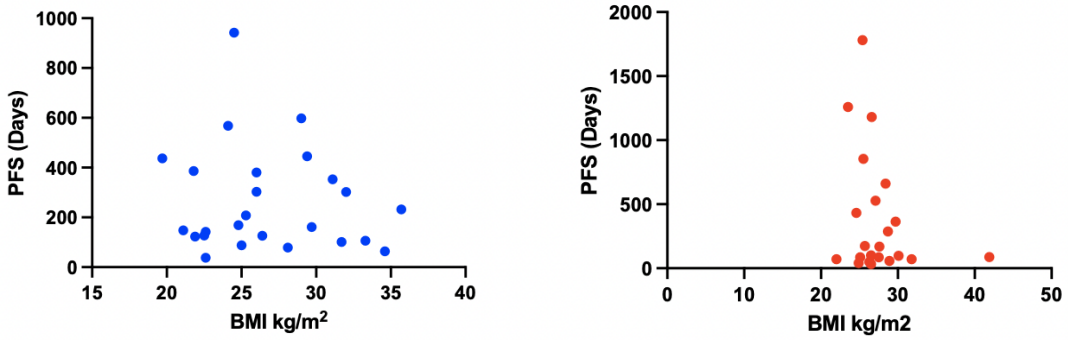

Figure 19: The correlation between BMI and PFS (days) between the groups (FDT: blue, r = -0.12 p=0.5, WAT: red, r = -0.12 p=0.58)

There was no significant correlation between BMI and PFS in the FDT (blue, r = -0.12 p=0.57) or WAT (red, r = -0.12 p=0.58) groups.

Finally, bearing in mind that ICI treated response in general has reportedly been associated with treatment response, (McQuade et al. 2018; Roccuzzo et al. 2023) the relationship

between BMI and PFS was examined. Although BMI was inversely correlated with PFS, the relationship was not significant (r = -0.17 p=0.25).

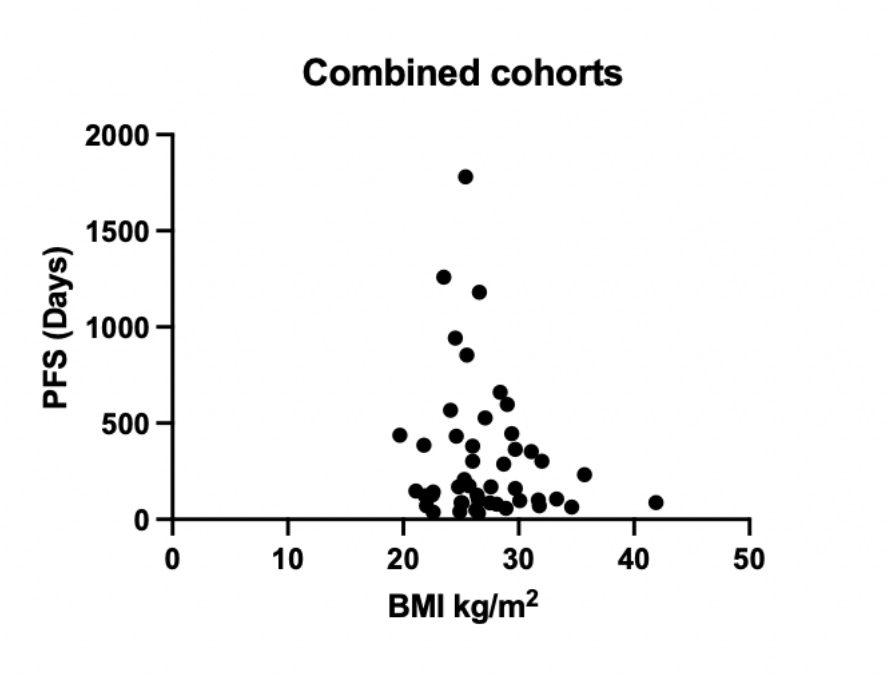

Figure 20: BMI and treatment response in both groups combined. There was no significant correlation between BMI and PFS in the cohort as a whole.

Aim number two

To examine whether the use of fixed-dose therapy (FDT)- or weight-adapted therapy (WAT) with ICI treatment influenced progression-free and overall survival rates.

Given the success of ICI in general, the impact of FDT and WAT on treatment outcomes in particular was ascertained. Progression-free survival was measured in days from the date of treatment initiation to the first evidence of radiological progress according to RECIST 1.1 criteria. Overall survival was measured in days from the date of treatment initiation until death or the last day of follow-up (31.12.2020) whichever came sooner. It should be borne in mind that OS was undoubtedly influenced by subsequent lines of treatment including surgery, ICI (anti-PD1 monotherapy or combined anti-PD1 and anti-CTLA4 treatment), BRAF/MEK inhibitor therapy or chemotherapy (dacarbazine) (Klee et al. 2022).

As anticipated from the literature (Robert, Long, et al. 2015b; Ribas et al. 2015; Elassaiss-Schaap et al. 2017; Ogungbenro et al. 2018) there was no significant effect of the dosing modality on PFS. The median PFS was 208 days in the FDT group compared to 174 days in the WAT group (Log-Rank Mantel-Cox Test, p = 0.595).

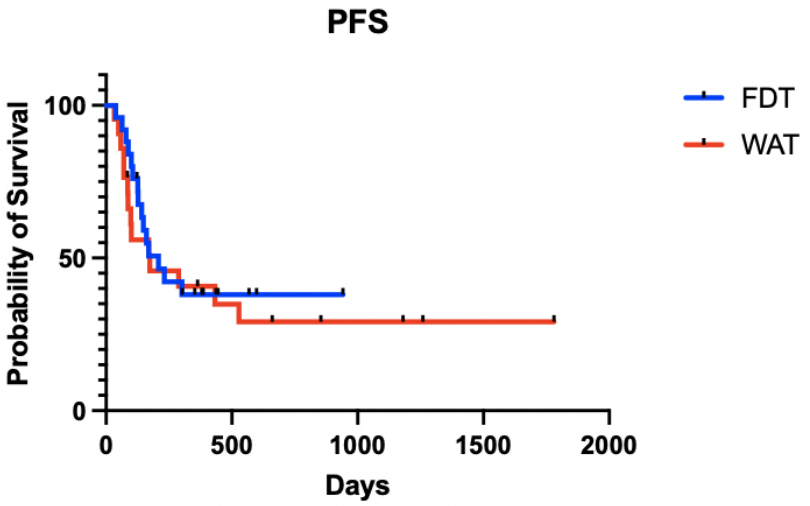

Figure 21: PFS and dosing modality. There was no significant effect of dosing modality on PFS.

Similarly, there was no significant difference rates of overall survival between the groups. The median OS was undefined in the FDT and 980 days in the WAT cohorts respectively (Log-Rank Mantel-Cox Test, p = 0.502).

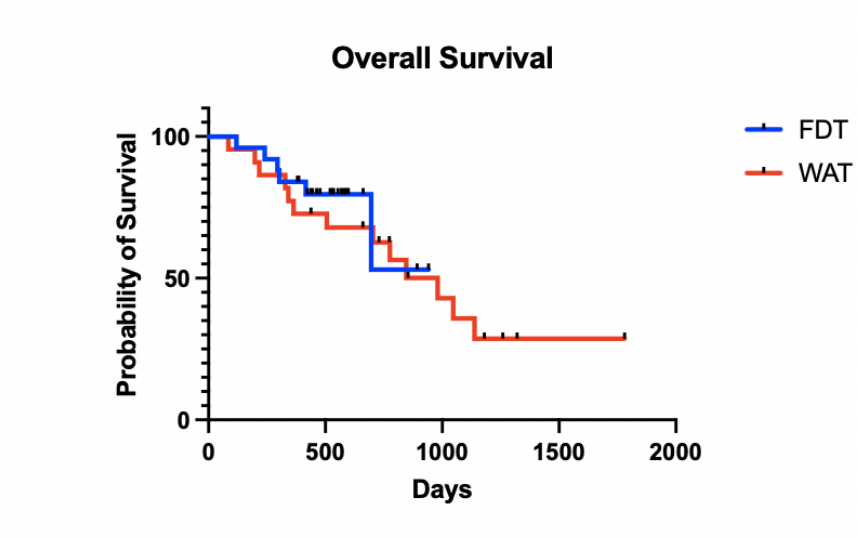

Figure 22: Overall survival and dosing modality. There was no significant effect of dosing modality on OS

Aim number three

To establish which factors may affect PFS in patients treated with FDT or WAT.

Although there were no significant differences between the cohorts in terms of PFS overall, the influence of factors associated which have been associated with response to ICI therapy in metastatic melanoma were investigated. These factors were separated into patient-, tumor- and treatment- specific factors. The patient specific factors were age (Nebhan et al. 2021; Wong et al. 2023), sex (Conforti et al. 2018; Jang et al. 2021), body-mass index (McQuade et al. 2018; Roccuzzo et al. 2023; Yeung et al. 2022), diabetes mellitus and cardiovascular disease (Yekeduz et al. 2022; Cortellini et al. 2023; Agostinetto, Ceppi, et al. 2021; Agostinetto, Eiger, et al. 2021). The melanoma tumor specific factors encompassed BRAF status and serum S100 concentrations (Wagner et al. 2018; Heppt et al. 2017; van Not et al. 2022; Murciano-Goroff et al. 2022; Vasudevan et al. 2023). Finally, bearing in the mind the positive impact of the development of irAEs on treatment response to ICI, the development of irAEs was examined as a treatment specific factor (Schadendorf et al. 2017; Blum, Rouhani, and Sullivan 2023; Hussaini et al. 2021; Fan et al. 2021).

The following patient-, tumor and treatment specific factors were documented form the electronic patient records.

	Fixed Dose Therapy (FDT)	Weight Adapted Therapy (WAT)
Total Number of Patients		
Number	25	22
Sex		
Male	17	15
Female	8	7
Age (years)		
<70	11	5
≥70	14	17
Mutation Status		
BRAF	8	2
NRAS	9	9
cKit	1	2
ECOG Status		
0	14	19
1	10	3
2	1	0
Melanoma Stage		
IIc	0	2
III	16	10
IV	9	10
S100 elevated		
Yes	3	5
No	22	17
Cardiovascular Disease		
Yes	10	10
No	15	12
Diabetes		
Yes	7	6
No	18	16
Body Mass Index		
<25	10	4
≥25	15	18

Table 9: Patient-, tumor- and treatment factors determined from the electronic case records

The median PFS in patients under 70 years was not met in the FDT group and 98 days in the WAT group. The equivalent figures were 155.5 and 288 days of patients with 70 years and over in the FDT and WAT groups respectively, with no significant differences between the groups. Similarly, there were no statistical differences in PFS between the groups according to sex or body mass index.

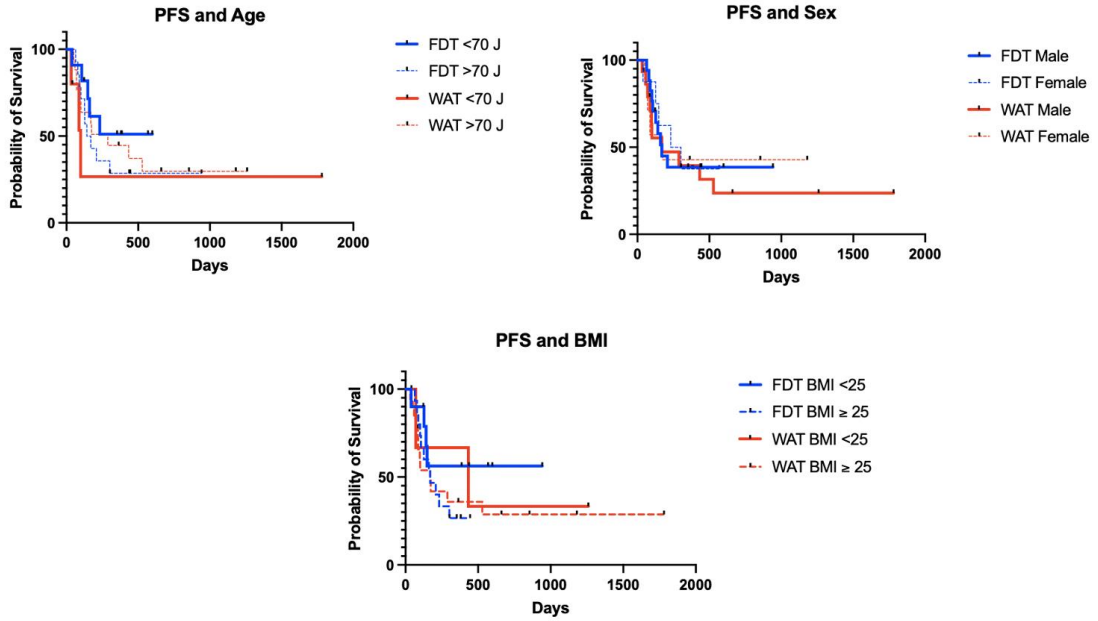

Figure 23: PFS and patient-specific factors. There were no significant differences between the groups.

In terms of co-morbidities, there was also no significant difference in PFS depending on the presence of diabetes or coronary heart disease.

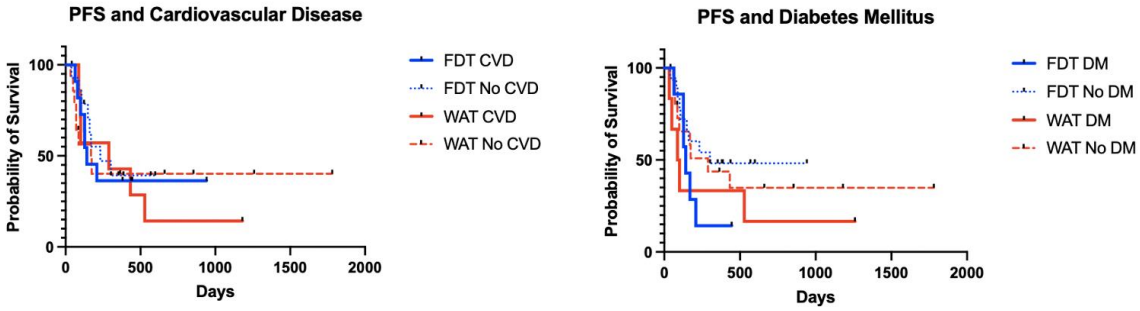

Figure 24: PFS and comorbidities. There were no significant differences in PFS according to patient-specific factors.

Furthermore, whilst the presence of a BRAF mutation did not affect PFS in either group, an elevated S100 was associated with a significantly worse PFS in the FDT group ($p<0.001$). Patients in the FDT cohort with an elevated S100 had a median PFS of 79 days compared to that of 232 days when the S100 levels were within normal limits. In the WAT cohort the median PFS was not significantly different with 86 days when S100 was elevated compared to 288 days when the S100 concentration was normal ($p=0.14$).

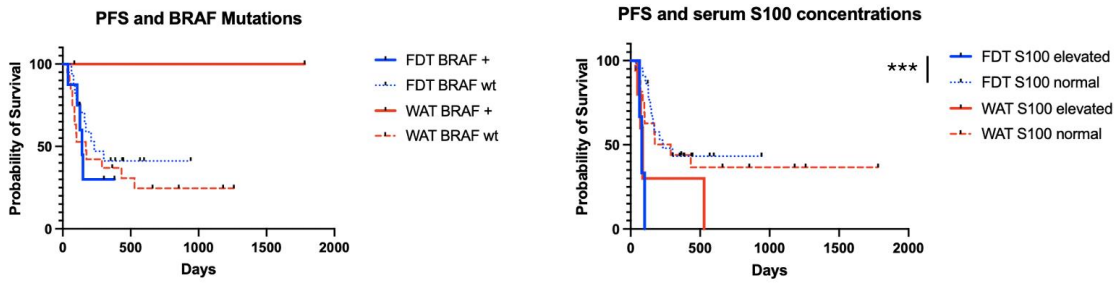

Figure 25: PFS and melanoma specific factors. An elevated S100 concentration was associated with a significantly decreased PFS in the FDT cohort ($p<0.001$).

Finally, the incidence of irAEs was determined between the groups in addition to their potential influence on PFS. The range of irAEs is shown below. Dermatological irAEs were the most common, neurological the least common.

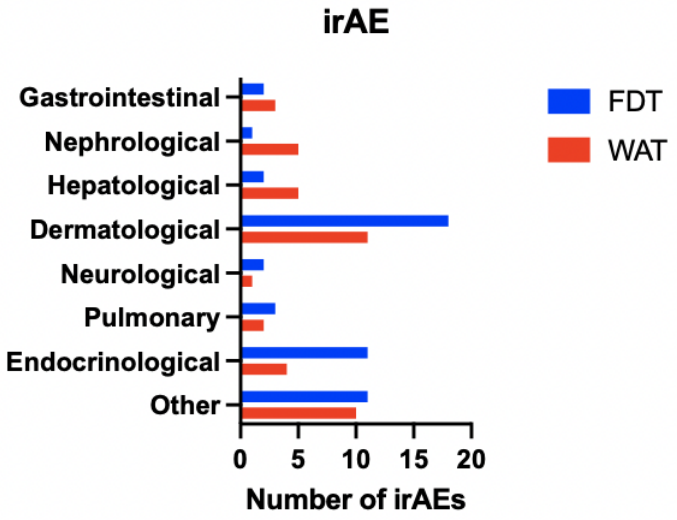

Figure 26: The range and incidence of irAEs in both groups

There was no difference in the overall number or incidence of irAEs between the cohorts.

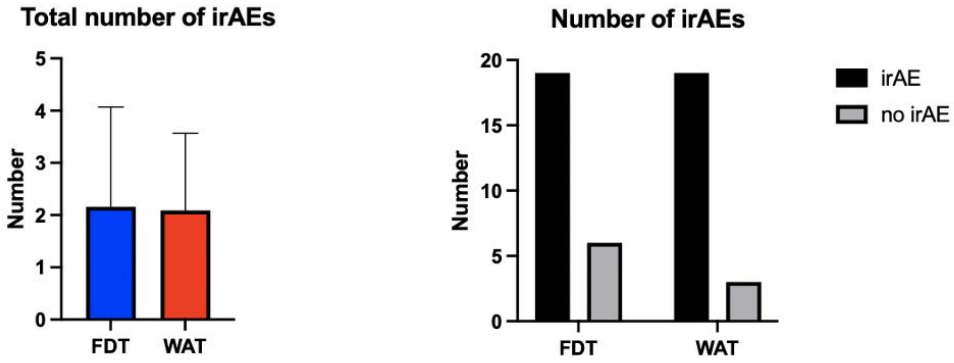

Figure 27: Number and incidence of irAEs

Consistent with this finding, there was no significant effect of the incidence or number of irAEs on PFS.

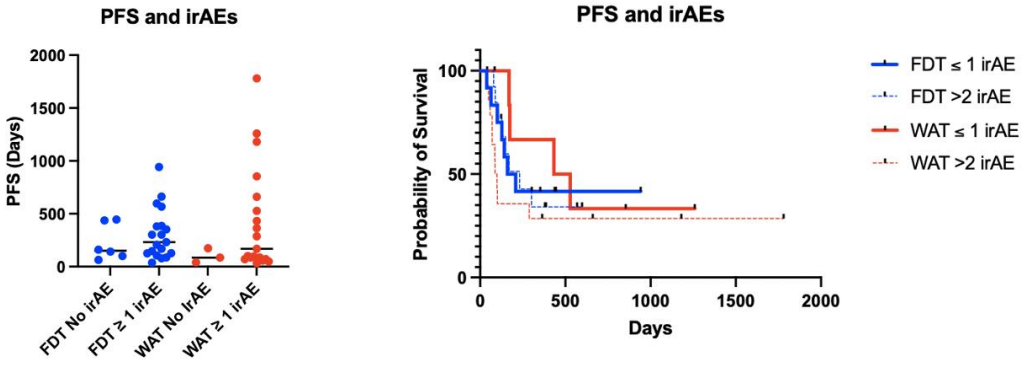

Figure 28: The effect of irAEs on PFS

Discussion

Although Ipilimumab was first licensed in the European Union over a decade ago, shortly followed by Pembrolizumab and Nivolumab in 2015, their use continues to dramatically improve the treatment landscape for patients with locally advanced and/or metastatic melanoma.(Skudalski et al. 2022) In fact, both anti-PD1 have now been licenced for use in patients from Stage IIB disease; patients whose primary tumor has a Breslow thickness of > 2 mm with ulceration (pT3b) following surgical resection in the *absence* of metastases (Luke et al. 2022; Kirkwood et al. 2023). In addition to commencing treatment in Stage II disease, anti-PD1 based immune checkpoint therapy is now well established in the adjuvant setting in Stage III (Nivolumab and Pembrolizumab) and Stage IV disease (Nivolumab).(Cohen and Tanabe 2023; Eggermont et al. 2021; Larkin et al. 2023; Weber et al. 2017; Carlino, Larkin, and Long 2021)

Notably, the combination of Ipilimumab and Nivolumab in patients with resected Stage IIIB-IIID or Stage IV melanoma in the Checkpoint 915 phase III clinical trial failed to improve PFS when compared to patients treated with Nivolumab monotherapy.(Weber et al. 2023) This is of particular relevance to this thesis given the use of complex dosing schedules. In the Checkpoint 915 clinical trial Nivolumab 240 mg once every 2 weeks was administered plus Ipilimumab 1 mg/kg once every 6 weeks. In contrast, Nivolumab 480 mg was administered once every 4 weeks in the control group. Therefore, not only were different FDT dosing schedules used in both groups, but Ipilimumab was administered in a WAT dosing regimen.

Ultimately the 2-year relapse free survival (RFS) in the adjuvant Nivolumab plus Ipilimumab was 64.6% compared to 63.2% in the Nivolumab monotherapy cohort and there was no difference even when programmed death-ligand 1 expression < 1%, with a 2-year RFS of 53.6% in the combined immunotherapy versus 52.4% in the Nivolumab monotherapy group.

The incidence of Grade 3-4 AEs was 32.6% versus 12.8% in the Nivolumab plus Ipilimumab versus Nivolumab monotherapy cohorts, respectively.

Whilst it has been speculated that the incidence of AEs may have led to early discontinuation in the combined immunotherapy cohort and subsequently reduced treatment efficacy, the rates of discontinuation in the cohorts were similar and therefore do not support this hypothesis.(Augustin and Luke 2023; Weber et al. 2023) Moreover, the incidence of irAE correlates with treatment response in terms of overall response rate (ORR), PFS and OS and grade 3 and above toxicities resulted in superior ORRs.(Schadendorf et al. 2017; Hussaini et al. 2021)

Another more likely explanation is the dosing schedules selected for the study may have impacted on RFS rates. Indeed, Augustin and Luke 2023 have proposed that the cumulative dose of Ipilimumab was insufficient, reflected in the relatively low levels of toxicity. The Checkmate 067 study established Ipilimumab 3 mg/kg and Nivolumab 1 mg/kg as the standard dose in the treatment of melanoma, although it was hoped that reducing the dose of Ipilimumab in the Checkpoint 915 trial would maintain efficacy and increase tolerability.(Larkin et al. 2015; Jameson-Lee and Luke 2021) which was not the case.

Based on pharmacokinetic data and established flat exposure-response relationships for efficacy and safety, Nivolumab fixed dosing, independent of body weight was introduced without the need for additional clinical trials.(Zhao et al. 2017; Long et al. 2018; Bei et al. 2020) Similar data for Pembrolizumab suggested that weight-dependent dosing offered no advantage over fixed dosing exposure.(Freshwater et al. 2017) Modelling and simulation data have also supported the equivalence of Pembrolizumab 400 mg every 6 weeks to 200 mg and 2 mg/kg every three weeks across various tumor types.(Lala et al. 2020)

However, on a cautionary note, Leven et al. 2019 reported that based on a careful review of pharmacokinetics and exposure-response relationships in the application of immune

checkpoint inhibitors, there was a correlation between overall survival of melanoma patients and anti-PD1 clearance. Namely, that drug clearance reduces as disease status improves and that this reduction correlates with an improvement in ECOG performance status. Furthermore, the magnitude of this reduction was increased in patients with increased survival.(Bajaj et al. 2017).

In fact, not only efficacy but also the incidence of irAEs may also be influenced by the dosing schedule. To the end, Kahler et al. 2020 reported a case series of patients with type I Diabetes following the introduction of the Pembrolizumab 400 mg on a 6-weekly schedule.). Indeed, 20% of the patients, predominantly in the adjuvant setting, developed Diabetes presenting with diabetic ketoacidosis. The median time to the development of symptoms was 4 infusions and the median time from last infusion to diagnosis was 26 days. To provide some context, the expected incidence of immune checkpoint mediated diabetes lies between 1-2 % (Akturk and Michels 2020).

It should be noted that clinical studies patients with autoimmune disease are frequently excluded (Weber et al. 2017; Robert, Long, et al. 2015a) and in clinical practice HbA1c and random serum glucose measurements are not routine.(Kahler et al. 2020) At present, the acute onset of polyuria, polydipsia, weight loss, and lethargy in the context of hyperglycemia should raise suspicion of diabetes, with urinary ketones, acid-base status, and electrolytes necessary to screen for diabetic ketoacidosis. Antibodies, insulin, and C-peptide levels should also be sent to support diagnosis and therapy initiated. In contrast to other irAEs, immunosuppression with corticosteroids is not recommended.(Schneider et al. 2021)

Therefore, in order to examine the efficacy and tolerability of FDT versus WAT dosing of immune checkpoint inhibitors, a retrospective analysis of the electronic records of all patients treated in our tertiary referral centre was performed. Whilst the majority of the patient were male (68%) there was no significant difference in sex between the FAT and WAT cohorts.

Furthermore, the cohorts were similar in terms of age, melanoma subtype and which anti-PD1 antibody was used (Nivolumab versus Pembrolizumab). There was however an increased percentage of patients treated in the palliative setting in the WAT (36%) group when compared to that in the FDT group (21%). The over-representation of patients treated in the palliative setting in the WAT group reflects the fact that Nivolumab and Pembrolizumab first became available in the adjuvant setting in 2018 and the change from WAT to FDT according to the products' SmPCs during the time of the study. However, there was no statistical difference in ECOG performance status at the outset of treatment between the groups (Fisher's exact test, p=0.17).

Given that renal function have been associated with changes in the pharmacokinetics of immune checkpoint therapy, in addition to treatment response, these parameters were compared between the groups.(Elassaiss-Schaap et al. 2017; Zhao et al. 2017; Long et al. 2018; Leven et al. 2019) Whilst there was no significant difference in serum creatinine between the cohorts, the estimated GFR according to Chronic Kidney Disease Epidemiology Collaboration equation was significantly lower in the WAT cohort. This likely reflects the increased proportion of patients treated in the palliative context in this group. Importantly, there was no correlation between the estimated GFR and PFS in either group.

Indeed, the safety and efficacy of immune checkpoint inhibitors in patients with end-stage renal failure and dialysis has not revealed any marked difference in the incidence of irAEs or treatment response (Hirsch et al. 2020; Kitchlu et al. 2021). Consistent with the literature there was no significant correlation between estimated GFR and PFS or OS in either cohort. This provides reassuring real-world data that chronic renal impairment does not impact upon the efficacy of anit-PD1-based immune checkpoint inhibition, regardless of whether the treatment is given in a weight dependent or fixed dose manner.

On the other hand, it should be borne in mind that the phase III clinical trials frequently exclude patients with renal impairment, as measured by a GFR < 40 or serum creatinine > 1.5 x the upper limit of normal.(Weber et al. 2023; Robert, Schachter, et al. 2015) As a result, there is a distinct lack of prospective data on the efficacy and adverse event profile of immune checkpoint inhibitors across the spectrum of renal impairment. Moreover, retrospective and registry analyses of treatment outcomes in patients with end-stage renal failure and/or those requiring dialysis have reported poorer outcomes in these patient groups.(Wang et al. 2022; Tiu et al. 2023) Whether these poorer outcomes are due to multiple co-morbidities, primary or secondary resistance to treatment, tumor progression or the effect of concomitant immunosuppression in the case of organ-transplant patients is unclear. Whilst our cohorts did not include patients with end-stage and/or dialysis-dependent renal impairment, it was reassuring to confirm that pre-treatment renal function did not affect PFS or OS of patients receiving immune checkpoint therapy in melanoma, irrespective of the method of administration or treatment schedule.

Turning to the conflicting evidence of an association between BMI and response to immune checkpoint inhibitor therapy, BMI was recorded prior to therapy. There was no significant difference between the FDT and WAT groups in terms of average BMI. BMI was not correlated with treatment response in terms of PFS in the cohort as a whole, nor when the FDT and WAT groups were analyzed separately. Moreover, BMI was not correlated with overall survival (data not shown).

The association between treatment response to immune checkpoint inhibitor therapy and body mass index remains controversial. Initial reports suggested that BMI correlated with an improved response to immune checkpoint therapy (McQuade et al. 2018) in males. This study was a retrospective multi-cohort analysis of over 2000 patients treated over a decade and included patients treated with immune checkpoint-, targeted- and chemotherapy. The association between obesity and improved PFS and OS was reported in men treated with

immune checkpoint- or targeted therapy for metastatic melanoma. Moreover, the association has been replicated in across a range of solid tumor entities, including non-small cell lung cancer and Merkel cell carcinoma, and in meta-analyses.(Nie, Chen, Wang, Yuan, et al. 2021; Kichenadasse et al. 2020; Incorvaia et al. 2023). The findings is also indirectly supported by the increased incidence of irAEs in patients with obesity, often a marked of treatment response.(Bastacky et al. 2021; McQuade et al. 2023; Cortellini et al. 2020) Ultimately these findings led to the term the “obesity paradox.”(Lee et al. 2023; Langan et al. 2018; Hahn et al. 2023). Whilst the underlying mechanisms are unclear, adipokines, including leptin, oxidative phosphorylation and a hypoxic tumor microenvironment and the gastrointestinal microbiome have all been postulated to play a role.(Najjar et al. 2019; Hahn et al. 2023; Vétizou et al. 2015; Langan et al. 2018)

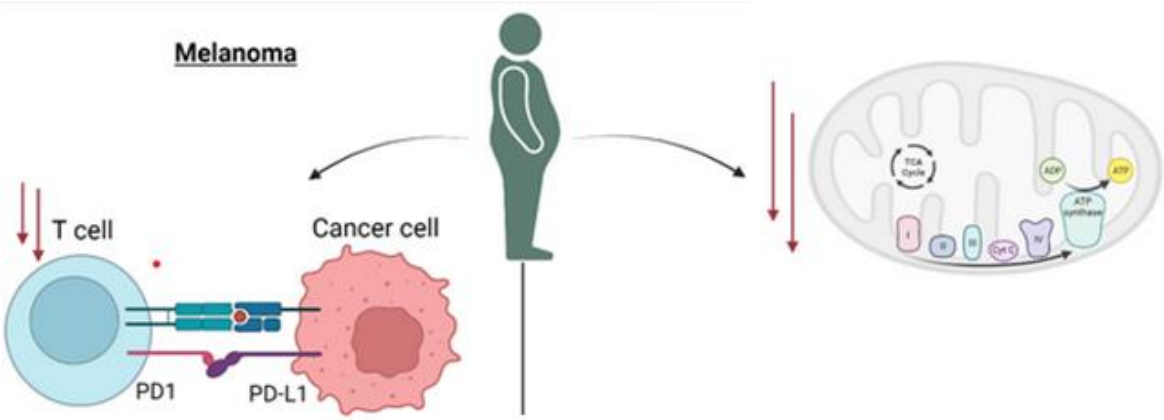

Figure 29: Possible mechanisms underlying the “obesity paradox” including leptin induced T-Cell dysfunction and decreased oxidative phosphorylation. (Hahn u. a. 2023b)

However, recent studies and meta-analyses have cast doubt over the association between obesity and treatment response to immune checkpoint inhibitors *per se*, and point to a more nuanced understanding of the relationship between body weight and treatment response mediated through systemic inflammation, sarcopenia, subcutaneous or visceral adipose tissue distribution and even whether the immune checkpoint treatment was administered in the first or subsequent lines of therapy.(Mengoni et al. 2023; Lee et al. 2022; Donnelly et al. 2019; Naik et al. 2019; Di Filippo et al. 2021) In addition, Antoun et al.(Antoun et al. 2023) recently reported

no association between obesity and immune checkpoint therapy response in melanoma and that the association in the context of non-small cell lung cancer disappeared when controlling for weight loss and sarcopenia.

Any association between immune checkpoint therapy response and obesity in melanoma patients remains to be proven, but in the meantime, this study did not provide any evidence that BMI impacted upon treatment response in either the FDT or WAT cohort.

Similarly, there was no evidence that the use of FDT or WAT influenced either PFS or OS. The median PFS measured 208 (FDT) versus 174 days (WAT) and median OS was not reached in the FDT and 980 days in WDT cohort (p=0.502). These data support the available pharmacokinetic data that led to the change from WAT to FDT for both Pembrolizumab and Nivolumab.(Freshwater et al. 2017; Elassaiss-Schaap et al. 2017; Zhao et al. 2017; Bei et al. 2020; Lala et al. 2020). Given that the WAT cohort had significantly worse renal function at the outset of treatment, coupled with a higher proportion of patients being treated in the palliative context, the lack of difference in PFS and OS between the cohorts is even more reassuring.

Although there was no difference in PFS and OS in general depending on that method of immune checkpoint inhibitor administration, the factors which have been reported to influence treatment response were analysed individually. These factors were clustered into patient-specific, melanoma-specific, and treatment-related irAEs.

There were no significant differences between PFS in the FDT and WAT cohorts in terms of body mass index, sex (male versus female), age (<70 years, ≥ 70 years). The relationship between sex and response to immune checkpoint inhibitor therapy is controversial.(Poletto et al. 2023) Given the sexual dimorphism in the immune system, it is readily conceivable that the effect of immune checkpoint inhibitor immunotherapy may be sex-dependent. Indeed, the initial meta-analyses seemed to support this hypothesis. For example, Conforti et al. 2018 analysed

data from over 11 000 patients treated with anti-PD1 and anti-CTLA4 immunotherapy for a range of cancer entities and concluded that the although treatment improved survival in both sexes, the magnitude of the improvement was sex-dependent and increased in males. In is worth pointing out that there were almost twice as many males as females in the analysis, probably reflecting recruitment into clinical trials. The data was also based on clinical trial data and not real-world clinical practice. Finally, as the authors pointed out, it is possible that other sex-dependent variables may have confounded the analysis.(Conforti et al. 2018) On the other hand, a national cohort study from the Dutch Melanoma Registry with almost 4000 patients reported a similar safety profile in irAEs between the sexes but a 10% survival advantage for females, especially those ≥ 60 years and with a BRAF mutation.(van der Kooij et al. 2021) To complicate the picture further, Wu et al. 2018 reported that the type of immune checkpoint inhibitor played a role with the overall survival of patients treated with CTLA-4 inhibitors was more influenced by sex that those treated with PD-1 inhibitors. Furthermore, although the OS and PFS survival curves were better for males than females, the differences were not statistically significant.

Despite the seemingly conflicting results, the literature to date does suggest that sex may play a role in the response to immune checkpoint inhibitor therapy, but that it is difficult to tease out the magnitude of the effect and control for potentially confounding variables. Indeed, given that the incidence of melanoma itself seems to consistently differ between the sexes (Olsen et al. 2020) and that men with melanoma had a worse prognosis that women prior to the widespread use of immune checkpoint inhibitors (El Sharouni et al. 2019) the role of sex in melanoma biology deserves renewed attention, but cannot yet be recommended as a reliable and robust predictor of response to treatment. Future studies should however address the extent to which sex may offer new insights into tumor biology which could be harnessed to potentially provide patient specific treatment.

Data on the effect of age on response to immune checkpoint immunotherapy provide little evidence of difference in terms of treatment efficacy. The most recent meta-analysis by Kim et

al. 2022 examined data from almost 18 000 patients and reported no significant differences in PFS and OS according to age across a range of solid tumors. However, there was a benefit in terms of PFS in younger patients with melanoma when compared to patients ≥ 65 years which the authors speculated may be due to declining immune function in older patients. These results were in line with another study which failed to identify age as an important predictor of response to immune checkpoint inhibitor.(Huang et al. 2020) Similarly, a meta-analysis from Nie, Chen, Wang, Zhou, et al. 2021 found that anti-PD1 and anti-PD-L1 therapy retained efficacy in the ≥ 75 year old population, but there was a significant difference in OS between the two groups.

An important limitation of the studies to date is the lack of consensus around what age is defined as elderly, the lack of data on potentially confounding co-morbidites, including immunosuppression, the under-representation of elderly patients in clinical trials and the lack of corroborating data including irAEs in these populations. Furthermore, with an aging population, the number of very elderly patients, defined as ≥ 80 years,(Rai et al. 2023) is likely to increase. To date, the data on efficacy and tolerability in this population is sparse. Until this data become available, caution must continue to be exercised when considering immune checkpoint therapy in the elderly population, especially when considering combined anti-CTLA4 and anti-PD1 treatment which results in Grade 3 to 4 adverse events in up to two-thirds of patients.(Larkin et al. 2019) The combination of an anti-PD1 and anti-lymphocyte activating gene (LAG3) inhibitor may represent a more tolerable alternative in the management of metastatic melanoma, (Tawbi et al. 2022; Albrecht et al. 2023) but the survival benefit of the combination does not seem to be superior to anti-PD1 monotherapy.(Long et al. 2023)

Turning to the influence of co-morbidities on treatment response, there was no effect of cardiovascular disease or diabetes with either the FDT or WAT cohort. There have been reports that type II diabetes, specifically those on anti-diabetic medication, have worse outcomes under immune checkpoint therapy.(Cortellini et al. 2023; Yekeduz et al. 2022) More

recently, poorer outcomes in patients with type II diabetes treated with combined anti-PD1 and anti-LAG3 checkpoint inhibitors have been reported, presumed due to decreased LAG3 tissue expression in patients with diabetes. (Mallardo et al. 2023) In contrast, a retrospective case-control study conducted at 4 university centres and evaluation over 12 000 patients, found no difference in treatment response, measured in overall survival, between patients with type I diabetes and controls. (Hilder et al. 2023)

Whilst an effect of pre-existing conditions including diabetes and cardiovascular disease on the efficacy of immune checkpoint immunotherapy in melanoma is certainly conceivable, its magnitude is currently unknown and there is no evidence of FDT or WAT on outcomes. The focus should remain close monitoring of patients with for the development of Diabetes and Myocarditis, which are permanent and potentially fatal.(Zhang et al. 2020; Kurzhals et al. 2021; Czarnecka et al. 2022)

There was a significant difference in PFS in the FDT cohort according to whether patients had an elevation or normal serum S100 concentration. This is in keeping with the prognostic value of S100 in metastatic melanoma and response to immune checkpoint inhibition treatment.(Chatziioannou et al. 2023; Simetic et al. 2020; Gebhardt, Lichtenberger, and Utikal 2016; Burgermeister et al. 2022) It should be borne in mind that S100 is a less reliable marker of disease recurrence in the adjuvant setting.(Kurzhals et al. 2022) In any case, there was no effect of FDT versus WAT on PFS according to serum S100 concentrations or BRAF status. Clinically, there has been a move towards up front immune checkpoint therapy in BRAF mutated patients based on results from the CheckMate 067 trial (Wolchok et al. 2022) which reported a median PFS of 16.8 and 11.2 months in BRAF-mutant and BRAF wild-type patients respectively. Furthermore, combined immune checkpoint immunotherapy (anti-PD1 and anti-CTLA4) resulted in superior overall response rate when administered up front as compared to use in the second line setting.(Ascierto et al. 2023; Atkins et al. 2023)

Turning towards the irAEs, dermatological and endocrinological irAEs were amongst the most frequent, as reported in the literature.(Byrne et al. 2021; Martins et al. 2019) There was no difference in the total number of irAEs between the FDT and WAT groups and the incidence of irAEs did not translate into significantly differences in PFS. In fact, the most recent meta-analysis and systematic review of irAEs in over 40 000 patients being treated for a range of tumor entities only confirmed mild correlations between the immune checkpoint therapy effects on irAE rates and OS.(Amoroso et al. 2023) Moreover, the effect of irAEs on OS may be strongest depending on both the affected organ system and tumor type, for example cutaneous irAEs in the treatment of melanoma with immune checkpoint inhibitors.(Zhang et al. 2023)

Whilst irAE seem to correlate with OS, depending on their number and severity, which organ system is affected, treatment- (anti-PD1 monotherapy versus combined anti-PD1 and anti-CTLA4 treatment) and tumor type, this study only examined PFS and was not large, nor long enough to determine any effects of irAE on OS. However, it is reassuring that neither FDT nor WDT, even in an adjuvant setting, resulted in significantly more irAEs.

Strengths of this thesis

The main strength of the study was the real-world nature of the data. There was no pre-selection of patients according to tumor burden, performance status or co-morbidities, affording extrapolation of the data to routine clinical practice. Another key advantage was the availability of the full range of clinical parameters, from standard laboratory tests to mutational status and corresponding treatment parameters, from treatment setting and number of treatment cycles to the nature and number of irAEs that were encountered. In contrast to meta-analyses and registry-based data, the full range of patient, disease and treatment specific factors were available for analysis. This allowed internal validation of the PFS data with the incidence of irAEs to provide robust and convincing data that FDT and WDT were not associated with significant differences efficacy as measured by PFS and OS, or tolerability, as measured by irAE. The effects of treatment were also assessed in the first-line setting. This data also sits well with other recent reports of the lack of effect of dosing schedules on patient outcomes (Bei et al. 2020; Leroy et al. 2024) and confirms the utility of monitoring serum S100 concentrations during immune checkpoint treatment.(Gebhardt, Lichtenberger, and Utikal 2016; Wagner et al. 2018; Chatziioannou et al. 2023)

Limitations of this thesis

Given the regulatory and SmPcs changes that occurred between 2018 and 2023 the study was unavoidably retrospective in nature. Moreover, there was an over-representation of male patients in both the FDT and WAT cohorts. It is also important to acknowledge that both patients treated in the palliative and adjuvant setting were analysed together. This limitation meant that both disease progression and recurrence were recorded together. However, there was no difference in age or performance status between the FDT and WAT cohorts allowing comparisons to be made. The number of patients was also a limitation in the study, although this was unavoidable due to its monocentric nature and the exclusion of treatment in the second line setting to avoid a potentially confounding variable. The move to almost exclusively

FDT in 2018 means that overall survival data between the groups must also be critically evaluated. Despite the limitations it is reassuring report that lack of differences in efficacy, supported by similar levels of irAEs, between the groups. This finding supports the pharmacokinetic and limited recently reported real-world data.(Leroy et al. 2024)

Conclusion

In the real-world setting, across both palliative and adjuvant treatment settings, there was no evidence of a difference between the overall response rates of patients with metastatic or locally advanced melanoma to immune checkpoint inhibitor therapy based on the dosing schedule. Patients in the FDT and WAT cohorts had a similar median PFS and experienced a similar profile and number of irAEs. Moreover, immune checkpoint inhibitors efficacy was not influenced by impaired renal function or body mass index. Finally, patient- and treatment specific factors did not affect treatment response in either group. As expected, increased serum S100 concentrations were associated with a poorer response to treatment as was seen in the FDT cohort. Although this difference was not observed in the WAT group, there was no difference overall between the groups in terms of PFS according to S100 concentrations. Given that FDT was introduced in 2018, the period of follow-up was not the same between the groups in terms of OS. However, there was no indication that OS differed over the time of the study. Prospective multi-centric trials are needed to confirm the findings reported here, specifically in patients with moderate and/or high-risk obesity (BMI ≥ 35) who are under-represented here. The use of FDT, especially in patients weighing over 80 kg, may result in significant health care savings, but these should be based on sound clinical evidence with not risk of impaired efficacy.(Leroy et al. 2024)

Summary

Changes in the dosing schedules of immune checkpoint inhibitors, specifically Nivolumab and Pembrolizumab in the treatment of metastatic melanoma, were introduced based largely on pharmacokinetic and analysis of pre-existing clinical study data, obviating the need for new clinical trials. Indeed, the clinical trials often recruit patients with a good performance status, normal renal function and without brain metastases.

Therefore, to evaluate the extent to which renal function and body mass index impact upon the efficacy of ICI treatment in patients with advanced melanoma and determine whether fixed-dose therapy (FDT)- or weight-adapted therapy (WAT) influenced progression-free and overall survival and the incidence of immune-related adverse events, the electronic case notes of all patients (n=77) in whom treatment with immunotherapy was initiated in the Department of Dermatology of the University clinic Schleswig-Holstein, Campus Lübeck, for locally advanced or metastatic melanoma between the 1st of January 2017 and the 31st of December 2020 were retrospectively analysed.

Although patients in the WAT group had a higher proportion of patients treated in the palliative setting and the renal function was significant worse, there was no correlation between renal function and BMI and PFS. Moreover, there was no difference between the groups in terms of PFS, OS and the number and nature of irAEs. An elevated serum S100 concentration was associated with a decreased mean PFS, but there was no overall difference between the WAT and FDT groups. Dermatological irAEs and endocrinopathies were amongst the most common irAEs. Consistent with the lack of dosing schedule (FDT versus WAT) in PFS, there was no difference in PFS according to irAEs between the cohorts.

This study, although inherently limited by its retrospective and monocentric nature, provides reassuring evidence that dosing schedule does not influence efficacy or the irAE profile of immune checkpoint inhibitor therapy in the management of locally advanced and/metastatic melanoma. Prospective, multicentric studies are required to corroborate these data, especially in patients with high-risk obesity to ensure cost savings do not compromise efficacy and patient safety.

German Summary

Einleitung:

Da die Inzidenz des malignen Melanoms weltweit in den letzten Jahren deutlich zunimmt, steigt gleichzeitig die Bedeutung neuer Behandlungsansätze wie zum Beispiel der Immuntherapie. Seit der Zulassung von Pembrolizumab im Jahr 2014 in den USA ist die Anzahl neuer Immuntherapeutika im palliativen sowie adjuvanten Setting deutlich gestiegen. Hierbei traten einige neue Aspekte und Veränderungen in den Vordergrund der Behandlung, zum Beispiel der Wechsel von Gewichtsadaptierter Immuntherapie auf die Therapie mit fester Dosierung Änderungen der Dosierungsschemata von Immun-Checkpoint-Inhibitoren, insbesondere von Nivolumab und Pembrolizumab zur Behandlung des metastasierten malignen Melanoms, wurden weitgehend auf der Grundlage der Pharmakokinetik und der Analyse bereits vorhandener klinischer Studiendaten eingeführt, so dass keine neuen klinischen Studien erforderlich waren. In die klinischen Studien werden häufig Patienten mit gutem ECOG-Status, normaler Nierenfunktion und ohne Hirnmetastasen aufgenommen.

Ziele:

Aus diesem Grund sollte untersucht werden, inwieweit sich die Nierenfunktion und der Body-Mass-Index auf die Wirksamkeit der ICI-Behandlung bei Patienten mit fortgeschrittenem Melanom auswirken, und es sollte festgestellt werden, ob die Fixdosis-Therapie(FDT) oder die gewichtsadaptierte Therapie (WAT), das progressionsfreie(PFS) und das Gesamtüberleben(OS) sowie das Auftreten immunbedingter Nebenwirkungen (irAE) beeinflusst. Die elektronischen Akten der Patienten (n=77), bei denen in der Hautklinik des Universitätsklinikums Schleswig-Holstein, Campus Lübeck, zwischen dem 1. Januar 2017 und dem 31. Dezember 2020 eine Behandlung mit Immuntherapie bei lokal fortgeschrittenem oder metastasiertem malignem Melanom begonnen wurde, wurden retrospektiv ausgewertet.

Hierbei lag das Hauptaugenmerk auf folgenden Punkten:

1. Es sollte ermittelt werden, inwieweit die Nierenfunktion und der Body-Mass-Index die Wirksamkeit der Immuntherapie bei Patienten mit fortgeschrittenem Melanom beeinflussen.
2. Es sollte weiterhin geprüft werden, ob die Verwendung einer gewichtsunabhängigen Dosierung oder einer gewichtsadaptierten Dosierung der Immuntherapie die progressionsfreie und die Gesamtüberlebenszeit beeinflusst.
3. Ebenfalls sollte festgestellt werden, welche Faktoren die progressionsfreie sowie die Gesamtüberlebenszeit bei Patienten, die mit gewichtsunabhängigen oder einer gewichtsabhängigen Dosisbehandelt werden, beeinflussen können. Hierzu zählten unter anderem die Nierenfunktion, der BMI, die S100-Konzentration im Serum, sowie die Immuntherapie bedingten Nebenwirkungen.

Ergebnisse

Obwohl in der Gewichtsabhängigen Dosierungsgruppe ein höherer Anteil der Patienten im palliativen Setting behandelt wurde und die Nierenfunktion deutlich schlechter war, gab es keine Korrelation zwischen Nierenfunktion und BMI sowie Progressionsfreier Überlebenszeit. Darüber hinaus gab es keinen Unterschied zwischen den Gruppen in Bezug auf PFS, OS und die Anzahl und Art der irAE. Eine erhöhte S100-Konzentration im Serum war mit einem verringerten mittleren PFS verbunden, aber insgesamt gab es keinen Unterschied zwischen der WAT- und der FDT-Gruppe. Dermatologisch assoziierte irAEs und Endokrinopathien gehörten zu den häufigsten irAE. In Übereinstimmung mit dem fehlenden Einfluss des Dosierungsschemas (FDT versus WAT) auf das PFS gab es keinen Unterschied zwischen den Kohorten in Bezug auf irAE.

Diskussion

Obwohl diese Studie aufgrund ihres retrospektiven und monozentrischen Charakters naturgemäß begrenzt in ihrer Aussagekraft ist, liefert sie starke Hinweise darauf, dass das Dosierungsschema keinen Einfluss auf die Wirksamkeit oder das irAE-Profil der Immun-Checkpoint-Inhibitor-Therapie bei der Behandlung des lokal fortgeschrittenen und/oder

metastasierten Melanoms hat. Um eine genauere Einschätzung der Therapieeffektivität zu ermöglichen, sind prospektive, multizentrische Studien erforderlich. Dies könnte helfen die untersuchten Daten und Thesen zu untermauern, insbesondere bei Patienten mit höhergradiger Adipositas, um sicherzustellen, dass Kosteneinsparungen nicht die Wirksamkeit und die Sicherheit der Patienten beeinträchtigen.

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List of Figures

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Presentations and Publications arising from this thesis

Eine "reale" retrospektive Analyse der Wirksamkeit und unerwünschten Ereignissen bei der gewichtsabhängigen versus fest dosierte Immuncheckpoint-Therapie bei metastasiertem malignem Melanom

Ständer HF, Langan EA

ePoster and Presentation

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Attachments

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verkürztes Verfahren / Anzeige

Titel: A retrospective analysis of the factors influencing the efficacy and side effect profile of fixed versus body weight-dependent immune checkpoint inhibition in the treatment of advanced skin cancer.
Ihre E-Mail vom 29. September 2020

Sehr geehrter Herr Dr. Langan,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission über Ihr geplantes Vorhaben.
Es werden ausschließlich anonymisierte Daten verarbeitet.

Folgende Unterlagen lagen vor:

- Ihre E-Mail vom 29. September 2020
- Studienprotokoll vom 18. September 2020

Die Ethik-Kommission nimmt das von Ihnen in Ihrem Anschreiben beschriebene Vorhaben zur Kenntnis.
Eine Behandlung im normalen Antragsverfahren wird nicht für notwendig erachtet.

Mit freundlichen Grüßen

Prof. Dr. med. Alexander Katalinic
Vorsitzender

Curriculum Vitae