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ANALYSIS OF CLINICAL PROGNOSTIC FACTORS OF PD-1 IMMUNE CHECKPOINT INHIBITOR TREATMENT IN MALIGNANT MELANOMA AND CUTANEOUS SQUAMOUS CELL CARCINOMA

PhD thesis

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LIST OF ABBREVIATIONS

AE:	Adverse event
AEs:	Adverse events
AJCC:	American Joint Committee on Cancer
ALM:	Acral lentiginous melanoma
AM:	Advanced melanoma
ASCO:	American Society of Clinical Oncology
BRAF:	A human gene that encodes a protein called B-Raf
CI:	Confidence interval
CLL:	Chronic lymphoid leukemia
CR:	Complete Remission
cSCC:	Cutaneous Squamous Cell Carcinoma
CT:	Computed Tomography
CTCAE:	Common Terminology Criteria for Adverse Events
CTLA-4:	Cytotoxic T lymphocyte-associated antigen-4
DCR:	Disease Control Rate
DM:	Diabetes mellitus
DeM:	Desmoplastic melanoma
ECOG:	Eastern Cooperative Oncology Group
ECOG PS:	Eastern Cooperative Oncology Group Performance Status
EMA:	European Medicines Agency
ESMO:	European Society for Medical Oncology
FDA:	Food and Drug Administration
GFR:	Glomerular filtration rate
HR:	Hazard Ratio
HT:	Hypertonia
ICI:	Immune checkpoint inhibitor
ICIs:	Immune checkpoint inhibitors
ImAE:	Immune-mediated adverse event
ImAEs:	Immune-mediated adverse events
IrAE:	Immune-related adverse event
IrAEs:	Immune-related adverse events

IHD:	Ischemic heart disease
IO:	Immunotherapy
iRECIST:	immune Response Evaluation Criteria in Solid Tumors
KTRs:	Kidney Transplant Recipients
LDH:	Lactate dehydrogenase
LMM:	Lentigo Maligna Melanoma
MRI:	Magnetic Resonance Imaging
mTOR:	Mammalian target of rapamycin
NE:	No evaluable
NM:	Nodular melanoma
OS:	Overall Survival
ORR:	Objective Response Rate
PD:	Progressive disease
PD-1:	Programmed cell death protein-1
PD-L1:	Programmed cell death-ligand-1
PFS:	Progression free survival
PR:	Partial remission
ptx:	Unknown T stage of primary melanoma
PTX:	Pneumothorax
RECIST:	Response Evaluation Criteria in Solid Tumors
RR:	Response Rate
RT:	Radiotherapy
RwPSF:	Real-world progression free survival
RwOS:	Real-world objective survival
SCC:	Squamous Cell Carcinoma
SD:	Stabile disease
SLN:	Sentinel Lymph Node
SLNB:	sentinel lymph node biopsy
SOT:	Solid organ transplant
SSM:	Superficial spreading melanoma
TCR:	T-cell receptor
TIL:	Tumor-infiltrating lymphocytes

TLR:	T-lymphocyte receptor
TNM:	TNM Classification of malignant tumors
TT:	Targeted Therapy
VS:	Versus
WBRT:	Whole brain radiotherapy

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1. INTRODUCTION

In the recent years, immune checkpoint inhibitors (ICIs) have made a major impact on the treatment of different cancers. ICIs act by anti-tumoral immune system activation. Among ICIs, programmed cell death protein-1 (PD-1) inhibitors are the clinically most important group. (Abaza et al., 2023; Chalmers et al., 2017) Advanced melanoma (AM) was one of the first malignancies, where PD-1 inhibitors were introduced, as this disease did not have any effective treatment options. (Lazaroff & Bolotin, 2023) Also, melanomas harbor a large mutational load, therefore different tumor-specific antigens can trigger the host immune response. Still, melanomas can effectively avoid immunosurveillance by different immune-inhibitory pathways, such as immune checkpoint molecules. Checkpoint pathways have a key role in the maintenance of immune homeostasis by the inhibition of autoimmune responses. (Willsmore et al., 2021)

Expressed on the surface of various cells, including tumor cells, Programmed cell death-ligand-1 (PD-L1) is a major regulator of the immune system, by activating the PD-1 receptor on T-cells. The PD-1 inhibitors are monoclonal antibodies that block the interaction of PD-L1 and PD-1, therefore they induce T-cell mediated anti-tumoral immunity. (Abaza et al., 2023; Willsmore et al., 2021) Based on various clinical trials, PD-1/PD-L1 inhibitors have proven to be efficient in the therapy in different advanced or metastatic malignant conditions, such as melanoma, cutaneous squamous cell carcinoma (cSCC), non-small cell lung, hepatocellular, gastric, colorectal, and breast cancers. (Abaza et al., 2023)

Ipilimumab, an anti-cytotoxic T lymphocyte-associated antigen (CTLA)-4 antibody was the first immune-checkpoint inhibitor, which was approved both by the FDA and EMA in 2011 for the therapy of stage IV melanoma. (Garbe et al., 2022; Schadendorf et al., 2015) The response rate to ipilimumab is only about 15%, but a smaller portion of AM patients previously treated with different drugs could achieve notable long-term remissions. (Garbe et al., 2022; Hodi et al., 2018; Hodi et al., 2010; Schadendorf et al., 2015) As PD-1 antibodies have emerged, the role of ipilimumab has shifted: currently it is not administered as a first-line therapy any longer. Today, ipilimumab is given in combination with PD-1 antibodies first-line or as a second-line therapy. (Garbe et al., 2022)

Nivolumab and pembrolizumab are anti-PD-1 antibodies for the treatment of unresectable melanoma with both FDA and EMA approval. A fully human IgG4 anti-PD-1 antibody, nivolumab improved progression free survival (PFS) and overall survival (OS) in comparison with dacarbazine (CheckMate-066 trial) and ipilimumab (CheckMate-067 trial). (Wolchok et al., 2022) A humanized IgG4 anti-PD-1 antibody, pembrolizumab improved PFS and OS compared to ipilimumab (KEYNOTE-006 trial). (Larkin et al., 2015; Robert et al., 2019; Wolchok et al., 2022)

PD1-ICI were approved as first-line therapy in 2015 reaching 26–40% response rates in AM patients. Compared to chemotherapy, PD1-ICI achieved higher survival rates. (Larkin et al., 2015; Robert et al., 2019) Further studies have revealed that PD-1 ICI can provide a more tolerable safety profile and importantly, higher efficacy. (Arheden et al., 2019; Aroldi & Middleton, 2022; Bastacky et al., 2021; Weber et al., 2017) While with the administration of ICIs a long-term response can be achieved, AEs are usually manageable with the use of systemic corticosteroids or other immunomodulators, treatment cessation and supportive care. (Arheden et al., 2019; Bastacky et al., 2021; Weber et al., 2017)

Furthermore, PD-1 ICI were recently also approved as a novel adjuvant treatment option for stage III melanoma. It was shown, that PD-1 ICI, compared to placebo treatment and also ipilimumab significantly decrease the hazard ratios of the recurrence of melanoma. (Garbe et al., 2022)

The approval of immunotherapeutic agents is given based on phase III clinical studies. These studies establish strict inclusion and exclusion criteria. Therefore, patients with autoimmune diseases, patients with active brain metastases and those with ECOG (Eastern Cooperative Oncology Group) status of ≥2 could not be included. On the contrary, most of AM patients in the clinical practice do not meet these inclusion and exclusion criteria. Furthermore, median OS was found to be significantly different in eligible patients in comparison with those patients that were not eligible (18.3 vs. 5.43 months). (Hodi et al., 2018; Hodi et al., 2010) Therefore, the published efficacy and safety data of phase III clinical trials may not correlate well with real-world clinical scenarios. Based on the results of registry studies, since the introduction of ICI, the survival of AM patients has significantly increased. (Arheden et al., 2019; Aroldi & Middleton, 2022)

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In the past decade, not only the treatment of AM had changed substantially, but the treatment of the second most common skin cancer, advanced cSCC has also shown significant developments.

The majority of primary cSCCs have an indolent behavior. Prognosis is usually very good with 5-years cure rates more than 90% and dissemination occurs in only 5% of the patients. (Brougham, Dennett, Cameron, & Tan, 2012; Stratigos et al., 2020) The gold standard treatment of cSCC is still surgery with or without radiotherapy. Advanced cSCC comprise the locally advanced (la-cSCC) and metastatic cutaneous squamous cell carcinoma (m-cSCC), that cannot be treated successfully by curative surgery or radiotherapy. (Lebas, Marchal, Rorive, & Nikkels, 2021; Stratigos et al., 2020)

Advanced cSCC has a poor prognosis with standard systemic therapy such as platinum based cytotoxic chemotherapy or epidermal growth factor receptor (EGFR) inhibitors. While in certain cases cSSC might respond to these treatments, but mostly the response is not long-term. (Migden et al., 2020; Migden et al., 2018)

The introduction of cemiplimab, an ICI drug has resulted in a major improvement in the therapy of la-cSCC. It is a recombinant IgG4 human mono-clonal anti-PD-1 inhibitor antibody that was approved for the treatment of advanced cSCC by the FDA in 2018 and the EMA in 2019 after successful phase II clinical trials. (Brougham et al., 2012; Guillaume, Puzenat, Popescu, Aubin, & Nardin, 2021; Lebas et al., 2021; Migden et al., 2020; Migden et al., 2018; Stratigos et al., 2020; Valentin et al., 2021)

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2. OBJECTIVES

Real-world evidence is the clinically most relevant measure of the efficacy and safety of new therapies. Most of the published data is based on clinical trials, where patients were enrolled based on strict inclusion and exclusion criteria which often have different characteristics than those patients treated in the everyday clinical practice. In both of our present studies, we investigated real-world patients, to assess clinically relevant survival data in this patient population.

In our first study, we retrospectively analyzed treatment outcomes from AM patients treated with an anti-PD1 agent (nivolumab or pembrolizumab) during a 77 month-long observation period. In the second study, we evaluated patients with la-cSCC or m-cSCC, under PD-1 inhibitor cemiplimab therapy. We aimed to identify predictive markers based on treatment efficacy and adverse events (AE) characteristics.

2.1. The primary endpoints of both studies included the OS, PFS, the objective response rate (ORR) and disease control rate (DCR).

2.2 The secondary endpoints were the assessment of safety data. The administration of ICI in AM and advanced cSSC patients results in substantially improved clinical outcomes. However, these drugs are associated with immune-related adverse events (irAEs). Here we aimed to evaluate the occurrence of side effects and the possible correlation of their severity and frequency with the survival of the patients.

2.3. In both studies, we aimed to find potential novel biomarkers that may be capable of the prediction of response to ICIs.

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3. METHODS

In this work, two retrospective descriptive analyses were carried out. The first study focused on unresectable stage III (M0) or stage IV melanoma (M1a–d) patients under PD-1 inhibitor treatment with pembrolizumab or nivolumab. The topic of the second study was the PD-1 inhibitor cemiplimab therapy of locally advanced or/and metastatic cSCC patients. Both of the investigations were performed at the Department of Dermatology, Venereology and Dermatooncology, Faculty of Medicine, Semmelweis University, Budapest, Hungary. Our electronic medical records software (MedSolution, T-Systems Hungary, Budapest, Hungary) was utilized for the collection of clinical data.

3.1. Study I.: AM treated with a single PD-1 inhibitor agent nivolumab or pembrolizumab

3.1.1. Clinical data

This retrospective analysis investigated patient records between 1 May 2015 and 31 October 2021 retrieved from the e-MedSolution system. The inclusion criteria comprised patients with metastatic or inoperable cutaneous AM who have received at least two cycles of standard dose PD-1 inhibitor treatment as monotherapy during the study period. We excluded individuals with primary mucosal melanoma or primary uveal melanoma and patients with incomplete medical records. The data cut-off date was 30 June 2021 with a minimum follow-up period of four months.

At our outpatient dermato-oncology clinic, the investigated patients were treated with either intravenous nivolumab or pembrolizumab. Nivolumab was given either at a dosage of 3 mg/kg every 2 weeks or a flat dose of 240 mg every 2-4 weeks. Pembrolizumab was administered at a dose of 2 mg/kg every 3 weeks or a fixed flat dose of 200 mg every 3 weeks or alternatively, 400 mg every 6 weeks.

We selected nivolumab or pembrolizumab based on their availability and the Hungarian AM treatment guideline, which has been revised during the investigated period. Nivolumab or pembrolizumab treatment was administered until unacceptable toxicity, disease progression, death or stoppage of the drug by the treating dermato-oncologist for other reasons. The study included patients who had received prior

treatment with BRAF/MEK inhibitors, whole brain radiotherapy (WBRT) or superficial radiotherapy.

We collected data on patient demographics, primary melanoma subtype, stage at initial presentation, BRAF mutation status and lactate dehydrogenase (LDH) level and baseline characteristics prior the initiation of nivolumab or pembrolizumab therapy.

We analyzed the treatment duration, treatment efficacy based on clinical evaluation and imaging data, including magnetic resonance imaging (MRI) and computed tomography (CT) and the reason behind the cessation of the treatment.

The severity and type of treatment-emergent AEs were investigated according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 classification.

3.1.2. Statistical Analysis:

Real-world OS (rwOS) was established based on the start date of anti-PD1 therapy and the date of the last follow-up or the demise of the patient. Real-world progression-free survival (rwPFS) was determined from the start of the treatment until the date of disease progression or death or until the last follow-up if there was no progression. Descriptive analyses were performed using Mann-Whitney U test or Fisher's exact test, as applicable. Estimations of the rates of RwOS and rwPFS were made utilizing the Kaplan-Meier method. The log-rank test was used to compare differences between survival curves for each risk factor. Parameters that were significant in univariate evaluation were selected for multivariate Cox proportional hazard regression analysis. The confidence interval was set to 95% and a p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed the version 25.0 of the IBM SPSS Statistics for Windows software (IBM Corp, Armonk, New York, USA).

3.2. Study II: Locally advanced or metastatic cSSC treated with PD-1 inhibitor cemiplimab

Data was collected regarding the time period between the 1st of February 2020 and the 31st of January 2023. Patients with locally advanced cSCC and/or metastatic cSCC treated with intravenous cemiplimab during the study period, for at least two cycles of standard cemiplimab dose (350 mg every 3 weeks) were included. We did not exclude

solid organ transplant recipients or immunocompromised patients with poor performance status. In addition, we did not set any upper age limit for inclusion.

3.2.1. Data collection

We collected retrospective data from the e-MedSolution system including patient demographics, disease stage at first presentation, laboratory results and baseline characteristics prior to the start of cemiplimab treatment. The data cut-off date was set to 31 January 2023. The minimum follow-up period was three months. Staging was performed according to the 8th edition of the TNM classification for invasive cSCC by the UICC and AJCC (2017). (12) The patients' performance status was assessed using the Eastern Cooperative Oncology Group (ECOG). (13)

We retrieved data regarding the OS, PFS, ORR, DCR and treatment-related AE. To classify the treatment outcomes, we used the terms partial response (PR), complete response (CR), progressive disease (PD), and stable disease (SD). The physician treating the patients categorized the response based on the immune-related Response Evaluation Criteria in Solid Tumors (iRECIST) criteria. The treatment-related AE were characterized using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Cemiplimab treatment was given until disease progression, demise of the patient, unacceptable toxicity, or if the treating dermato-oncologist decided to discontinue the drug for different reasons.

3.2.2. Statistical analysis

We determined the real-world OS (rwOS) using the date of initiation of cemiplimab therapy and date of the demise of the patient or the date of last follow-up. Real-world progression-free survival (rwPFS) was calculated from the initiation of the treatment and the date of disease progression or demise of the patient or in patients without progression, the date of the last follow-up. We analyzed the tumor responses (CR, PR, SD, PD), as well as the ORR and DCR. RwOS and rwPFS times estimations were performed by the Kaplan–Meier survival analysis method, while log-rank test was used to compare differences between subgroups. Fisherʹs exact test or Mann–Whitney U test was applied for descriptive analysis. $P < 0.05$ was considered statistically significant with the

confidence interval set to 95%. All statistical analyses were performed using the version 25.0 of the IBM SPSS Statistics for Windows software.

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4. RESULTS

4.1. Study I.: AM treated with a single PD-1 inhibitor agent nivolumab or pembrolizumab

4.1.1. Patient characteristics

We identified 126 patients that were treated with PD-1 ICI monotherapy at our department. A total of seven patients were excluded from the analysis, as three patients were diagnosed with ocular melanoma and four patients had mucosal melanoma. Therefore, we were able to include a total of 119 patients who had been treated with the PD-1 ICI nivolumab or pembrolizumab between 1 May 2015 and 31 October 2021. Demographic and clinical characteristics of the patients at baseline are detailed in **Table 1.**

The mean follow-up duration from the initiation of treatment was 45.1 weeks (range 17.3-112.1), with a median of 14 doses of pembrolizumab or nivolumab (range 7-32). The median age of the patients was 69 years, and 68 (57.1%) patients were male. 117 patients (98.28%) had an ECOG PS of 0 or 1, with only two patients having a PS of ≥ 2. At the beginning of the anti-PD1 therapy, 9 patients (7.56%) had an elevated LDH level. 52 patients (43.7%) were administered nivolumab treatment, while 66 (55.5%) received pembrolizumab. One patient developed a severe adverse skin reaction (grade 3) after initiating nivolumab treatment therefore this patient was switched to pembrolizumab. 81 patients (68.1%)received PD1 ICI as first-line treatment, while 38 (31.9%) received it as second- or third-line therapy. At treatment initiation, M1c status was identified in 56 cases (47.04%).

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Table 1. Demographic and clinical characteristics of the investigated patients with advanced melanoma under nivolumab or pembrolizumab monotherapy (Kuzmanovszki et al., 2022)

	Median (IQR) or N (%)			
	Total sample* (N=119)	**Non-responders* (N=98)**	**Responders* (N=20)**	**p-value****
Age (years)	69.0 (57.0-75.0)	68.5 (57.0-75.0)	68.5 (53.5-79.25)	0.622
≥ 70 years	62 (52.1)	52 (83.9)	10 (16.1)	0.811
< 70 years	57 (47.9)	46 (80.7)	10 (17.5)	
Gender				
male	68 (57.1)	54 (79.4)	13 (19.1)	0.466
female	51 (42.9)	44 (86.3)	7 (13.7)	
Total number of doses	14.0 (7.0-32.0)	12.0 (6.0-26.0)	24.0 (17.5-44.5)	0.002
Treatment duration (weeks)	45.1 (17.3-112.1)	37.6 (16.1-92.3)	118.0 (56.0-192.4)	<0.001
Primary tumor characteristics				
occult	21 (17.6)	16 (76.2)	5 (23.8)	0.670
superficial spreading melanoma (SSM)	23 (19.3)	21 (91.3)	2 (8.7)	
nodular melanoma (NM)	33 (27.7)	28 (84.8)	5 (15.2)	

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Median (IQR) or N (%)

	Total sample* (N=119)	**Non-responders* (N=98)**	**Responders* (N=20)**	**p-value****
acral lentiginous (ALM)	15 (12.6)	13 (86.7)	2 (13.3)	
lentigo maligna melanoma (LMM)	2 (1.7)	2 (100.0)	-	
desmoplastic melanoma (DeM)	2 (1.7)	2 (100.0)	-	
not classified	23 (19.3)	16 (69.6)	6 (26.1)	
T				
ptx or no primary tumor	35 (29.4)	25 (71.4)	10 (28.6)	
pT1a	3 (2.5)	3 (100.0)	-	
pT2a	6 (5.0)	6 (100.0)	-	
pT2b	5 (4.2)	5 (100.0)	-	0.082
pT3a	9 (7.6)	8 (88.9)	1 (11.1)	
pT3b	16 (13.4)	16 (100.0)	-	
pT4a	9 (7.6)	9 (100.0)	-	
pT4b	36 (30.3)	26 (72.2)	9 (25.0)	
TIL				
brisk	15 (12.6)	12 (80.0)	3 (20.0)	0.316

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Median (IQR) or N (%)

	Total sample* (N=119)	**Non-responders* (N=98)**	**Responders* (N=20)**	**p-value****
non-brisk	12 (10.1)	7 (58.3)	4 (33.3)	
absent	18 (15.1)	16 (88.9)	2 (11.1)	
unknown	74 (62.2)	63 (85.1)	11 (14.9)	
N				
no	57 (47.9)	51 (89.5)	6 (30.0)	0.158
yes	58 (48.7)	44 (75.9)	13 (65.0)	
unknown	4 (3.4)	3 (75.0)	1 (5.0)	
M AJCC 8th edition				
M0	1 (0.8)	1 (100.0)	-	
M1a	22 (18.5)	19 (86.4)	3 (13.6)	0.136
M1b	15 (12.6)	13 (86.7)	2 (13.3)	
M1c	56 (47.04)	41 (73.2)	14 (25.0)	
M1d	25 (21.0)	24 (96.0)	1 (4.0)	
Disease stage				
III	1 (0.8)	1 (100.0)	-	1.000

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	Median (IQR) or N (%)			
	Total sample* (N=119)	**Non-responders* (N=98)**	**Responders* (N=20)**	**p-value****
IV	118 (99.2)	97 (82.2)	20 (16.9)	
Treatment NE=1				
nivolumab	52 (43.7)	45 (86.5)	6 (11.5)	0.220
pembrolizumab	66 (55.5)	52 (78.8)	14 (21.2)	
Line of treatment				
first	81 (68.1)	66 (81.5)	14 (17.3)	1.000
second + third	38 (31.9)	32 (84.2)	6 (15.8)	
Reason for treatment cessation				
did not stop	36 (30.3)	24 (66.7)	11 (30.6)	
AE	13 (10.9)	9 (69.2)	4 (30.8)	
PD	49 (41.2)	48 (98.0)	1 (2.0)	<0.001
Exit	19 (16.0)	17 (89.5)	2 (10.5)	
CR	2 (1.7)	-	2 (100.0)	
IrAE				
no	64 (53.8)	56 (87.5)	7 (10.9)	0.058

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Median (IQR) or N (%)

	Total sample* (N=119)	**Non-responders* (N=98)**	**Responders* (N=20)**	**p-value****
IrAE = 1	24 (20.2)	16 (66.7)	8 (33.3)	
IrAE > 1	31 (26.1)	26 (83.9)	5 (16.1)	
irAE toxicity				
no IrAE	66 (55.5)	58 (87.9)	7 (10.6)	
G1-2	37 (31.1)	28 (75.7)	9 (15.4)	0.126
G3-4	16 (13.4)	12 (75.0)	4 (25.0)	
Brain metastases				
no	94 (79.0)	74 (78.7)	19 (20.2)	0.070
yes	25 (21.0)	24 (96.0)	1 (4.0)	
Lactate dehydrogenase (LDH)				
normal LDH	110 (92.4)	90 (81.8)	19 (17.3)	0.706
elevated LDH	9 (7.6)	8 (88.9)	1 (11.1)	
BRAF				
wild type	88 (73.9)	70 (79.5)	17 (19.3)	0.272

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Median (IQR) or N (%)

	Total sample* (N=119)	**Non-responders* (N=98)**	**Responders* (N=20)**	**p-value****
positive	31 (26.1)	28 (90.3)	3 (9.7)	
	Total sample (N=31)	**Non-responders (N=28)**	**Responders (N=3)**	
BRAF mutation genotype				
V600E	22 (71.0)	20 (90.9)	2 (9.1)	
V600K	8 (25.8)	7 (87.5)	1 (12.5)	1.000
V600 others	1 (3.2)	1 (100.0)	-	

CR— complete response, PR—partial response, SD —stable disease, PD—progressive disease, LDH—Lactate dehydrogenase, AJCC — American Joint Committee on Cancer

***** We categorized patients as "Non-responders" (stable disease and progressive disease) and "Responders" (partial and complete responses) based on their response to treatment. One responder was excluded since the therapy response was NE (no evaluable). ** Mann-Whitney U test or Fisher's exact test. A p-value<0.05 was considered statistically significant.

Regarding the histological characteristics of the primary melanoma, 36 patients (30.3%) had pT4b melanoma, 35 patients (29.4%) had pTx (where the Breslow thickness of the primary melanoma could not be determined) or occult melanoma. 33 cases (27.7%) were identified as NM subtype, 23 (19.3%) were SSM, and certain cases could not be

classified. Based on tumor-infiltrating lymphocytes (TIL) within the primary melanoma, we found that 15 (12.6%) were brisk and 74 (62.2%) were unknown. 98 patients (82.32%) were diagnosed with primary cutaneous melanoma, while 21 (17.65%) had occult primary melanoma.

88 patients (73,9%) had BRAF wild-type melanoma, while 31 patients (26.1%) were shown to harbor BRAF V600 mutation. Seven patients (5.88%) with BRAF-positive melanoma received nivolumab or pembrolizumab as first-line therapy (**Table 3**). Among patients with BRAF V600 mutation, 24 (20.16%) received previous BRAF-MEK inhibitor treatment. 25 patients (21%) had brain metastases at the time of treatment initiation (**Table 2**).

irAEs developed in 55 out of 119 patients (46.3%). Among these patients, 31 (26.1%) had more than one irAE (refer to **Table 6**). In 49 patients (41.2%) treatment was discontinued due to disease progression, while it was stopped due to unacceptable toxicity in 13 patients (10.9%) and CR in two patients (1.7%) (**Table 1**). During the study period, 19 patients (16%) passed away, two of them as a result of complications of COVID-19 infection.

Table 2. Treatment of brain metastases in our AM patients under treatment with nivoliumab or pembrolizumab (Kuzmanovszki et al., 2022)

	Total sample (N=25)	**Non-responders (SD+PD) (N=24)**	**Responders (CR+PR) (N=1)**	
Brain metastases – Treatment				
stereotaxy	13 (52.0)	12 (50.0)	1 (100.0)	
WBRT	7 (28.0)	7 (29.2)	-	
both	3 (12.0)	3 (12.5)	-	0.916
no treatment	1 (4.0)	1 (4.2)	-	
operation	1 (4.0)	1 (4.2)	-	

CR— complete response, PR—partial response, SD —stable disease, PD—progressive disease, WBRT —whole brain radiation therapy
* We categorized patients as “Non-responders” (stable disease and progressive disease) and “Responders” (partial and complete responses) based on their response to treatment. One responder was excluded since the therapy response was NE (no evaluable). ** Mann-Whitney U test or Fisher’s exact test. A p-value<0.05 was considered statistically significant.

4.1.2. Efficacy - Survival data

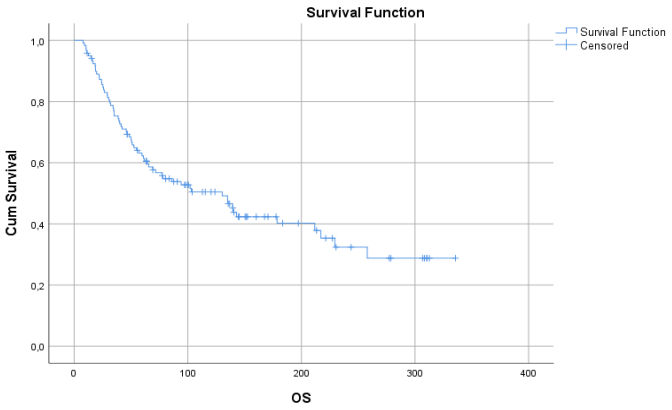
ORR, defined as the rate of patients with CR and PR, was found to be 16.8%. The DCR, defined as patients with CR, PR and stable disease, was 52.08% (**Table 3**). The ORR for treatment-naïve patients and patients treated with PD1 ICI as not first-line was very similar, at 17.2% and 15.78%, respectively. ORR for patients with BRAF wild-type was 19.31%, while for those with BRAF mutation it was 9.67%. Only seven out of 31 patients with BRAF V600 mutation were administered anti-PD1 ICI as first-line therapy. Among the patients with BRAF mutation, CR was observed in two cases and PR in only one case.

We analysed the demographic and clinical features of patients who achieved an objective response (responders, n = 20) and those who did not (non-responders, defined as patients who achieved SD or PD as best response, n = 98). Data on one case was not available (NA) (**Table 1**). In addition, we have examined the association of survival outcomes with of these parameters (**Table 4**).

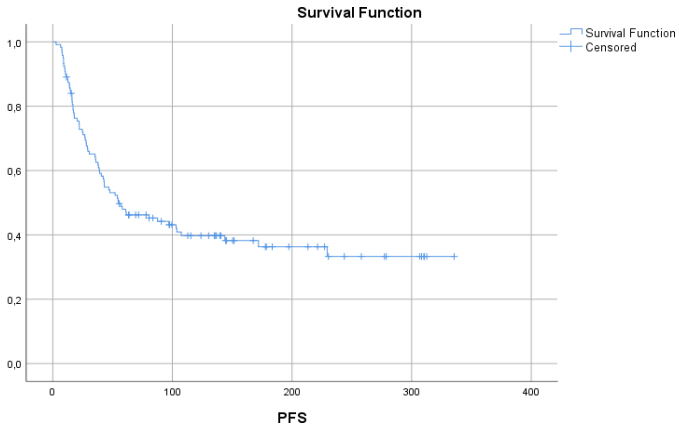
The median OS for the whole population was found to be 130 weeks (**Figure 1.a**), while the PSF was 54 weeks (**Figure 1.b**). In patients younger than 70 years of age, median OS was 135 weeks, while for older patients median OS was 86 weeks, and the mPFS was almost same in the two groups (54.5 weeks, p = 0.982) (**Table 4**). Shorter median OS and PFS were identified in patients with BRAF-mutant melanoma compared to those with BRAF wild-type melanoma, median OS was 71 weeks vs 130 weeks (HR for death for patients with BRAF mutation was 1.96, 95% CI 1.02–3.77 p = 0.004 **Table 5**) median PS was 35 weeks vs 58 weeks (HR for progression 2.68, 95% CI 1.26-5.72 p = 0.011) (**Figure 1.c,d**).

DOI:10.14753/SE.2025.3128

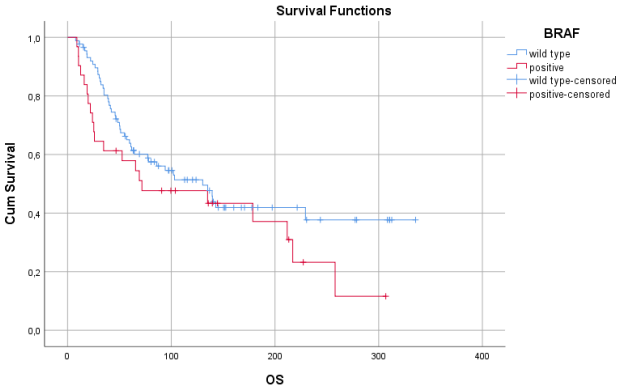
A)



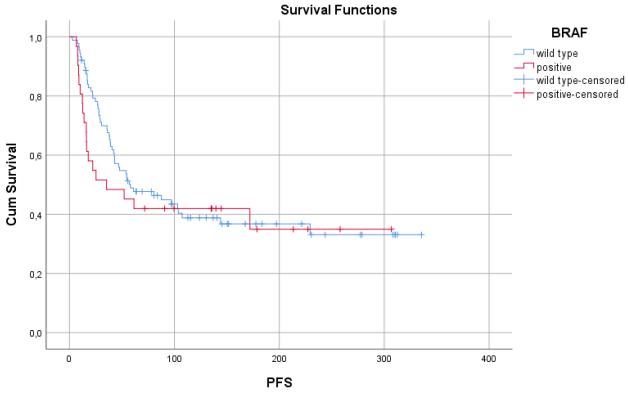
B)



C)



D)



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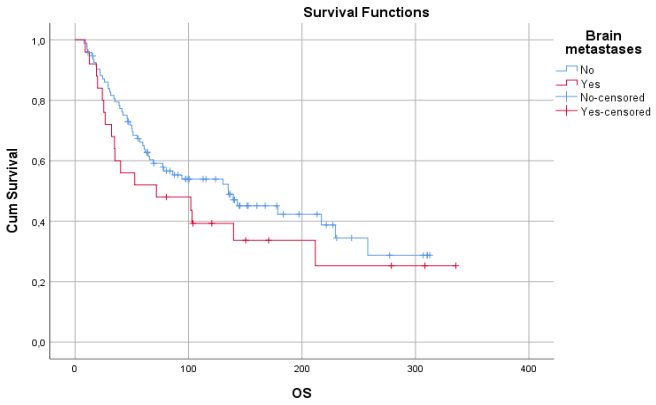
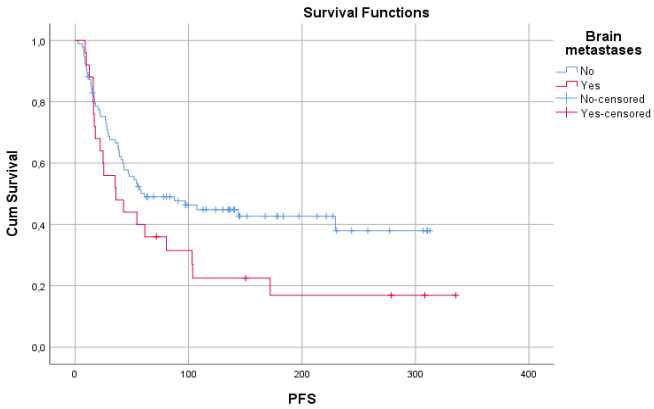
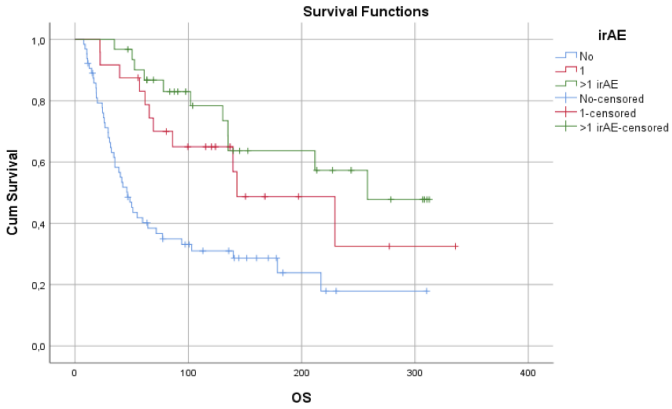
E)



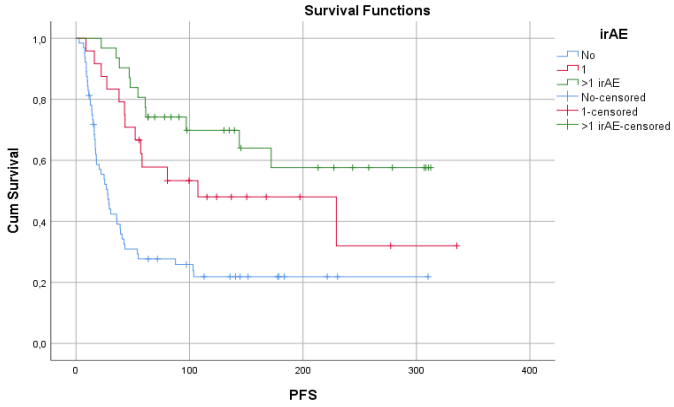
F)



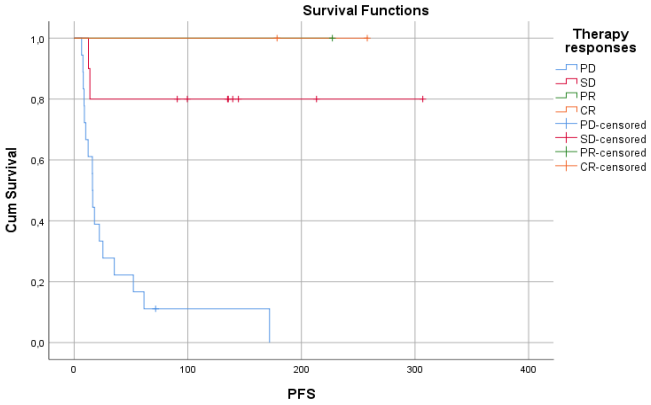
G)



H)



I)



J)

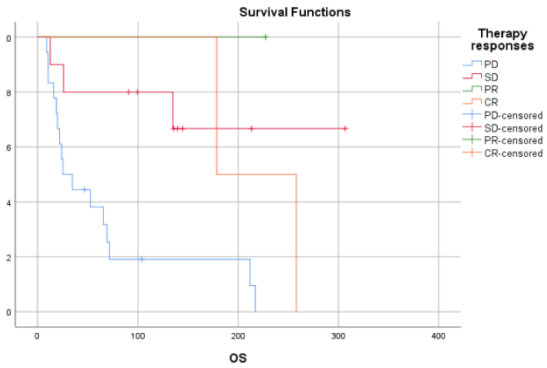


Figure 1. Kaplan-Meier survival estimates (**A**) OS in whole population (**B**) PFS for whole population (**C**) OS according to BRAF status, HR for death for patients with BRAF mutation was 1.96 (95% CI 1.02–3.77 $p = 0.004$) (**D**) PFS according to BRAF status, HR for progression for patients with BRAF mutation was 2.68 (95% CI 1.26-5.72 $p = 0.011$) (**E**) OS according to presence of brain metastases, HR for death 0.84 (95% CI 0.09–7.73 $p = 0.880$), (**F**) PFS according to presence of brain metastases, HR for progression 1.62 (95% CI 0.18-14.25 $p = 0.666$), (**G**) OS according to irAE, HR for death 0.3 (95% CI 0.14–0.64 $p = 0.02$), (**H**) PFS according to irAE, HR for progression 0.26 (95% CI 0.13-0.54 $p = 0.000$), (**I**) OS according to response of therapy, HR for death 0.14 (95% CI 0.05–0.43 $p = 0.001$), (**J**) PFS according to response of therapy, HR for progression 2.06 (95% CI 0.24-17.84 $p = 0.511$),
OS—overall survival, PFS—progression free survival, HR—hazard ratio, NR not reached, CR complete response, PR—partial response, SD—stable disease, PD—progressive disease.

Table 3. Response rates to nivolumab or pembrolizumab in the investigated patients with advanced melanoma (Kuzmanovszki et al., 2022)

	All patients			**BRAF positive**			**BRAF wild type**		
Responses	**Total N=119**	**First line of treatment N=81**	**≥2nd line of treatment N=38**	**Total N=31**	**First line of treatment N=7**	**≥2nd line of treatment N=24**	**Total N=88**	**First line of treatment N=74**	**≥2nd line of treatment N=14**
CR	8 (6.72%)	3 (3.7%)	5 (13.15%)	2 (6.45%)	0	2 (8.33%)	6 (6.81%)	3 (4.05%)	3 (21.42%)
PR	12 (10.08%)	11 (13.5%)	1 (2.63%)	1 (3.22%)	0	1 (4.16%)	11 (12.5%)	11 (14.86%)	0
SD	42 (35.28%)	28 (34.56%)	14 (36.84%)	10 (32.2%)	1 (14.28%)	9 (37.5%)	32 (36.36%)	27 (36.48%)	5 (35.71%)
PD	56 (47.04%)	38 (46.9%)	18 (47.36%)	18 (58.06%)	6 (85.71%)	12 (50%)	38 (43.18%)	32 (43.24%)	6 (42.85%)

NE	1 (0.84%)	1 (1,23 %)	0	0	0	0	1 (1.13. %)	1 (1.35 %)	0
DCR*	52.08%	51.76 %	52.62 %	41.87 %	14.28 %	49.99 %	55.67 %	55.39 %	35.71 %
ORR ***	**16.8%**	**17.2%**	**15.78 %**	**9.67 %**	**14.28 %**	**12.49 %**	**19.31 %**	**18.91 %**	**21.42 %**

*CR = complete responses; DCR = disease control rate; NA =Not Available; PD = Progressive diseases; ORR = Objective response rate; PR = partial responses; SD = stable diseases * DCR = CR + PR + SD ** ORR = CR + PR.*

We observed that BRAF-mutant melanoma patients with previous BRAF inhibitor (with or without a MEK inhibitor) treatment, who did not receive PD1 ICI as first line therapy had longer survival compared to patients with a BRAF mutation who did not receive BRAF inhibitor therapy. The median progression-free survival (mPFS) was 61 weeks compared to 12 weeks (p = 0.022) (**Table 4**). Patients without brain metastases had a longer OS and PFS compared to patients with brain metastases (median OS 135 weeks vs 71 weeks; hazard ratio [HR] for death for patients with brain metastases was 0.84, 95% confidence interval [CI] 0.09–7.73, p =0.880, median PFS 61 weeks vs 36 weeks; HR for progression 1.62, 95% CI 0.18 14.25, p = 0.666) as shown in **Figure 1 (e,f)**, **Table 4-5**.

Patients who experienced more than one irAE had a longer OS and PFS compared to those who did not have irAE. The median OS was 258 weeks for patients with >1 irAE and 46 weeks for those without irAE (HR for death 0.21, 95% CI 0.10-0.44, p < 0.001). The median PFS was not reached for patients with >1 irAE and HR was 0.17 (95% CI 0.08-0.35, p < 0.001) for those without irAE (**Figure 1.g,h, Table 4-5**). The presence of Grade 3-4 ir-AE was associated with a better outcome (HR for death 0.14, 95% CI 0.02-1.03 p < 0.053), the HR for progression of 0.11 (95% CI 0.01-0.89, p =0.038) (**Table 5**). Patients who received simultaneous treatment with radiotherapy and ICI monotherapy had a significantly prolonged OS (p < 0.010) (**Table 4**).

Table 4. Survival analysis of advanced melanoma treated with PD-1 inhibitor monotherapy [23]

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		N	Median OS (weeks)	LCI	UCI	p-values (log-rank)	Median PFS (weeks)	LCI	UCI	p-values (log-rank)
All patients (median)		**119**	**130.29**	81.02	179.57	-	**54.86**	19.75	89.97	-
Age (years)	<70	62	**135.14**	81.05	189.23	0.324	**54.57**	1.75	107.40	0.982
	≥70	57	**86.00**	8.31	163.69		**54.86**	17.97	91.75	
Gender	male	68	**139.43**	58.53	220.33	0.304	**97.14**	14.38	179.90	0.139
	female	51	**77.29**	36.17	118.42		**46.86**	27.59	66.13	
T	ptx or occult primary tumor	35	**229.430**	86.48	372.38	**0.020**	**143.86**	0.00	293.85	**0.003**
	pT1a	3	**86.00**	22.68	149.33		**43.14**	36.29	49.99	
	pT2a	6	**24.00**	16.80	31.20		**13.86**	7.34	20.38	

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		N	Median OS (weeks)	LCI	UCI	p-values (log-rank)	Median PFS (weeks)	LCI	UCI	p-values (log-rank)
	pT2b	5	**142.86**	-	-		**30.57**	0.00	69.82	
	pT3a	9	**-**	-	-		**54.00**	48.57	59.44	
	pT3b	16	**48.43**	0.00	145.11		**35.71**	19.76	51.66	
	pT4a	9	**-**	-	-		**80.43**	0.00	190.64	
TIL	unknown	74	**86.00**	42.27	129.73	0.381	**42.71**	26.02	59.40	0.285
	brisk	15	**229.43**	9.08	449.78		**229.43**	0.00	502.56	
	non-brisk	12	**142.86**	15.73	269.99		**80.43**	-	-	
	absent	18	**-**	-	-		**97.14**	-	-	
N	no	57	**139.43**	36.68	242.18	0.289	**87.57**	33.31	141.83	0.179
	yes	58	**103.14**	22.90	183.38		**43.00**	22.75	63.26	

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		N	Median OS (weeks)	LCI	UCI	p-values (log-rank)	Median PFS (weeks)	LCI	UCI	p-values (log-rank)
	unknown	4	**32.14**	27.24	37.04		**17.29**	5.11	29.47	
MAJCC 8th edition	M0	1	**61.71**	-	-	0.109	**27.14**	-	-	0.085
	M1a	22	**57.00**	16.54	97.47		**37.86**	21.45	54.27	
	M1b	15	**-**	-	-		**-**	-	-	
	M1c	56	**178.57**	86.87	270.27		**107.43**	0.00	228.49	
	M1d	25	**52.57**	0.00	134.24		**35.29**	13.53	57.05	
Line of treatment	first	81	**94.14**	33.01	155.27	0.596	**46.86**	30.03	63.69	0.175
	second + third	38	**178.57**	20.51	336.63		**172.00**	0.00	382.17	
Treatment NA=1	nivolumab	52	**86.00**	19.	152.68	0.358	**43.14**	23.74	62.54	0.606

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		N	Median OS (weeks)	LCI	UCI	p-values (log-rank)	Median PFS (weeks)	LCI	UCI	p-values (log-rank)
				33						
	pembrolizumab	66	**139.71**	67.66	211.76		**61.43**	4.67	118.19	
irAE	no	64	**46.43**	34.53	58.33		**27.86**	19.92	35.80	
	irAE=1	24	**142.86**	52.49	233.23	**<0.001**	**107.43**	0.00	245.26	**<0.001**
	>1irAE	31	**258.00**	-	-		**-**	-	-	
BRAF	wild-type	88	**130.29**	80.80	179.78	0.161	**58.14**	19.19	97.09	0.462
	positive	31	**71.71**	0.00	172.50		**35.29**	0.00	82.81	
Brain metastases	no	94	**135.14**	57.31	212.97	0.259	**61.00**	4.44	117.56	0.063

		N	Median OS (weeks)	LCI	UCI	p-values (log-rank)	Median PFS (weeks)	LCI	UCI	p-values (log-rank)
	yes	25	**71.71**	0.00	169.70		**36.00**	7.57	64.43	
Response of the treatments	PD+SD	98	**71.71**	40.01	103.42	**<0.001**	**42.14**	31.64	52.64	**<0.001**
	CR+PR	20	-	-	-		-	-	-	
Received radiation therapy	no	86	**86.00**	21.93	150.07	**0.010**	**43.14**	22.36	63.92	0.326
	yes	33	-	-	-		**80.43**	25.14	135.72	
BRAF-wild type (n=88)										
Line of treatment	first	74	**103.14**	41.07	165.21	0.392	**57.00**	19.62	94.38	0.218
	second + third	14	**229.43**	43.62	415.25		**229.43**	-	-	
BRAF V600 mutation (n=31)										

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		N	Median OS (weeks)	LCI	UCI	p-values (log-rank)	Median PFS (weeks)	LCI	UCI	p-values (log-rank)
Line of treatment	first	7	**69.14**	0.00	159.09	0.312	**12.29**	6.77	17.81	**0.022**
	second + third	24	**71.71**	0.00	222.94		**61.43**	0.00	225.52	

CR— complete response, PR—partial response, SD —stable disease, PD—progressive disease, LDH—Lactate dehydrogenase, NA—Not Available, AJCC — American Joint Committee on Cancer; LCI = lower bound of the 95% confidence interval; PD+SD = progressive disease and stable disease; PR+CR = partial responders and complete responders; UCI = upper bound of the 95% confidence interval A p-value<0.05 was considered statistically significant.

Table 5. Cox regression analysis of the patients - anti-PD-1 monotherapy in advanced melanoma (Kuzmanovszki et al., 2022)

	Survival		**Progression-free survival**	
	HR for death (OS) (95% CI)	**p-value**	**HR for progression-free (PFS) (95% CI)**	**p-value**
Age group / 70 years+	1.66 (0.96-2.88)	0.072	1.12 (0.67-1.86)	0.675
Gender / female	1.16 (0.69-1.96)	0.570	1.23 (0.74-2.02)	0.423

Line of treatment / advanced setting	1.04 (0.53-2.06)	0.906	0.50 (0.24-1.03)	0.060
IrAE		0.000		0.000
IrAE = 1	0.31 (0.14-0.65)	**0.002**	0.31 (0.15-0.62)	**0.001**
IrAE > 1	0.21 (0.10-0.44)	**0.000**	0.17 (0.08-0.35)	**0.000**
M		0.119		0.501
M / M1a	0.38 (0.04-3.27)	0.375	0.34 (0.04-2.91)	0.325
M / M1b	0.10 (0.01-1.08)	0.058	0.16 (0.02-1.63)	0.123
M / M1c	0.26 (0.03-2.26)	0.221	0.27 (0.03-2.33)	0.232
M / M1d	0.41 (0.02-8.94)	0.567	0.21 (0.01-4.35)	0.312
BRAF / positive	1.96 (1.02-3.77)	**0.044**	2.68 (1.26-5.72)	**0.011**
Brain metastases / yes	0.84 (0.09-7.73)	0.880	1.62 (0.18-14.25)	0.666
Therapy responses / CR+PR	0.14 (0.05-0.43)	**0.001**	0.09 (0.03-0.30)	**0.000**
Grade of irAE		0.154		0.105
Grade of irAE / G1-G2	0.26 (0.05-1.40)	0.116	0.32 (0.06-1.72)	0.184
Grade of irAE / G3-G4	0.14 (0.02-1.03)	0.053	0.11 (0.01-0.89)	**0.038**
Received radiation therapy / yes	0.48 (0.24-0.98)	**0,043**	0.85 (0.47-1.51)	0,573

CI = confidence interval; HR = Hazard ratio; CR+PR = complete remission and partial response; p-value<0.05 was considered statistically significant

4.1.3. Toxicity

55 patients (46.2%) experienced immune mediated AE (irAE). Mild irAE (grade 1-2) developed in 37 patients (31.08%), while severe irAE (grade 3-4) were observed in 18 patients (15.12%) (**Table 6**). No treatment-related deaths occurred. Hepato-pancreato-biliary irAEs were observed in 26.15%, while endocrine and gastrointestinal system iaAEs were observed in 23.52% and 19.32%, respectively. Among grade 3-4 IrAEs, colitis (9.24%) and pneumonitis (6.72%) were the most common. 42 patients (35.28%) required immunomodulatory treatment for irAEs, such as systemic steroids and infliximab in two cases. In 13 patients (10.92%) PD1 ICI was discontinued permanently due to the occurrence of AEs.

Table 6. Immune mediated adverse events **(**IrAE) - anti-PD-1 monotherapy in advanced melanomaM [23]

	Grade 1-2 N=37 (31.08%)	**Grade 3-4 N =18 (15.12%)**	**All Grade N =55 (46.2%)**
Endocrine	24 (20.16)	4 (3.36)	28 (23.52)
hypothyroidism	16 (13.44)	-	16 (13.44)
hyperthyroidism	2 (1.68)	-	2 (1.68)
hypopituitarism	6 (5.04)	4 (3.36)	10 (8.4)
respiratory	1 (0.84)	8 (6.72)	9 (7.56)
pneumonitis	1 (0.84)	8 (6.72)	9 (7.56)
Gastrointestinal	9 (7.56)	14 (11.76)	23 (19.32)
colitis	5 (4.2)	11 (9.24)	16 (13.44)
gastritis	4 (3.36)	2 (1.68)	6 (5.04)

terminalis ileitis	-	1 (.84)	1 (0.84)
Hepato-pancreato-biliary	25 (21)	6 (5.04)	31 (26.04)
hepatitis / ALT elevated	10 (8.4)	2 (1.68)	12 (10.08)
bilirubin elevated	6 (5.04)	-	6 (5.04)
pancreatitis	8 (6.72)	3 (2.52)	11 (7.56)
hyperlipidemia	1 (0.84)	1 (.84)	2 (1.68)
Musculoskeletal	9 (7.56)	2 (1.68)	11 (7.56)
myositis	5 (4.2)	2 (1.68)	7 (5.88)
arthritis	4 (3.36)	-	4 (3.36)
Renal	5 (4.2)	4 (3.36)	9 (7.56)
nephritis	5 (4.2)	4 (3.36)	9 (7.56)
Skin	12 (10.04)	3 (2.52)	15 (12.6)
vitiligo	5 (4.2)	-	5 (4.2)
dermatitis	5 (4.2)	3 (2.52)	8 (6.72)
bullous pemphigoid	2 (1.68)	-	2 (1.68)
Nervous system	4 (3.36)	1 (.84)	5 (4.2)
polyneuropathy	4 (3.36)	-	4 (3.36)
encephalitis	-	1 (.84)	1 (0.84)
Hematological	1 (0.84)		1 (0.84)
pancytopenia	1 (0.84)	-	1 (0.84)

Ophthalmic	3 (2.52)	1 (.84)	4 (3.36)
bulbitis	-	1 (.84)	1 (0.84)
conjunctivitis	1 (0.84)	-	1 (0.84)
uveitis, iridocyclitis	2 (1.68)	-	2 (1.68)
Oral cavity / ear	4 (3.36)		4 (3.36)
periodontitis	1 (0.84)	-	1 (0.84)
otitis media, otitis externa, sinusitis, ethmoiditis	3 (2.52)	-	3 (2.52)

4.2. Study II.: Locally advanced or metastatic cSSC treated with PD-1 inhibitor cemiplimab

4.2.1. Characteristics of the patients (Table 7)

25 patients were included, with a median age of 78 years (range: 65-82.5). 68% of the patients were male. 17 patients (68%) were over 70 years of age. Nine patients (36%) had a T4a stage of T, while two patients (8%) had an unknown T stage (Tx). 22 patients (80%) had locally advanced cSCC and five patients (20%) had distant, pulmonary metastases. Location of the primary tumor was the head and neck in 17 (68%) patients, the extremities in three (12%) patients, and the trunk in five (20%) patients. 19 patients (73%) were ECOG 0, five (20%) were ECOG 1 and one (4%) was ECOG 2.

At baseline, 14 (56%) patients had normal kidney function (≥ 60 GFR ml/L/m²L), eleven (44%) patients had GFR lower than 60 ml/L/m²L. Seven patients (28%) had significant anaemia with a hemoglobin level: 80-100 g/L.

Five (20%) patients had hypertension, two (8%) suffered from ischaemic heart disease, four (16%) had both hypertension and ischaemic heart disease, one (4%) patient

had diabetes mellitus, two (8%) patients had both diabetes and hypertension and six (24%) had hypertension, ischaemic heart disease and diabetes mellitus as well.

13 patients (52%) had a previous different malignant condition.Among these patients, eight patients (32%) had basal cell carcinoma, three (12%) had melanoma and four (16%) had a lymphoproliferative disorder.

Five of the 25 patients (20%) were immunocompromised, among which four (16%) had chronic lymphocytic leukaemia (CLL) and one was a kidney transplant recipient (**Table 7**).

Table 7. Demographic and clinical features of our patients under cemiplimab treatment for advanced cSSC (Kuzmanovszki et al., 2023)

	Total sample* (N=25)	**Responders* (N=13)**	**Non-responders* (N=12)**	**p-value****
Age (years)	78.00 (65.00-82.50)	78.00 (66.50-80.00)	79.50 (57.75-85.00)	0.564
≥ 70 years	17 (68.00%)	9 (69.23%)	8 (66.67%)	1.000
< 70 years	8 (32.00%)	4 (30.77%)	4 (33.33%)	
Received series (piece)	12.00 (4.50-19.50)	19.00 (12.00-20.50)	5.00 (3.00-11.75)	**<0.001**
Duration of treatment (weeks)	48.00 (16.43-72.43)	68.43 (51.22-82.85)	20.79 (9.04-40.97)	**<0.001**
OS (weeks)	53.57 (22.22-75.29)	76.43 (55.00-96.43)	25.07 (11.75-45.11)	**<0.001**
PFS (weeks)	25.07 (12.32-42.04)	73.71 (20.43-)	24.00 (10.29-40.86)	0.126
Gender				
male	17 (68.00%)	9 (52.94%)	8 (47.06%)	1.000
female	8 (32.00%)	4 (50.00%)	4 (50.00%)	

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	Total sample* (N=25)	Responders* (N=13)	Non-responders* (N=12)	p-value**
T				
Tx	2 (8.00%)	1 (50.00%)	1 (50.00%)	
T1	1 (4.00%)	0 (0.00%)	1 (100.00%)	
T2	6 (24.00%)	3 (50.00%)	3 (50.00%)	0.796
T3	7 (28.00%)	3 (42.86%)	4 (57.14%)	
T4a	9 (36.00%)	6 (66.67%)	3 (33.33%)	
N				
N0	13 (52.00%)	6 (46.15%)	7 (53.85%)	
N2a	1 (4.00%)	0 (0.00%)	1 (100.00%)	
N2b	1 (4.00%)	1 (100.00%)	0 (0.00%)	0.755
N2c	4 (16.00%)	3 (75.00%)	1 (25.00%)	
N3a	3 (12.00%)	2 (66.67%)	1 (33.33%)	
N3b	3 (12.00%)	1 (33.33%)	2 (66.67%)	
M				
M0	20 (80.00%)	11 (55.00%)	9 (45.00%)	0.645
M1	5 (20.00%)	2 (40.00%)	3 (60.00%)	
Localization of primer tumor				
head-neck	17 (68.00%)	9 (36%)	8 (32%)	
limb	3 (12%)	2 (8%)	1 (4%)	1.000
trunk	5 (20.00%)	2 (8%)	3 (12%)	
Site of metastases				
Locally advanced	14 (56.00%)	8 (57.14%)	6 (42.86%)	0.868

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	Total sample* (N=25)	**Responders* (N=13)**	**Non-responders* (N=12)**	**p-value****
Lymphonodular, in transit	6 (24.00%)	3 (50.00%)	3 (50.00%)	
Distant	5 (20.00%)	2 (40.00%)	3 (60.00%)	
Line of treatment				
First	22 (88.00%)	12 (54.55%)	10 (45.45%)	0.593
Second	3 (12.00%)	1 (33.33%)	2 (66.67%)	
Hemoglobin (g/L)				
Normal	15 (60.00%)	9 (60.00%)	6 (40.00%)	
80-100	7 (28.00%)	2 (28.57%)	5 (71.43%)	0.431
101-120	3 (12.00%)	2 (66.67%)	1 (33.33%)	
Creatinin (µmol/L)				
0	17 (68.00%)	10 (58.82%)	7 (41.18%)	
1	7 (28.00%)	3 (42.86%)	4 (57.14%)	0.509
2	1 (4.00%)	0 (0.00%)	1 (100.00%)	
GFR (ml/L/m²L)	64.00 (58.00-90.00)	64.00 (60.00-90.00)	64.00 (51.25-88.25)	0.568
≥ 60	14 (56.00%)	8 (57.14%)	6 (42.86%)	0.695
< 60	11 (44.00%)	5 (45.45%)	6 (54.55%)	
ECOG				
0	19 (76.00%)	11 (57.89%)	8 (42.11%)	
1	5 (20.00%)	2 (40.00%)	3 (60.00%)	0.467
2	1 (4.00%)	0 (0.00%)	1 (100.00%)	
Irradiation				
No	13 (52.00%)	6 (46.15%)	7 (53.85%)	0.695

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	Total sample* (N=25)	Responders* (N=13)	Non-responders* (N=12)	p-value**
Yes	12 (48%)	7 (58.33%)	5 (41.67%)	
Site of irradiation				
No	13 (52.00%)	6 (46.15%)	7 (53.85%)	
T	5 (20.00%)	3 (60.00%)	2 (40.00%)	0.753
N	5 (20.00%)	2 (40.00%)	3 (60.00%)	
Both	2 (8.00%)	2 (100.00%)	0 (0.00%)	
AE				
No	9 (36.00%)	7 (77.78%)	2 (22.22%)	0.097
Yes	16 (64.00%)	6 (37.50%)	10 (62.50%)	
Grade of AE (missing=1)			(missing=1)	
Gr 1-2	9 (37.50%)	3 (33.33%)	6 (66.67%)	
Gr: 3-4	6 (25.00%)	3 (50.00%)	3 (50.00%)	0.157
0	9 (37.50%)	7 (77.78%)	2 (22.22%)	
AE				
0	9 (37.50%)	7 (70.00%)	2 (22.22%)	
1	6 (24.00%)	3 (50.00%)	3 (50.00%)	0.308
> 1	9 (36.00%)	3 (33.33%)	6 (66.67%)	
Other disorders				
0	5 (20.00%)	2 (40.00%)	3 (60.00%)	
DM	1 (4.00%)	1 (100.00%)	0 (0.00%)	
HT	5 (20.00%)	3 (60.00%)	2 (40.00%)	0.442
IHD	2 (8.00%)	2 (100.00%)	0 (0.00%)	
HT+ IHD	4 (16.00%)	3 (75.00%)	1 (25.00%)	

	Total sample* (N=25)	Responders* (N=13)	Non-responders* (N=12)	p-value**
All 3	6 (24.00%)	2 (33.33%)	4 (66.67%)	
HT+DM	2 (8.00%)	0 (0.00%)	2 (100.00%)	
Other tumor				
No	12 (48.00%)	8 (66.67%)	4 (33.33%)	0.238
Yes	13 (52.00%)	5 (38.46%)	8 (61.54%)	
Immunodeficiency				
No	20 (80.00%)	10 (50.00%)	10 (50.00%)	1.000
Yes	5 (20.00%)	3 (60.00%)	2 (40.00%)	
CLL				
No	21 (84.00%)	11 (52.38%)	10 (47.62%)	1.000
Yes	4 (16.00%)	2 (50.00%)	2 (50.00%)	

AE = Adverse event; CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group Performance Status; GFR = Glomerular filtration rate; OS = Overall survival; PFS = Progression free survival, DM = diabetes mellitus; HT = hypertonia; IHD = ischemic heart disease,
* The Non-responders (Stable and progressive disease) and Responders (Partial and complete responses) subgroups were created based on the responders' therapy responses.
** Mann-Whitney U test or Fisher's exact test. A p-value<0.05 was considered statistically significant.

4.2.2. Treatment characteristics

For 22 patients (88%), cemiplimab was administered as first-line treatment and for three (12%) as second-line. Those patients who received second-line cemiplimab treatment had a histopathological diagnosis of mixed basosquamous carcinoma before treatment and were given vismodegib as a first-line agent without effect, repeated histopathological report confirmed the diagnosis of cSCC.

12 patients (48%) also underwent radiotherapy, including five patient (20%) who received treatment for locally advanced tumor, five patients (5%) were treated for the lymph nodes and two patients (8%) received treatment for both regions (**Table 7**).

Table 8. Survival data of the investigated cohort of in advanced cSSC patients treated with cemiplimab (Kuzmanovszki et al., 2023)

		N	**Mean survival (weeks)**	**LCI**	**UCI**	**p-values (log-rank)**
Total sample (median)		25	*85.06*	*59.01*	*111.10*	-
Age (years)	≥70	17	*87.05*	*56.78*	*117.31*	0.882
	< 70	8	*83.75*	*38.22*	*129.29*	
Gender	male	17	*90.13*	*59.18*	*121.09*	0.773
	female	8	*73.50*	*33.00*	*114.00*	
Primer tumor	Head-neck	17	*62.86*	*44.24*	*81.47*	0.833
	trunk	5	*93.23*	*31.18*	*155.28*	
	limb	3	104.10	24.46	183.74	
T	Tx	2	*50.22*	*0.00*	*101.60*	0.211
	T1	1	*16.14*	*16.14*	*16.14*	

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		N	Mean survival (weeks)	LCI	UCI	p-values (log-rank)
	T2	6	*71.90*	*38.85*	*104.95*	
	T3	7	*79.63*	*33.06*	*126.21*	
	T4a	9	*108.70*	*66.90*	*150.50*	
N	N0	13	-	-	-	0.742
	N2a	1	-	-	-	
	N2b	1	-	-	-	
	N2c	4	-	-	-	
	N3a	3	-	-	-	
	N3b	3	-	-	-	
M	M0	20	*89.38*	*61.01*	*117.75*	0.390
	M1	5	*42.37*	*16.75*	*67.99*	
Site of metastases	Locally advanced	14	*91.38*	*58.57*	*124.19*	0.675
	In transit	6	*65.88*	*29.76*	*101.99*	
	Distant	5	*42.37*	*16.75*	*67.99*	
GFR (ml/L/m2L)	≥ 60	14	*94.81*	*59.40*	*130.22*	0.265

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		N	Mean survival (weeks)	LCI	UCI	p-values (log-rank)
	< 60	11	*56.76*	*31.99*	*81.54*	
Site of irradiation	No	13	*93.26*	*56.93*	*129.58*	0.964
	T	5	*63.22*	*34.08*	*92.35*	
	N	5	*48.63*	*28.70*	*68.55*	
	Both	2	*47.07*	*10.15*	*83.99*	
Irradiation	No	13	*93.26*	*56.93*	*129.58*	0.643
	Yes	12	*58.11*	*38.50*	*77.71*	
Grade of AE (missing=1)	Gr 1-2	9	*87.03*	*47.34*	*126.72*	0.806
	Gr: 3-4	6	*53.38*	*15.35*	*91.42*	
	0	9	*70.03*	*43.48*	*96.58*	
AE	0	10	*95.36*	*55.04*	*135.68*	0.197
	1	6	*72.60*	*49.54*	*95.66*	
	> 1	9	*62.08*	*19.04*	*105.12*	

		N	Mean survival (weeks)	LCI	UCI	p-values (log-rank)
Other disorders	0	5	-	-	-	**0.036**
	DM	1	-	-	-	
	HT	5	-	-	-	
	IHD	2	-	-	-	
	HT+IHD	4	-	-	-	
	All 3	6	-	-	-	
	HT+DM	2	-	-	-	
Other tumor	No	12	*96.38*	*58.49*	*134.28*	0.304
	Yes	13	*55.00*	*34.54*	*75.46*	
Therapy responses	PD+SD	13	*35.94*	*14.41*	*57.47*	**<0.001**
	PR+CR	12	*129.30*	*98.97*	*159.63*	

LCI = lower bound of the 95% confidence interval; PD+SD = progressive disease and stable disease; PR+CR = partial responds and complete responds; UCI = upper bound of the 95% confidence interval
A p-value<0.05 was considered statistically significant. The italic values refer to Mean and bold values refer to Mean overall survival weeks.

4.2.3. Treatment outcomes

The ORR was calculated to be 52% in the total investigated population, 60% in the immunocompromised subgroup, 55% in la-cSCC, and 40% in m-cSCC (**Table 9**). The DCR was found to be overall 76%, while immunocompromised patients achieved a higher rate of 80%, la-cSCC 80%, and m-cSCC 60% (**Table 9**). We compared demographic and clinical characteristics between cSCC patients who achieved ORR

(responders, n=13), and patients who achieved SD or PD as their best response (non-responders, n=12) (**Table 8**). We also investigated the association of the analyzed parameters with survival outcomes.

Table 9. ORR and DCR - cemiplimab treatment in advanced cSSC (Kuzmanovszki et al., 2023)

Responses	**Total (N=25)**	**Immundeficiency (N=5)**	**la cSCC (N=20)**	**m cSCC (N=5)**
CR	3 (12%)	0	3 (15%)	0
PR	10 (40%)	3 (60%)	8 (40%)	2 (40%)
SD	6 (24%)	1 (20%)	5 (25%)	1 (20%)
PD	6 (24%)	1 (20%)	4 (20%)	2 (40%)
ORR*	**13 (52%)**	**3 (60%)**	**11 (55%)**	**2 (40%)**
DCR**	**19 (76%)**	**4 (80%)**	**16 (80%)**	**3.(60%)**

CR = complete responses; PR = partial responses; SD = stable diseases; PD = Progressive diseases; ORR = Objective response rate; DCR = disease control rate
ORR = CR + PR, ** DCR = CR + PR + SD,

At the time point of data extraction, cemiplimab therapy was ongoing in ten (40%) patients and the median treatment duration was 48 weeks. 15 patients (60%) is continued cemiplimab, including six cases (24%) as a result of disease progression, six patients (24%) due to toxicity and two patients (8%) deceased due to unrelated causes (not related to the tumor or the received therapy).

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Median OS and PFS have not yet been achieved. Based on the high ORR data, the PFS and OS values were close, thus we used the mean OS value for the basis for the survival analysis.

The mean OS was found to be 85.06 weeks (**Figure 2**). In patients older than 70 years, the mean survival was similar (87.05 weeks) to younger patients (<70 years) 83.75 weeks).

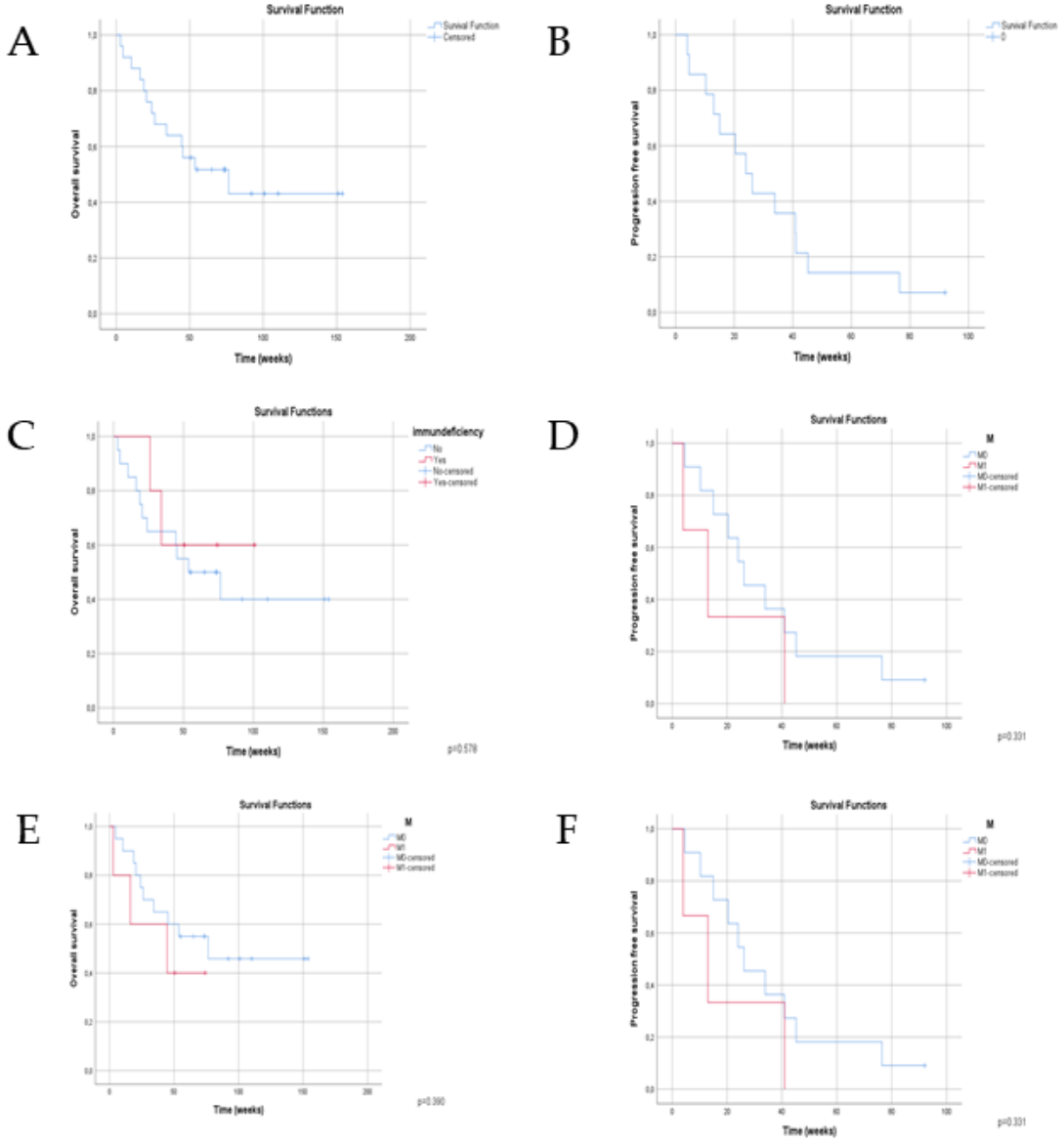

Figure 2. Kaplan – Meier curves for overall survival (2.A), progression free survival (2.B), OS in patients with immundeficiency (2.C), PFS in patients with

immunodeficiency (2.D), OS in patients with distant metastasis (2.E) and PFS in patients with distant metastasis (2.F).

A shorter mean survival was found in patients with M1 status with distant metastases (42.37 weeks) in comparison with patients with locally advanced (91.38 weeks) and regional in transit and/or lymph node metastases (65.88 weeks). The survival data of patients with immunosuppression was similar to the overall study population.

The occurrence of any irAE was associated with a worse outcome. Those patients, who did not develop any AE during cemiplimab treatment had a longer mean survival (76.43 weeks versus 45.29 weeks p=0.542). The mean survival was shorter in patients with decreased renal function (GFR <60 ml/L/m²L) (**Table 8**).

4.2.4. Toxicity

Overall, 34 AEs were identified. 16 (64%) patients experienced at least one irAEs: nine (36%) experienced grade 3-4 AEs and 11 cases (10 patients, 40%) led to hospitalization. Six (24%) patients had severe irAE leading to treatment discontinuation. No fatal AEs developed (grade 5).

The AEs that occurred the most commonly were thyroiditis (occurring in 24% of the patients), nephritis (16%), anemia (16%), colitis (12%), and pancreatitis (12%) (**Table 10**). Grade 3 or higher AE that developed in two patients were pneumonitis and nephritis, AEs that developed in one patient were severe colitis, neutropenia, pancreatitis, myositis, and one patient developed pneumothorax (PTX).

Three of the five immunocompromised patients irAE, but none of these patients discontinued cemiplimab due to toxicity. Following cemiplimab therapy, the renal function of the patient, who had undergone a kidney transplantation, declined. The initial GFR was 66 ml/L/m²L, which decreased to 30 ml/L/m²L after 10 months of therapy. Nevertheless, cemiplimab therapy resulted in a partial remission of the cSCC. The worsening of renal function may also be a result of the concomitant bisphosphonate infusion from cycle 6 due to bone involvement. Cemiplimab treatment did not lead to rejection of the transplanted kidney.

Table 10. Adverse events - cemiplimab treatment in advanced cSSC (Kuzmanovszki et al., 2023)

AE (type)	AE (all): 34 No. of patients: 19 (76%)	AE grade 1-2: 23 No. of patients: 17 (68%)	AE grade 3-4: 9 No. of patients: 9 (36%)	AE led to hospitalization: 11 No. of patients: 10 (40%)	AE led to permanent discontinou-ation of treatment: 8 No. of patients: 6 (24%)
anaemia	4 (16)	4 (16)	0	0	0
neutropenia	1 (4)	0	1 (4)	1 (4)	1 (4)
eosinophilia	1 (4)	1 (4)	0	0	0
fatigue	2 (8)	2 (8)	0	0	0
thyroiditis	6 (24)	6 (24)	0	0	0
[1]IDDM	2 (8)	1 (4)	0	1 (4)	0
pancreatitis	3 (12)	2 (8)	1 (4)	1 (4)	1 (4)
pneuminitis	2 (8)	0	2 (8)	2 (8)	2 (8)
colitis	3 (12)	2 (8)	1 (4)	1 (4)	1 (4)
myositis	1 (4)	0	1 (4)	1 (4)	1 (4)
nephritis	4 (16)	2 (8)	2 (8)	2 (8)	2 (8)
skin reaction	2 (8)	2 (8)	0	1 (4)	0

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infection	2 (8)	2 (8)	0	0	0
[2]PTX	1 (4)	0	1 (4)	1 (4)	0

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5. DISCUSSION

Two retrospective analyses were carried out at the same centre. In the first study we evaluated the data of patients with AM under anti-PD1 ICI monotherapy between 2015 and 2021, including nivolumab or pembrolizumab. In the second study, we investigated patients with advanced unresectable cSCC treated with anti-PD-1 agent cemiplimab.

Study I.

In the first cohort, 119 patients with AM were included. Several patients were of advanced age (≥ 70 years), had poor performance status (≥ 2 ECOG), received prior treatment, suffered from brain metastases (stage M1d disease) or active autoimmune disease requiring systemic steroid treatment or harbored BRAF V600 mutation. The majority of the investigated patients would not be eligible to be enrolled in phase III clinical trials. (Hamid et al., 2021; Robert et al., 2023; Robert et al., 2015; Robert et al., 2019; Schachter et al., 2017)

The median OS was 30 months (130 weeks) in our real-world analysis compared with 37.3 months median OS observed in the Checkmate-066, and 32.7 months in the Keynote-006 phase III clinical trials. Nevertheless, our investigated patients achieved 12.5 months (54 weeks) median PFS, which was superior compared to the median PFS observed in these phase III trials, where it was 5.1 and 8.4 in months, respectively. (Hamid et al., 2021; Robert et al., 2023; Robert et al., 2019) The outcomes of our study implies that the survival benefits from anti-PD-1 ICI therapy for AM in the everyday clinical practice is comparable to that was found in phase III trials. [12, 27, 29, 30] Moreover, the increased PFS observed in our patient cohort indicates that PD-1 ICI has a great benefit for patients with AM. In contrast, we observed lower ORR (16.8%) in our cohort when compared to the outcomes of the clinical trial (42% and 41%, respectively). (Hamid et al., 2019; Robert et al., 2021)

The increased PFS and low ORR could be explained by the low ratio of patients who achieved CR (6.7%) or PR (10.08%) developed a long-term immune response to the tumor cells. While a long-term survival could be expected in these patients, the median prolonged OS not achieved during the observation period.

It could be anticipated, that those patients that have negative prognostic factors including poor performance status (ECOG PS ≥ 2), elevated LDH, or brain metastases (stage M1d) might have benefited less from PD-1 ICI. Yet, in our patient cohort, most of the patients had ECOG PS 0-1 (117, 98.28%), nine (7.56%) patients had an elevated LDH level at the start of PD1-ICI and only two patients had an ECOG performance status ≥ 2. Hence, there was no significant correlation with the outcome.

Brain metastases in AM have a very poor prognosis, with a median survival of 3 to 6 months. (Franklin et al., 2023; Frinton et al., 2017; Sherman et al., 2023; Tan et al., 2022) Also in our study, anti-PD1 ICI provided limited results in AM patients with brain metastases (median OS: 71 weeks). Dual immune checkpoint inhibition with concomitant ipilimumab and nivolumab has led to encouraging outcomes in previous clinical trials in patients with asymptomatic brain metastases. (Long et al., 2018; Sherman et al., 2023; Tawbi et al., 2018) Studies describing real-world evidence regarding the outcomes in anti-PD1 ICI were also published recently. A study from the Netherlands on patients with no, asymptomatic or symptomatic brain metastases, the probability for 4-year OS were 48% (95% CI: 41–55), 45% (95% CI: 35–57) and 32% (95% CI: 23–46). (van Zeijl et al., 2023) A different multicentre retrospective study analyzed patients with AM under ipilimumab and nivolumab treatment between 2015 and 2020. Out of 697 patients 472 were treatment-naïve of which 138 (29.2%) had brain metastases. Patients with brain metastases had a median OS of 38.7 months (95% CI 18.6-NR). (Serra-Bellver et al., 2022)

It was also investigated whether anti-PD-1 ICIs administered as first-, second- or third-line treatment had on impact on survival. Patients who were given PD-1 ICIs as second- or third-line treatment achieved superior outcomes compared to those who received them first-line. The explanation of this could be that patients with BRAF-positive AM under previous BRAF and MEK inhibitor treatment had a fast regression in the tumor burden. Nevertheless, among the BRAF wild-type AM patients treated with anti-PD1 ICI as second-line treatment, just a few patients were given ipilimumab as first-line. For these patients, a significantly longer period was required for the therapeutic response to develop. Most of the AM patients with BRAF wild-type tumors that were administered second-line anti-PD1 monotherapy had received chemotherapy as first-line treatment.

Based on our results, patients with BRAF wild-type tumors achieved more favorable survival outcomes in comparison with patients with BRAF V600-mutant tumors. This could be explained by that those patients with BRAF-mutant tumors were given combination treatment with BRAF and MEK inhibitors or were administered BRAF inhibitor monotherapy (77.4% of patients with BRAF mutations).

Nevertheless, the few patients who were not under previous BRAF targeted therapy (5.8%) showed inferior survival outcomes. In the background of these findings, a possible explanation is that these patients had a high tumor burden and already suffered from symptoms as a result of AM. Patients who were administered a combination of a BRAF and a MEK inhibitor as first-line therapy had a quick improvement in their symptoms and also achieved a fast decrease in their tumor burden.

Currently it is debated if in the treatment of BRAF V600-mutant AM anti-PD1 ICI or a combination of BRAF and MEK inhibitors should be preferred as a first-line treatment in AM, and if the treatment of choice influences the survival outcomes. We are at a time of a paradigm shift, based on the results of the recent phase II SECOMBIT and phase III DREAMSeq trials. (Ascierto et al., 2024; Atkins, 2023; Atkins et al., 2023) The trials reached to the conclusion that AM patients with BRAFV600-mutant tumors who were treated with a combination of ipilimumab and nivolumab followed by targeted therapy may have a longer long-term OS than those who first received the two treatments in the reverse order. [5, 38-41]

In a recent real-world study based on an electronic health record-derived database of 280 cancer clinics in the United States of America, overall OS in patients with BRAF-mutant AM was assessed. In this study, it was observed that AM patients who received anti-PD1 ICI in first-line had longer median OS of 30.0 months vs 15.5 months in those who did not receive it as first-line therapy. (Atkins et al., 2022)

In our study, AM patients who received RT and anti-PD1 ICI concurrently had a higher OS ($p = 0.010$). Data is limited efficacy of RT in AM patients under anti-PD1 ICI treatment. 25 patients with AM who were given a combination of RT and anti-PD1 ICI achieved superior outcomes in both the irradiated and non-irradiated areas in prospective clinical trials. Abscopal effect was hypothesized to be in the background of these results. (Roger et al., 2018) In addition, a further study found that this combination could result in a significant benefit in 225 patients with advanced mucosal melanoma. (Umeda et al.,

2021) Abscopal effect was found to be induced in 39% of AM patients in a prospective study where a combination of RT and ICI treatment was given to patients who did not respond to anti-PD1 ICI. (Funck-Brentano et al., 2020)

irAEs induced by ICI can be treated with prompt initiation of systemic corticosteroids or different immunomodulators. In the present analysis, mild irAEs (grade 1 or 2) occurred in only 15.12%, while severe irAEs (grade 3 or 4) were reported in 31.08% of the patients. These rates are similar to those reported in different clinical trials. (Robert et al., 2015; Schachter et al., 2017; Suo et al., 2020)

A significantly longer OS and PFS was found in patients with one or more irAE (>1 irAE) had compared to those without the occurrence of irAE. Survival outcomes were also affected by the grade of toxicity, as patients with grade 3-4 irAE achieved significantly superior PFS. The occurrence of irAEs proved to be an independent predictive marker for PFS and OS.

It was observed that there is an association between the occurrence of irAEs in patients under anti-PD1 ICI and improved therapeutic outcomes at week 12. (Suo et al., 2020) In a pooled analysis of four clinical trials, the development of AEs in patients under nivolumab therapy showed an associated improved ORR. (Weber et al., 2017)) It was also published that there is a strong association between the occurrence of any irAE and response to anti-PD-1 ICI. Obesity was significantly associated with the development of irAE, but there was no significant association with age or gender. (Bastacky et al., 2021) A further Hungarian retrospective single-center real-world analysis investigating 222 AM patients under PD1 monotherapy revealed a significant correlation between irAEs and treatment outcomes. (Eikenes et al., 2023)

Study II.

In our second study, we investigated a cohort of 25 patients treated with PD1 ICI cemiplimab therapy for unresectable cSCC. Many of these had unfavourable characteristics such as older age (≥70 years), immunocompromised state, chronic kidney disease or polymorbidity. Many of these patients could not be included in the relevant phase III trials as they could not meet the inclusion and exclusion criteria.(Migden et al., 2020; Migden et al., 2018; Rischin et al., 2021; Rischin et al., 2020) The EMPOWER-CSCC-1 study also excluded patients with performance status higher than 1, active

autoimmune condition, infections and lymphoproliferative disorders. (Migden et al., 2018)

Our analysis revealed an ORR of 52%, compared to 44% (95% CI 32-55) in the corresponding phase II clinical trials. (Migden et al., 2020) A similar rate of CR (12% vs 11.3%) was found in our study as observed in the updated analysis of the EMPOWER-CSCC-1 clinical trial. However, the rate of PR was revealed to be higher in our study (40% vs 33.9%). (Migden et al., 2018) A possible explanation is that with a longer follow-up time certain patients who only achieved PR could later reach CR. (Migden et al., 2018; Rischin et al., 2021; Rischin et al., 2020)

Moreover, 88% of the patients in our analysis were administered cemiplimab as a first-line systemic agent compared to 66% in the phase II clinical trial. (Mager, Gardeen, Carr, & Shahwan, 2023; Rischin et al., 2020)

Systemic glucocorticoids or other immunosuppressives are often needed to manage IrAEs that occur due to cemiplimab therapy. (Wang et al., 2019) In our study, severe irAEs (grade 3 or 4) were observed in 36% of the investigated patients, while mild irAEs (grade 1 or 2) developed in 60%. The most frequent mild irAE was thyroiditis (24%) and the most common grade 3-4 irAE was pneumonitis and nephritis. In the relevant phase II clinical trial, 44% of patients experienced grade 3-4 treatment-related AEs, the of which the most common were hypertension (8%) and pneumonia (5%). (Migden et al., 2020) The most common treatment-related AEs in another phase II clinical study were fatigue (27.0%) and diarrhoea (23.5%). (Mager et al., 2023; Rischin et al., 2020) Patients with advanced cSCC are often elderly individuals with many concomitant diseases. As expected, in our analysis with a median age of 78 years, a high mean number of comorbidities were found. Although no increase in the risk of severe irAEs were found in elderly patients (Samani et al., 2020), even milder irAEs could result in severe complications in these patients.

The previous real-world studies have observed optimal outcomes for patients with advanced cSCC under anti-PD1 treatment. A retrospective observational multicentric study of 46 patients with advanced cSCC treated with anti-PD1 ICI observed an ORR of 58.7%, with 15.2% of CRs and a DCR of 80.4% [18]. In a further study from France, 61 patients treated with cemiplimab reported an ORR of 50.4% and a DCR of 59.6%. (Hober et al., 2021) In a retrospective cohort study evaluating elderly patients, 23 responses

(76.7%) with nine CRs (30%) were reached, with an overall response in four out of five immunosuppressed patients. (Strippoli et al., 2021) A further study by Denaro *et al*. evaluated 20 ultra-octogenarian patients with cSCC who received cemiplimab treatment revealed that in the majority of patients clinical improvement, such as tumor shrinkage and pain relief was observed. This study confirmed the effectiveness of cemiplimab in elderly patients in a real-life setting, with no novel safety issues. (Denaro et al., 2023)

Our analysis revealed a higher ORR and DCR in patients with locally advanced SCC compared to patients with distant metastases (ORR: 55% vs 40%; DCR: 80% vs 60%) and a longer mean survival. In a recent German observational, retrospective, multicentric study, it was revealed that distant metastases did not have an impact on the response compared to locally advanced tumors. Two predictive factors were found in this study. Patients with elevated LDH levels at the initiation of therapy and patients with primary tumors located on the lower extremities had worse therapeutic outcomes. In their study, only one-tenth of the patients stopped treatment due to toxicity, indicating optimal tolerability. (Salzmann et al., 2020) A further real-world study revealed a better response to immunotherapy in head and neck cSCC patients. In contrast, genital cSCC had the poorest treatment outcomes. (Baggi et al., 2021) In our 25 patients, only three (12%) had cSCC on the extremities and five (20%) on the trunk, with shorter survival in patients with head and neck primary tumors. At the initiation of cemiplimab therapy, all patients had serum LDH levels within normal range.

A 65 to 250-fold increase in the risk of cSCC was found in solid organ transplant patients on immunosuppression compared to healthy individuals.(Eisemann et al., 2014; Wu & Orengo, 2002) Most patients with cSCC harbor hypermutated tumors due to the sun exposure. (Chalmers et al., 2017; Eisemann et al., 2014; Hanania & Lewis, 2022; Portuguese et al., 2022) Taken together with the fact, that cSCC patients are often immunocompromised, this renders them a suitable candidate for immunotherapy. (Migden et al., 2020; Rischin et al., 2021)

The findings of our present study revealed that immunocompromised patients treated with cemiplimab have promising outcomes, in contrast to the fact that they are excluded from the major clinical trials. On the other hand, prior studies have observed that the risk of graft rejection, particularly in case of liver transplant recipients is higher in the case of anti-PD-1 ICI treatment. (Hober et al., 2021; Portuguese et al., 2022) In

addition, there is an ongoing clinical trial investigating the efficacy and safety of cemiplimab in combination with everolimus or sirolimus and systemic corticosteroid therapy in kidney transplant patients with advanced cSCC. (Hober et al., 2021) A further phase I clinical trial evaluating cemiplimab following cross-taper to a mammalian target of rapamycin (mTOR) inhibitor and pulsed dose glucocorticoids for kidney transplant recipients with advanced cSCC revealed favorable outcomes without the occurrence of kidney rejection. (Hanna et al., 2024)

In patients who suffer from lymphoproliferative disorders a high ORR was observed. This underlines the results of previous studies in which PD1 showed favorable outcomes in this subgroup. (Leiter et al., 2020)

We observed a small increase in survival outcomes in case of GFR >60 and haemoglobin >100g/L at the initiation of cemiplimab treatment. In contract, no differences were found regarding median age, sex, T and N stage, irradiation, the presence of any other disease or tumor and the occurrence of AE.

Our present analyses have certain limitations, which include a retrospective setting, that results in significant selection bias. Also, our first study is limited by the fact that AE reporting was based on previous medical records, in which grade 1-2 irAEs may have been underreported. Main limitations of our second study include a monocentric setting, low number of investigated patients, heterogeneous patient population, and lack of long-term follow-up data.

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6. CONCLUSION

In our first retrospective study, while baseline characteristics of the investigated patients were different from those reported in clinical trials, we observed promising long-term outcomes in AM patients under anti-PD-1 monotherapy in a real-world setting. This analysis revealed that the development of one or more irAEs showed an association with the response to anti-PD-1 ICI treatment and also proved to be an independent predictive marker for both PFS and OS.

Our second study revealed that similarly to the previous clinical trials that involved a specific population, cemiplimab showed a high efficacy with an acceptable safety profile in real-world patients. We observed that cemiplimab was effective in elderly and immunocompromised patients with polymorbidity.

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7. SUMMARY

In recent years, PD-1 inhibitor ICIs have gained a significant role in the treatment of various malignant tumors, including malignant melanoma and cSCC. PD-1 inhibitors exert their effect by activating the anti-tumor immune system. They are monoclonal antibodies that block the binding of PD-L1 expressed on the surface of tumor cells to PD-1 on the surface of T cells, thereby inducing T cell-mediated antitumor immunity.

In both of our studies, we analyzed data from patients treated in everyday practice to assess real-world, clinically relevant survival outcomes. In our first study, we retrospectively analyzed the survival results of AM patients treated with a PD1 inhibitor nivolumab or pembrolizumab during a 77-month observation period. In our second study, we evaluated the data of PD1 inhibitor cemiplimab therapy inpatients with la-cSCC or m-cSCC.

We aimed to identify predictive markers based on treatment efficacy and side effect characteristics.

In our first study, the baseline characteristics of the patients studied differed from those reported in clinical trials, as several patients were of advanced age (≥ 70 years), poor performance (≥ 2 ECOG), received prior treatment, had brain metastasis (stage M1d disease) or carried BRAF V600 mutation. The majority of the examined patients would not be eligible for inclusion in phase II or III clinical trials. We observed promising and long-term outcomes in AM patients on anti-PD-1 monotherapy in a real-world setting. This analysis showed that the development of one or more irAEs was associated with superior response to anti-PD-1 ICI treatment and also proved to be an independent predictive marker for both PFS and OS.

The second study demonstrated that cemiplimab exhibited high efficacy with an acceptable safety profile, comparable to previous population-based clinical trials. It was observed that cemiplimab was effective in elderly and immunocompromised patients with multiple comorbidities.

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