Aus der

Universitäts-Hautklinik Tübingen
Sektion Dermatologische Onkologie

Response to PD-1 based immunotherapy in patients with preexisting autoimmune diseases receiving active immunosuppression

Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von

Sattler, Jens Sören

2026

Aus der

Universitäts-Hautklinik Tübingen
Sektion Dermatologische Onkologie

Ansprechen auf eine PD-1-basierte Immuntherapie bei Patient:innen mit vorbestehenden Autoimmunerkrankungen, die eine aktive Immunsuppression erhalten

Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von

Sattler, Jens Sören

2026

Dekanin: Professorin Dr. S. Y. Brucker

1. Berichterstatter: Professor Dr. L Flatz
2. Berichterstatter: Professor Dr. M. D. Fischer

Tag der Disputation: 13.05.2026

Für Romi und Jakob

Table of content

List of abbreviations III
List of figures V
List of tables VIII
1. Introduction 1
1.1 Malignant Melanoma 1
1.2 Diagnostic criteria and clinical staging 2
1.3 Therapy 5
1.3.1 Immune checkpoint and inhibition 5
1.4 Immune related adverse events (irAEs) 9
1.4.1 Immune checkpoint inhibition in patients with pre-existing autoimmune disease with or without active immunosuppression 11
1.5 Objective and research question of the dissertation 12
2. Material and methods 13
2.1 Data collection and assessment 13
2.2 Patient collective and classification of variables 14
2.3 Statistical Analysis 14
3. Results 16
3.1 Description of the patient collective 16
3.2 Analysis parameters 20
3.2.1 Patient characteristics 20
3.2.2 Primary tumour characteristics 21
3.2.3 Laboratory parameters 23
3.2.4 Prognostic factors 27
3.2.5 Therapy regimen 29
3.2.6 Immune related adverse events (irAEs) 31
3.3 Best and Overall Response Rate (BOR) according to RECIST 32
3.3.1 BOR according to RECIST and therapy regimen 34
3.4 Survival analysis 37
3.4.1 Age 37
3.4.2 Sex 39
3.4.3 Stage at initial diagnosis 41
3.4.4 Mutation status 43

3.4.5 Location of primary tumour 44
3.4.6 Histological subtype 46
3.4.7 Laboratory parameters 47
3.4.8 Pre-existing autoimmune disease 50
3.4.9 Immunosuppressive therapy 51
3.4.10 Prognostic factors 52
3.5 Influence of systemic therapies on overall survival 57
3.5.1 Therapy regimen 57
3.5.2 First-line vs second-line therapy 61
3.5.3 Progression Free Survival (PFS) under active immunosuppression 63
3.5.4 Progression Free Survival per first or second-line therapy 68
4. Discussion 74
4.1 Patient characteristics 74
4.1.1 Age and sex 74
4.2 Primary tumour characteristics 75
4.2.1 Location of primary tumour 75
4.2.2 Histological subtype 75
4.2.3 Laboratory parameters 76
4.3 Prognostic factors 77
4.3.1 Metastases 77
4.4 Survival analysis 78
4.4.1 Analytic parameters 78
4.4.2 Active immunosuppression and PD-1 based therapy 80
4.4.3 PFS and active immunosuppression 81
4.4.4 irAEs 81
4.5 Conclusions 82
4.6 Performance and Limitation 83
5. Summary 84
6. Bibliography 86
7. Erklärungen zum Eigenanteil 98
8. Acknowledgement 99

List of abbreviations

A	AJCC	American Joint Committee on Cancer
	95% CI	95% confidence interval
	ADL	Activities of daily living
	ALM	Acral lentiginous melanoma
	APC	Antigen presenting cell
B	BAnz	Bundesanzeiger
	bDMARD	Biological disease-modifying anti-rheumatic drug
	BOR	Best overall response
	CM	Choroidal melanoma
	CR	Complete response
	CS	Corticosteroids
	CT	Chemotherapy
	CTCAE	Common Terminology Criteria for Adverse Events
	CTLA4	Cytotoxic T-lymphocyte-associated protein 4
C	cTNM	Clinical tumour, nodal, distant metastases
	DC	Dendritic cell
D	DGVSO	Datenschutzgrundverordnung
	DMI	Diabetes mellitus type I
E	EMA	European Medicines Agency
	EU	European Union
	HNSCC	Head and neck squamous cell carcinoma
	IBD	Inflammatory bowel disease
	ICI	Immune checkpoint inhibitors
	IFN-γ	Interferon γ
	IL	Interleukin
	IQR	Interquartile Range
I	irAE	Immune related adverse event
	LDH	Lactate dehydrogenase
L	LMM	Lentigo maligna melanoma
M	M	Definition of distant metastasis
	Mdn	Median
	MHC	Major histocompatibility complex
	mm	millimetre
	mOS	Median Overall Survival
	mPFS	Median Progression Free Survival
	MTX	Methotrexate
	MuM	Mucosal melanoma
N	N	Definition of regional lymph node
	NaM	Naevus associated melanoma
	NM	Nodular melanoma
	NSCLC	Non-small cell lung cancer
O	OM	Occult melanoma
	PAD	Preexisting autoimmune disease
	PD	Progressive disease
P	PD-1	Programmed death cell receptor 1
	PD-L1	Programmed death cell receptor ligand 1

	PD-L2	Programmed death cell receptor ligand 2
	PFS	Progression free survival
	PR	Partial response
R	RECIST	Response Evaluation Criteria in Solid Tumours
S	S100	S100 protein (tumour marker)
	SD	Stable disease
	SHP-2	Tyrosine phosphatase
	SSM	Superficial spreading melanoma
T	T	Definition of primary tumour
	TCR	T cell receptor
	TNF	Tumour necrosis factor
	TT	Targeted therapy

List of figures

Figure 1: T cell activation and mechanism of PD-1 axis inhibition and the role of anti-PD-1-antibodies 8
Figure 2: Age groups 20
Figure 3: Sex 20
Figure 4: Stage at first diagnosis 21
Figure 5: BRAF mutation status 22
Figure 6: Localisation of primary tumour 22
Figure 7: Histological subtypes 23
Figure 8: LDH 24
Figure 9: S100 24
Figure 10: Autoimmune diseases 26
Figure 11: Number of immunosuppressive agents 26
Figure 12: Immunosuppressive agents 27
Figure 13: Number of metastatic organs 28
Figure 14: Brain metastases 28
Figure 15: Liver metastases 29
Figure 16: Systemic therapies 29
Figure 17: irAEs under PD-1 therapy ± PAD 32
Figure 18: irAEs under PD-1 therapy + PAD 32
Figure 19: mOS age group – PAD ± immunosuppression 38
Figure 20: mOS age group – PAD + immunosuppression 39
Figure 21: mOS sex – PAD ± immunosuppression 40
Figure 22: mOS sex – PAD + immunosuppression 41
Figure 23: mOS stage at initial diagnosis – PAD ± immunosuppression 42
Figure 24: mOS stage at initial diagnosis – PAD + immunosuppression 42
Figure 25: mOS BRAF mutation – PAD ± immunosuppression 43
Figure 26: mOS BRAF mutation – PAD + immunosuppression 44
Figure 27: mOS location of primary tumour – PAD ± immunosuppression 45
Figure 28: mOS location of primary tumour – PAD + immunosuppression 45
Figure 29: mOS histological subtype – PAD ± immunosuppression 46
Figure 30: mOS histological subtype – PAD + immunosuppression 47

Figure 31: mOS LDH – PAD ± immunosuppression 48
Figure 32: mOS LDH – PAD + immunosuppression 48
Figure 33: mOS S100 – PAD ± immunosuppression 49
Figure 34: mOS S100 – PAD + immunosuppression 50
Figure 35: mOS – PAD ± immunosuppression 51
Figure 36: mOS immunosuppressive therapy – PAD ± immunosuppression 52
Figure 37: mOS number of metastatic organs – PAD ± immunosuppression 53
Figure 38: mOS number of metastatic organs – PAD + immunosuppression 53
Figure 39: mOS brain metastases – PAD ± immunosuppression 54
Figure 40: mOS brain metastases – PAD + immunosuppression 55
Figure 41: mOS liver metastases – PAD ± immunosuppression 56
Figure 42: mOS liver metastases – PAD + immunosuppression 56
Figure 43: mOS systemic therapy – PAD ± immunosuppression 57
Figure 45: mOS PD-1 monotherapy – PAD ± immunosuppression 59
Figure 46: mOS PD-1 monotherapy – PAD + immunosuppression 59
Figure 47: mOS PD-1/CTLA-4 – PAD ± immunosuppression 60
Figure 48: mOS PD-1/CTLA-4 – PAD + immunosuppression 61
Figure 49: mOS first-line therapy – PAD ± immunosuppression 62
Figure 50: mOS first-line therapy – PAD + immunosuppression 62
Figure 51: mOS second-line therapy – PAD ± immunosuppression 63
Figure 53: PFS1 – PAD ± immunosuppression 64
Figure 54: PFS1 – PAD + immunosuppression 65
Figure 55: PFS1 PAD ± immunosuppression 66
Figure 56: PFS2 – PAD ± immunosuppression 67
Figure 57: PFS2 – PAD + immunosuppression 67
Figure 58: PFS2 PAD ± immunosuppression 68
Figure 59: PFS1 per first-line therapy – PAD ± immunosuppression 69
Figure 60: PFS1 per first-line therapy – PAD + immunosuppression 69
Figure 61: PFS1 per second-line therapy – PAD ± immunosuppression 70
Figure 62: PFS1 per second-line therapy - PAD + immunosuppression 71
Figure 63: PFS2 per first-line therapy – PAD ± immunosuppression 72
Figure 64: PFS2 per first-line therapy – PAD + immunosuppression 72

Figure 65: PFS2 per second-line therapy – PAD ± immunosuppression 73

List of tables

Table 1: Incidence and mortality of Malignant Melanoma in Germany 2008-2018 2
Table 2: Definition of Primary Tumour (T) 4
Table 3: Definition of Regional Lymph Node (N) 4
Table 4: Definition of Distant Metastasis (M) 4
Table 5: AJCC Clinical Prognostic Stage Groups (cTNM) 5
Table 6: Immune-related adverse events 10
Table 7: Patient characteristics, primary tumour characteristics, prognostic factors 16
Table 8: Patient characteristics. primary tumour characteristics. prognostic factors + immunosuppression 18
Table 9: Pre-existing autoimmune diseases 25
Table 10: First-line systemic therapy 30
Table 11: Second-line systemic therapy 31
Table 12: BOR (RECIST) PAD ± immunosuppression 33
Table 13: BOR (RECIST) PAD + immunosuppression 33
Table 14: BOR (RECIST) first-line PAD ± immunosuppression 34
Table 15: BOR (RECIST) first-line PAD + immunosuppression 35
Table 16: BOR (RECIST) second-line PAD ± immunosuppression 36
Table 17: BOR (RECIST) second-line PAD + immunosuppression 37

1. Introduction

1.1 Malignant Melanoma

Malignant melanomas (MMs) are highly aggressive skin tumours derived from melanocytic cells, demonstrating early lymphogenic and haematogenous spread. Consequently, prompt diagnosis, individual therapy and optimal aftercare are highly important.

Most common subtypes are superficial spreading melanoma (SSM; 66%), nodular melanoma (NM; 16%), lentigo maligna melanoma (LMM; 12%), acral lentiginous melanoma (ALM; 5%). (Rastrelli et al., 2014) Melanocytes appear in all tissues of the body so melanomas can not only arise on the skin but also on mucosal membrane (MuM). Rare representatives of these kinds are the choroidal (CM) or the meningeal melanoma. (Diem et al., 2016a; Matthews et al., 2017)

Development of MM is polyetiological. The most important risk factor is exposure to solar or artificial UV radiation, and even more sunburns, especially at a young age. Additional risk factors include the number of melanocytic naevi as well as familial and genetic predisposition.

Men and women are equally affected by malignant melanoma, but women are diagnosed about 8 years earlier at around 60 years of age. (Ferlay et al., 2013) In 2018 MM accounted for approximately 4.5% of all new tumours in Germany (female 4.7%, male 4.5%). (Friedrich & Kraywinkel, 2018)

MMs are mostly found on the torso (33%) followed by upper (24%) and lower (22%) limbs. Common predilection site in women are the lower limbs and the back in men, nevertheless even body parts with little to no sun exposure can develop skin cancer. (Kraywinkel et al., 2014)

Since introducing dermatological screening in Germany in 2008 case numbers and mortality remain on a stable but high level between 22.000 and 23.000 cases and 3.000 deaths per year (table 1) with an increase of early-stage but without a decrease in late-stage

melanomas. (Friedrich & Kraywinkel, 2018; "Gemeinsamer Bundesausschuss," 2008) It has yet to be determined whether new therapy approaches lead to a decreasing mortality rate and increasing survival rate since their approval in 2016. ("BAnz AT 11.01.2017 B4," 2016; "BAnz AT 13.03.2016 B3," 2016)

As the tumour stage progresses, the prognosis deteriorates rapidly. (Kraywinkel et al., 2014) Compared to the general population, overall survival decreases with each stage. While no differences can be observed in stage I, the 5- and 10-year survival in stage II drops to 90% and 84%, respectively. As progression commences, the relative 5- and 10-year survival in stage III decreases to 77% and 69%. (Gershenwald et al., 2017) According to their growth patterns, different subtypes of melanoma do have different prognosis, with higher mortality in NM and ALM. (Ward *et al.*, 2017)

Table 1: Incidence and mortality of Malignant Melanoma in Germany 2008-2018. Zentrum für Krebsregisterdaten im Robert Koch-Institut: Datenbankabfrage mit Schätzung der Inzidenz, Prävalenz und des Überlebens von Krebs in Deutschland auf Basis der epidemiologischen Landeskrebsregisterdaten (DOI: 10.18444/5.03.01.0005.0016.0001). Mortalitätsdaten bereitgestellt vom Statistischen Bundesamt. www.krebsdaten.de/abfrage, Letzte Aktualisierung: 21.12.2021. Abrufdatum: 26.05.2022

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
1a	20028	20571	20104	21848	22276	22027	22236	22181	22889	23326	22878
1b	24.4	25.1	25.6	27.2	27.7	27.3	27.5	27.2	27.8	28.2	27.6
1c	18.6	18.9	19.3	20.2	20.2	19.9	19.7	19.4	19.7	19.7	19.2
2a	2500	2657	2646	2921	2875	3042	3074	3054	2926	2835	2942
2b	3.0	3.2	3.3	3.6	3.6	3.8	3.8	3.7	3.6	3.4	3.5
2c	2.0	2.1	2.1	2.3	2.2	2.3	2.2	2.1	2.0	1.9	2.0

1 - incidence
2 - mortality
3 - survival rate
a - case numbers
b - raw rate per 100.000 population
c - age-standardised rate (EU rate) in Germany per 100.000 population

1.2 Diagnostic criteria and clinical staging

To determine the patients' prognosis and the follow-up schema, patients need to be classified according to their tumour stage. This is accomplished by standardized models published as "Cancer Staging Manual" by the American Joint Committee on Cancer (AJCC),

most recently in 2017. Depending on the tumour thickness, radiological assessment and sentinel lymph node biopsy may need to follow to excision of the tumour.

The clinicopathological classification of the primary tumour is important, on one hand, to be able to make diagnostic and therapeutic decisions and, on the other hand, to ensure the comparability of clinical studies. The TNM classification of the AJCC is a globally recognised method for staging melanomas. The continuous review and updating of the criteria are essential. Currently there are four stages with different numbers of subgroups. (Gershenwald et al., 2017)

For the current revised eighth version from 2017, more than 46,000 patients in stage I-III and information from around 10,000 patients in stage IV were evaluated and survival outcomes were analysed.

The German S3 guideline on diagnosis, therapy and follow-up of melanoma also uses the latest edition of the AJCC classification as a basis for the histo-pathological findings of malignant melanoma. ("S3 – Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms," 2020)

The most important prognostic factors according to TNM classification are the vertical tumour penetration depth in millimetres defined according to Breslow, as well as the presence of ulceration (T). Furthermore, the presence of lymph nodes (L) and distant metastases (M) are considered. The anatomical localisation of the metastases in the body (outside the lymphatic drainage area) and the level of serum lactate dehydrogenase (LDH) are decisive for the M classification. A specific serum LDH level is defined for each M1 subcategory. (Gershenwald et al., 2017) An elevated LDH level is prognostic for poor survival in the distant metastatic stage. Survival rates with elevated LDH compared to normal LDH levels are reduced by more than half. (Tio et al., 2018)

Table 2: Definition of Primary Tumour (T) (Gershenwald et al., 2017)

	Thickness	Ulceration status
TX	Primary tumour thickness cannot be assessed	
T0	No evidence of primary tumour	
Tis (melanoma in situ)	not applicable	not applicable
T1	≤1.0 mm	unknown/unspecified
T1a	<0.8 mm	-
T1b	<0.8 mm	+
	0.8-1.0 mm	-/+
T2		unknown
T2a	>1.0-2.0 mm	-
T2b		+
T3		unknown
T3a	>2.0-4.0 mm	-
T3b		+
T4		unknown
T4a	>4.0 mm	-
T4b		+

Table 3: Definition of Regional Lymph Node (N) (Gershenwald et al., 2017)

	No. of tumour-involved regional lymph nodes	in transit, satellite, and/or microsatellite metastases
NX	Regional nodes not assessed	-
N0	No regional metastases detected	-
N1		
N1a	1	-
N1b	1	-
N1c	No regional lymph node disease	+
N2		
N2a	2-3	-
N2b	2-3	-
N2c	1 clinically occult or clinically detected	+
N3		
N3a	≥4	-
N3b	≥4	-
N3c	≥2	+

a clinically occult (i.e., detected by SLN biopsy)
b ≥1 of which was clinically detected, or presence of any number of matted nodes
c clinically occult or clinically detected ± presence of any number of matted nodes

Table 4: Definition of Distant Metastasis (M). (Gershenwald et al., 2017)

	Anatomic site	LDH Level
M0	No evidence of distant metastasis	
M1	Evidence of distant metastasis	
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	not recorded/unspecified
M1a(0)		-
M1a(1)		+
M1b	Distant metastasis to lung with or without M1a sites of disease	not recorded/unspecified
M1b(0)		-
M1b(1)		+
M1c		not recorded/unspecified

M1c(0)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	-
M1c(1)		+
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	not recorded/unspecified
M1d(0)		-
M1d(1)		+

Table 5: AJCC Clinical Prognostic Stage Groups (cTNM) (Gershenwald et al., 2017)

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

1.3 Therapy

1.3.1 Immune checkpoint and inhibition

1.3.1.1 Programmed death cell receptor 1 (PD-1)

An important role in the tumour formation and progression is the capability of tumours to stay unrecognized to the human immune system. Immune editing enables tumours to remain hidden from t cells. (Dunn et al., 2002)

In recent years, immunotherapeutic agents that help to unveil cancer cells showed durable antitumour responses and are today considered standard therapy against a variety of cancer entities.

In order to fight cancer effectively, various steps must take place in the tumour microenvironment. (Chen & Mellman, 2013)

1. tumour antigens, preferably many mutated proteins, must be present through cell death of cancer cells (or vaccines in the future). (Boon et al., 2006)
2. in the lymph node, antigen-presenting cells (APCs) such as dendritic cells (DCs) present these tumour antigens on their surface to naïve T lymphocytes (T cells) via MHC I or MHC II molecules. (Fritz & Lenardo, 2019; Mellman & Steinman, 2001)

3. this leads to priming, i.e., proliferation and differentiation of the T lymphocytes (T effector cell) through an activation signal (i.e., Interleukin (IL)-2, IL-12). (Trombetta & Mellman, 2005) If there is no signal, regulator T cells (Treg) cause tumour tolerance. (Jiang et al., 2007)
4. the T effector cell has to be transported to the tumour by the bloodstream.
5. the T effector cell must penetrate the tumour tissue.

To prevent that from happening, tumours have a multitude of defence mechanisms. On the one hand, they can stimulate the migration of T reg cells, which counteracts the function of T effector cells. (Curiel et al., 2004) On the other hand, they can reduce the formation of MHC proteins to present fewer antigens to T effector cells. (Kooi et al., 1996; Wang et al., 1992) Most important for this work, however, is the upregulation of inhibitory surface proteins (e.g., PD-L1 and PD-L2) that downregulate the antitumour activity of T cells (see 7.).

6. tumour antigens on MHC I molecules in the tumour tissue are recognised by the specific T cell receptor (TCR) of the T effector cell. (Chen & Mellman, 2013)
7. The T effector cell eliminates the cancer cell.

One signalling pathway for killing cancer cells is between programmed death cell receptor 1 and its main ligand programmed death cell receptor ligand 1 (PD-1:PD-L1).
PD-1 was first discovered by 2018 Nobel Prize Laureate Tasuku Honjo and his working group. (Ishida et al., 1992; Okazaki & Honjo, 2007; Okazaki et al., 2002)

PD-1 is highly expressed on the surface of peripheral activated $CD8^+$ T cells to regulate response of the immune system, and functions as an inhibitory immune checkpoint. After binding to programmed death receptor ligand 1 or 2 (PD-L1 or PD-L2) intracellular mechanisms prevent cytotoxic T cells to start attacking tumour cells which are likely to overexpress PD-L1 and PD-L2 so that they are no longer identified as hazardous by the immune system. (Waldman et al., 2020)

After binding of PD-L1/2 to PD-1 an enzyme called tyrosine phosphatase (SHP-2) dephosphorylates numerous molecules later in the TCR signalling cascade which leads to decreased T cell activation and production of cytokines and subsequently limits destruction of tissue. (Baumeister et al., 2016; Keir et al., 2008)

PD-L1 is mainly expressed in cytokine-related inflamed tissue of normal cells, which prevents them from causing an autoimmune response, but also on tumour cells. (Baumeister et al., 2016; Ribas & Wolchok, 2018)

Past studies showed reactive upregulation of PD-L1 on tumour cells after T cell recognition, constantly active T cells tend to produce interferon-gamma (IFN-γ) which is then recognized by receptors located on tumour cells and functions as a strong stimulation for production of PD-L1. (Baumeister et al., 2016; Garcia-Diaz et al., 2017)

On the other hand, long term PD-1 activation leads to a complex epigenetic program and eventually to T cell exhaustion with dampened or even loss of defence mechanisms to fight tumour cells and results in growth of cancer. (Blank et al., 2019; Pardoll, 2012; Philip et al., 2017; Ribas, 2015; Sen et al., 2016)

Activation of T cells occur when (tumour) antigens are recognized by their specific T cell receptor (TCR) after being presented on major histocompatibility complexes (MHC) by antigen presenting cells (APCs) or tumour cells. (Fritz & Lenardo, 2019)

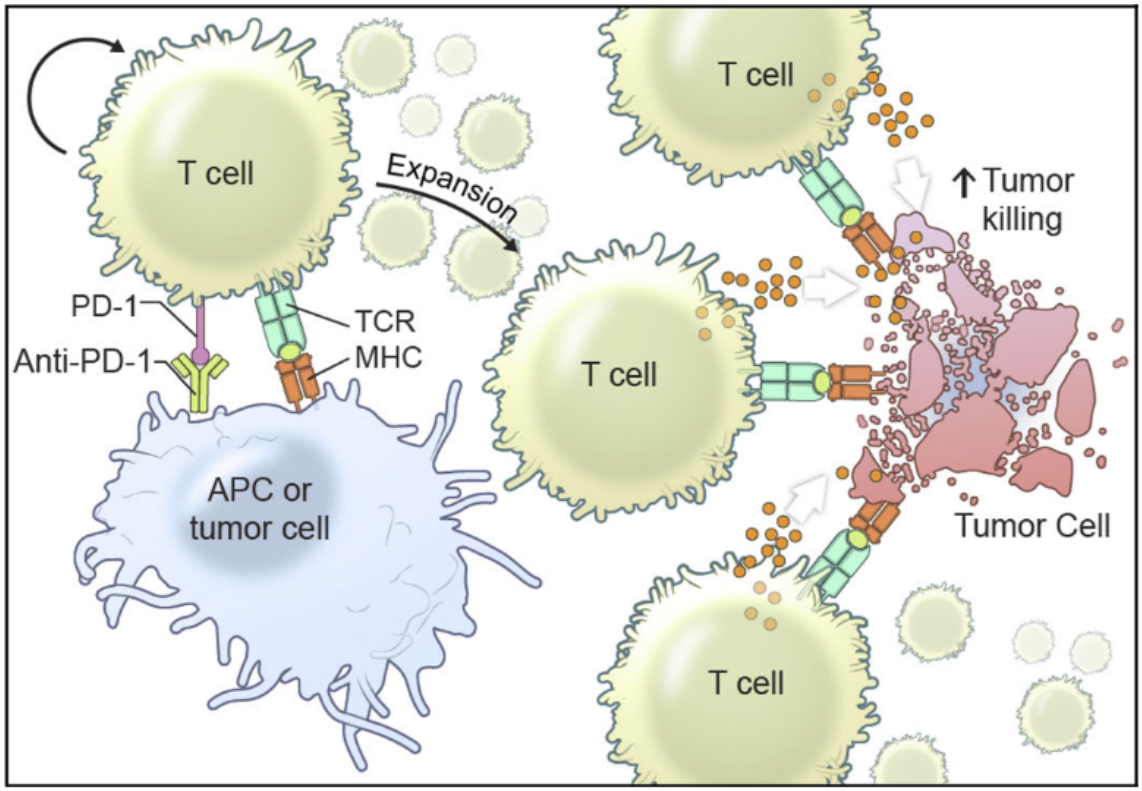

Figure 1: T cell activation and mechanism of PD-1 axis inhibition and the role of anti-PD-1-antibodies [18]

1.3.1.2 Immune Checkpoint Inhibitors (ICIs)

After decades of therapy with conventional chemotherapy with severe side effects and limited efficacy, a new group of promising therapeutics with better safety profiles emerged: immune checkpoint inhibitors. (Johnpulle et al., 2016; Reck et al., 2016)

About half of all patients with metastatic cancers could probably receive ICI therapy. (Haslam & Prasad, 2019)

Pembrolizumab and Nivolumab are humanized antibodies binding to inhibitory programmed death cell receptor 1.

After proving effectiveness and improved survival in various studies both Pembrolizumab and Nivolumab gained approval in Germany in 2016. ("BAnz AT 04.02.2016 B5," 2016; "BAnz AT 13.03.2016 B3," 2016; Eggermont et al., 2018; Hamid et al., 2013; Robert et al., 2015; Topalian et al., 2014; J. Weber et al., 2017; Wolchok et al., 2013)

According to the German S3-guideline malignant melanomas in clinical stage groups III A-D and IV without BRAF-mutation shall be treated with anti-PD-1-antibodies.("S3 – Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms," 2020). Observed objective response rates for malignant melanoma varied between approximately 30–40%, roughly three times higher than with Ipilimumab, another immunotherapy (CTLA-4 inhibitor). (Hamid et al., 2013; Robert et al., 2015; Topalian et al., 2012; Zhao et al., 2020). PD-1 inhibitors also showed efficacy in PD-L1 negative tumours. (Eggermont et al., 2018)

Pembrolizumab is authorized for therapy in following entities: Melanoma, non-small cell lung carcinoma (NSCLC), Hodgkin-Lymphoma, urothelial carcinoma, head and neck squamous cell carcinoma, (HNSCC), renal cell carcinoma (RCC), colorectal cancer (CRC), oesophageal carcinoma, triple-negative breast cancer (TNBC), endometrial carcinoma (EC), cervical carcinoma.("Fachinformation KEYTRUDA®," 2022)

Nivolumab is used to treat patients with NSCLC, advanced renal cell carcinoma, classical HNSCC, urothelial cancer, malignant pleural mesothelioma, colon or rectum carcinoma with microsatellite or mismatch repair deficient (dMMR), squamous oesophageal cancer, oesophageal cancer and gastro-oesophageal junction cancer after previous chemotherapy, radiotherapy and surgery, gastric (stomach), gastro-oesophageal junction or oesophageal adenocarcinoma. (EMA, 2018)

After binding of Anti-PD-1-antibody, tumour cells are no longer capable of deactivating cytotoxic t-cells and therefore the immune system can fight the tumour on its own. (Brahmer et al., 2012; Ribas, 2012; Topalian et al., 2012)

Therapy regimen requires Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks over the course of 30 minutes. ("Fachinformation KEYTRUDA®," 2022)

1.4 Immune related adverse events (irAEs)

Correct identification and management of adverse events are crucial to the evaluation of any given therapy.

The hyper-activation of immune system by ICI can have autoimmune repercussions that mostly involve the endocrine system, skin, liver, kidneys, and the gastrointestinal tract. (Eigentler et al., 2016; Hofmann et al., 2016; Zimmer et al., 2016)

Reported irAEs are experienced in approximately 79% of all patients without pre-existing auto-immune disease (PAD). (Hamid et al., 2013; Topalian et al., 2012; Tully et al., 2021) A study that observed patients over 4 years found irAEs after PD-1 monotherapy in 86% of cases (grade 3: 17%; grade 4: 5%) and after combined immunotherapy in 96% of cases (grade 3: 48%; grade 4: 11%). (Hodi et al., 2018; Postow et al., 2015)

Retrospective studies showed similar overall survival (OS) in patients with and without PAD (pre-existing autoimmune disease). (Danlos et al., 2018; Eggermont et al., 2020; Gutzmer et al., 2017; J. S. Weber et al., 2017)

In the past, numerous studies reported safe administration and favourable outcomes in PAD patients. Frequency of PAD flare-ups was seen in 23.0%–47.0%, frequency of irAEs in general between 29.0%–44.0% and a frequency of severe irAEs (CTCAE grades 3+4) in 10.0%–44.0% of cases. (Danlos et al., 2018; Gutzmer et al., 2017; Leonardi et al., 2018; Menzies et al., 2017)

Standardized evaluation of irAEs is achieved using National Cancer Institutes “Common Terminology Criteria for Adverse Events (CTCAE)”. CTCAEs are regularly improved and adapted. Current version is 5.0. published in November 2017. ("Common Terminology Criteria for Adverse Events (CTCAE)," 2017)

There are five grades to differentiate from: grade 1 (asymptomatic without the need of any intervention) to grade 5 (death related to adverse events). (Table 6)

Table 6: Immune-related adverse events. National Health Institute, Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Grade	**Symptoms**	**Consequences**
1 – mild	asymptomatic /mild	clinical / diagnostic observations only; intervention not indicated

2 – moderate		limiting age-appropriate instrumental ADL
3 – severe	hospitalization indicated	limiting self-care ADL
4 – life-threatening		urgent intervention indicated
5 - death related to irAE		

Therapy with ICIs can cause multiple immune related adverse events (irAEs). Depending on the affected organ system treatment should be withheld or even discontinued if (recurrent) grade 3 or grade 4 irAEs are diagnosed. (Haanen et al., 2022). Although patients may benefit from rechallenge of ICI therapy, it shall only be done after clearance by a multidisciplinary team and after a rigorous case-by-case assessment due to a higher risk of recurrence of high grade irAEs. (Haanen et al., 2020)

Treatment involves (high dose) corticosteroids (CS) in early stages and can be extended to biologic disease-modifying anti-rheumatic drugs (bDMARDs) such as TNF α inhibitors or various anti interleukin receptor inhibitors if side effects are uncontrollable under CS. (Haanen et al., 2022)

1.4.1 Immune checkpoint inhibition in patients with pre-existing autoimmune disease with or without active immunosuppression

Due to limited data on potential exacerbation of autoimmune diseases, patients with pre-existing autoimmune disease or active immunosuppression were generally excluded from clinical studies (Calabrese & Velcheti, 2017; Eggermont et al., 2018; Ribas et al., 2015; Robert et al., 2015; Schachter et al., 2017)

With continuous exclusion of PAD-patients and expanding numbers of treatment indications there is also an increasing population excluded from the potential benefits of ICIs. One example are the 13.5% of American patients with lung cancer with an autoimmune disease who, based on the clinical trials inclusion and exclusion criteria, could not receive PD-1 treatment. (Khan et al., 2016) Other than that, about 5% of the population are suffering from PADs. (Tobón et al., 2012)

Several retrospective studies have shown that patients with underlying autoimmune disease could profit from ICI therapy. (Gutzmer et al., 2017; Johnson et al., 2016; Menzies et al., 2017) Interestingly, response rate was somehow higher in patients with PAD compared to those without and highest in patients with active PAD. (Cortellini et al., 2019)

Patients with PAD experience immune-related side effects more often than patients without PAD but, at the same time, there is no statistical significance in frequency of grade 3-4 irAEs between the two groups. (Cortellini et al., 2019)

A flare-up of the existing autoimmune disease occurs in up to 80% of cases. (Hoa et al., 2021) The occurrence of a new PAD happens in 25% of cases and both in 9% of cases. (Abdel-Wahab et al., 2018; Placais et al., 2022) In comparison, in patients without a described autoimmune disease, irAEs can be seen in 82-95% of cases and grade 3-4 irAEs in 16-55% of cases. (Larkin et al., 2015)

Based on the previous reports, the rate of severe irAEs does not differ from that of patients without PAD.

1.5 Objective and research question of the dissertation

This thesis focuses on the question of the extent to which patients with PAD and active immunosuppression benefit from ICI therapy.

The following main questions are addressed:

1. What proportion of patients achieved a clinical response (CR, PR, SD) to PD-1-based immunotherapy?
2. Are there different outcomes when comparing mono and combined immunotherapy?
3. What irAEs occurred during therapy, how frequently did they arise, and do their frequency and severity differ from patients without PAD

2. Material and methods

2.1 Data collection and assessment

Collected data used in this retrospective study originate from patient's database of University Hospital Tübingen (SAP ISH GUI for Windows, Copyright 1993-2004) and the central malignant melanoma registry. We received ethics committee approval for this study (project number 640/2022BO2).

Patients who received treatment at the University Hospital Tübingen in the period from January 2015 to December 2021 were included. All patients listed had a diagnosis of AJCC v8 stage IV in the above-mentioned observation period.

Patients were treated with anti-PD-1 based immunotherapy (pembrolizumab or nivolumab monotherapy or nivolumab and ipilimumab combined immunotherapy). Pre-existing autoimmune diseases (PAD) and active immunosuppressive therapy and changes in therapy regimens were also recorded.

All information out of the patient's database were compiled in SPSS using the following criteria: sex and age, tumour-specific information such as the localisation of the primary tumour, the histological classification of the subtypes, the TNM stage at initial diagnosis, and the time of stage IV diagnosis.

BRAF, NRAS and cKIT mutation status of the primary tumour are also documented. Start of therapy, time of best response termination of systemic applications were recorded.

The localisation of organ metastases including radiological evaluation (CT, PET-CT, MRI) since progression to stage IV are described. The standard criteria for evaluating treatment response in solid tumours are the RECIST criteria from the year 2000. The assessment of treatment response according to RECIST was based on the following categories:

The overall collective was examined according to response to PD-1 therapy including therapy from the time of metastasis. Best overall response was assessed according to RECIST 1.1 criteria. (Eisenhauer et al., 2009; Schwartz et al., 2016)

- Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), progression free survival (PFS). Data include date of follow ups as well as cause of death if death occurred while collecting data.

2.2 Patient collective and classification of variables

Analysis was performed on patients with stage IV melanoma. Focus of the analysis was in patients with metastatic melanoma who received immunotherapy as first-line or second-line treatment. Unless otherwise stated, all analyses refer to patients with diagnosed, pre-existing autoimmune disease.

Some of the patients also received surgical or radiotherapy. However, these local therapies were not included in the analysis.

The following variables were included in the analysis: sex, age, location and subtype of primary melanoma, stage at initial diagnosis, clinical stage group (TNM), number of organs with metastases, presence of brain and liver metastases, BRAF mutation status, LDH and S100 levels at initial diagnosis, type of PAD as well as active immunosuppressive treatment of the underlying PAD.

Date of last contact or death was also documented. Follow-up and overall survival were defined as time between dates of diagnosis of stage IV disease and last contact or death from any cause. Progression Free survival 1 (PFS1) is the time between date of stage IV diagnosis and date of 1st disease progression.
Progression Free survival 2 (PFS2) is the time from the start of first-line therapy to progression under second-line.

2.3 Statistical Analysis

The entire patient population was evaluated using descriptive statistics frequency tables, cross-tabulations, and bar charts. For certain variables, the mean, median and standard deviation were calculated. Kaplan-Meier curves were used to determine survival curves and median survival time using log-rank tests for statistical significance testing.

Differences with a p-value of ≤ 0.05 are to be rated as significant. The 1-, 2- and 3-year survival rates were calculated with a confidence interval of 95%. Survival probabilities were calculated on the based on the date of stage IV diagnosis.

Statistical analysis was performed by using IBM SPSS Statistics Version 24.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Description of the patient collective

We included 939 patients diagnosed with stage IV melanoma between January 2015 and December 2021. 89 of these patients (9.5%) had PAD and are further examined in this study. 850 patients did not have a documented PAD. Median follow up was 29 months (95% CI: 22.7-34.9).

Table 7: Patient characteristics, primary tumour characteristics, prognostic factors

Patient characteristics	**PAD**	**Survival analysis**		
		mOS (months)	**95% CI**	**p-value**
Age distribution				0.433
< 60 y	31 (34.8%)	0	(0-0)	
60-75 y	28 (31.5%)	30.5	(10.7-50.4)	
> 75 y	30 (33.7%)	26.2	(22.3-53.8)	
Sex				0.877
female	46 (51.7%)	38	(13.6-62.4)	
male	43 (48.3%)	30.5	(8.1-52.9)	
PAD				
Rheumatoid Arthritis	24 (14.6%)			
Inflammatory Bowel Disease*	20 (12.2%)			
Psoriasis vulgaris	13 (7.9%)			
Polymyalgia rheumatica	6 (3.7%)			
Collagenosis**	5 (3.0%)			
Sarcoidosis	5 (3.0%)			
Hashimoto-Thyroiditis	3 (1.8%)			
Ankylosing spondylitis	3 (1.8%)			
Multiple Sclerosis	2 (1.2%)			
Diabetes mellitus I	2 (1.2%)			
Vitiligo	2 (1.2%)			
Grave's disease	2 (1.2%)			
Familial Mediterranean Fever	1 (0.6%)			
Antihaemolytic Anaemia	1 (0.6%)			
Morbus Ormond	1 (0.6%)			
Bullous Pemphigoid	1 (0.6%)			
Lab				
LDH				0.150
elevated	41 (46.0%)	22.9	(8.3-37.5)	
normal	43 (48.3%)	43.4	(24.1-62.8)	
S100				0.138
elevated	42 (47.1%)	25.2	(0.0-54.7)	
normal	42 (47.1%)	43.4	(16.8-70)	
Histological subtype				0.252
SSM	24 (27.9%)			

NM	20 (23.3%)	21.1	(0-43.5)	
unknown	4 (4.5%)			
other	40 (44.9%)	38.0	(20.3-52.6)	
Mutation				
BRAF	33 (37.5%)	25.2	(0.0-53.6)	0.848
KIT	2 (2.3%)			
NRAS	20 (22.7%)			
Systemic therapy				
ST	78 (87.6%)	38.4	(19.2-57.7)	0.084
PD-1 mono	26 (29.2%)	43.4	(11.3-75.5)	0.314
PD-1+CTLA4	43 (48.3%)	38	(19.8-56.3)	0.381
TT	31 (34.8%)			
CT	5 (5.6%)			
Immunosuppression				0.232
no	48 (53.9%)	22.9	(0.0-55.1)	
yes	41 (46.1%)	38.4	(25.5-51.3)	
Steroids	29 (34.9%)			
MTX	13 (15.7%)			
5-ASA (Mesalamine/Sulfasalazine)	9 (10.8%)			
Vedolizumab	3 (3.6%)			
Hydroxychloroquine	2 (2.4%)			
Adalimumab	2 (2.4%)			
Azathioprine	1 (1.2%)			
Tocilizumab	1 (1.2%)			
Number of immunosuppressants				
0	48 (54.5%)			
1	26 (29.5%)			
2	11 (12.5%)			
3	4 (4.5%)			
Number of metastatic organs				0.565
1-3	72 (83.1%)	38	(21.9-54.2)	
>3	17 (16.9%)	25.2	(2.4-47.9)	
Brain metastases				0.727
yes	33 (34.8%)	47.5	(1.6-93.3)	
no	56 (65.2%)	38	(23.2-52.9)	
Liver metastases				0.970
yes	32 (34.8%)	38.4	(15.8-61.0)	
no	57 (65.2%)	30.5	(7.5-53.5)	
Stage at first diagnosis				0.639
I	16 (18.0%)	0	(0-0)	
II	19 (21.3%)	30.5	(13.0-48.1)	
III	29 (32.6%)	10.5	(0-50.5)	
IV	18 (20.2%)	38.4	(17.8-59.0)	
Localisation of primary tumour				0.204
Head/Neck	19 (0.0%)	38.4	(16.4-60.5)	
Torso	23 (0.0%)	30.5	(0.7-60.4)	
Extremities	32 (0.0%)	10.5	(4.6-16.4)	

Ulcerative colitis. Crohn's disease

** SLE. Sjögren's syndrome. Dermatomyositis

Table 8: Patient characteristics. primary tumour characteristics. prognostic factors + immunosuppression

Patient characteristics Primary tumor characteristics Prognostic factors	PAD + immuno-suppression n=41	Survival analysis		
		mOS (months)	95% CI	p-value
Age distribution				0.267
< 60 y	10 (24.4%)	-		
60-75 y	14 (34.1%)	38.0	(9.4-66.7)	
> 75 y	17 (41.5%)	38.4	(15.4-61.4)	
Sex				0.315
female	19 (46.3%)	30.5	(9.6-51.5)	
male	22 (53.7%)	28.4	(37.5-39.3)	
Stage at first diagnosis	39 (0.0%)			0.155
I	9 (23.1%)	-	-	
II	10 (25.6%)	30.5	(14.6-46.4)	
III	14 (35.9%)	-	-	
IV	6 (15.4%)	36.8	(0.0-33.9)	
Mutation				
BRAF	19 (0.0%)			0.862
no		38.0	(23.0-53.0)	
yes		-	-	
KIT	1 (0.0%)			
no				
yes				
NRAS	7 (0.0%)			
Localisation of primary tumour	34 (0.0%)			0.967
Head/Neck	9 (26.5%)	38.4	(21.9-55.0)	
Torso	10 (29.4%)	30.5	(8.5-52.5)	
Extremities	15 (44.1%)	-	-	
Histological subtype				0.321
SSM	15 (36.6%)	-	-	
NM	8 (19.5%)	30.5	(7.8-53.2)	
OM	7 (17.1%)	-	-	
other	7 (17.1%)	38.4	(19.5-57.4)	
Laboratory parameters				
LDH				0.920
elevated	21 (52.5%)	21.2	(0.0-79.9)	
normal	19 (47.5%)	38.4	(21.5-54.6)	
S100				0.989
elevated	19 (46.3%)	38.4	(7.6-69.2)	
normal	22 (53.7%)	43.4	(21.7-65.1)	
Number of metastatic organs				0.765
1-3	31 (75.6%)	38.4	(27.0-49.9)	
>3	10 (24.4%)	-	-	
Brain metastases				0.560
yes	14 (34.1%)	-	-	
no	27 (65.9%)	38.4	(24.6-52.2)	
Liver metastases				0.463
yes	15 (36.6%)	-	-	

no	26 (63.4%)	38.0	(11.2-64.9)	
PAD				
Rheumatoid Arthritis	17 (41.5%)			
Inflammatory Bowel Disease*	11 (26.8%)			
Psoriasis vulgaris	2 (4.9%)			
Polymyalgia rheumatica	5 (12.2%)			
Collagenosis**	3 (7.3%)			
Sarcoidosis	1 (2.4%)			
Hashimoto-Thyroiditis	0 (0.0%)			
Morbus Bechterew	0 (0.0%)			
Multiple Sclerosis	0 (0.0%)			
Diabetes mellitus I	0 (0.0%)			
Vitiligo	0 (0.0%)			
Grave's disease	0 (0.0%)			
Fimilial Mediteranean Fever	1 (2.4%)			
Autohemolytic Anemia	0 (0.0%)			
Morbus Ormond	1 (2.4%)			
Bullous Pemphigoid	0 (0.0%)			
Systemic therapy				
ever ST	37 (90.2%)	38.4	(24.7-52.1)	0.460
ever PD-1 mono	13 (31.7%)	38.4	(6.1-70.8)	0.847
ever PD-1+CTLA4	19 (46.3%)	38.0	(21.4-54.7)	0.870
ever TT	18 (43.9%)			
ever CT	2 (4.9%)			
Immunosuppression				
no	0 (0.0%)			
yes	41 (100.0%)	38.4	(25.5-51.3)	
Corticosteroids	29 (70.7%)			
MTX	13 (31.7%)			
5-ASA (Mesalamine/Sulfasalazine)	9 (22.0%)			
Vedolizumab	3 (7.3%)			
Hydroxychloroquin	2 (4.9%)			
Adalimumab	2 (4.9%)			
Azathioprin	1 (2.4%)			
Tocilizumab	1 (2.4%)			
Number of Immunosuppressants				
0				
1	26 (63.4%)			
2	11 (26.8%)			
3	4 (9.8%)			

* Colitis ulcerosa, Crohn's disease

** SLE, Sjögren's syndrome, Dermatomyositis

3.2 Analysis parameters

3.2.1 Patient characteristics

3.2.1.1 Age and Sex

Overall patient collective ($n_{\pm}$=89) median age at stage IV diagnosis was 66.0 years (IQR 57.0-78.0). Youngest patient was 31 and oldest was 90 years old. Standard deviation was 13.11 years. Median age for patients with active immunosuppression (n_{+}= 41) was 72 years (IQR 59.5-79.5), youngest patient was 31 and oldest 89 years old. (Figure 2)
Majority of patients were female (52.3%, $n_{\pm}$=46) female and 47.7% ($n_{\pm}$=43) were male. There were more men receiving active immunosuppression (n_{+}=22 / 53,7%) than women (n_{+}=19 / 46,3%) (Figure 3)

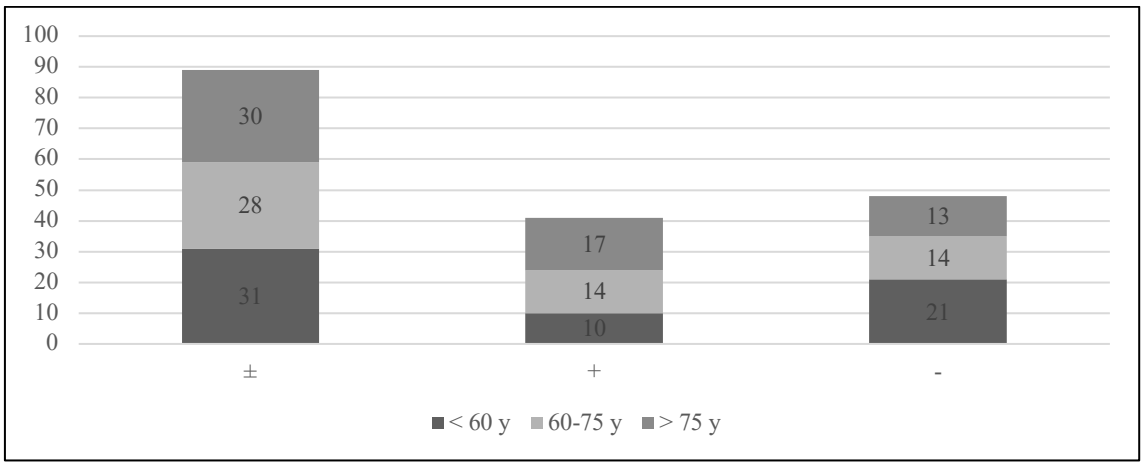

Figure 2: Age groups

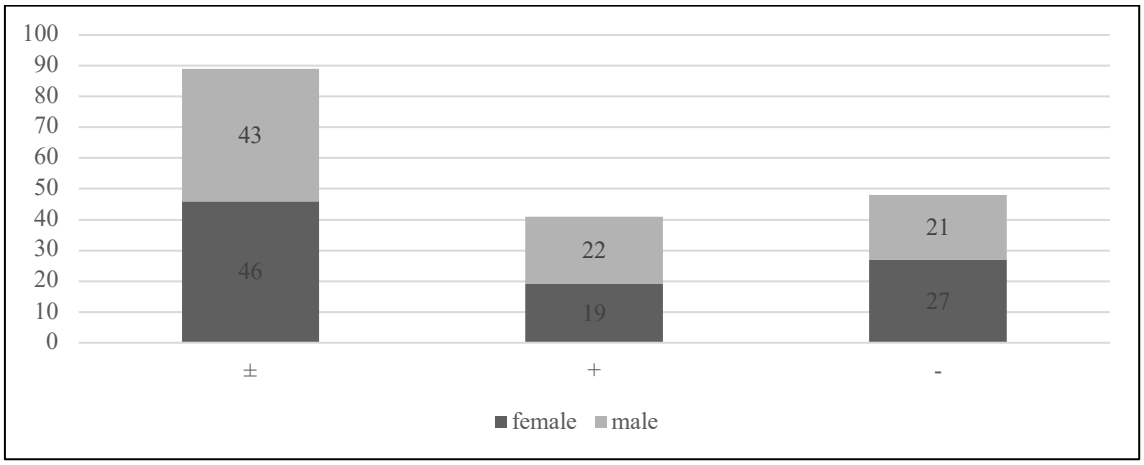

Figure 3: Sex

3.2.2 Primary tumour characteristics

3.2.2.1 Stage at initial diagnosis

The majority (32.6%, $n_{\pm}$=29) of the patient was first diagnosed with stage III melanoma. Fewer melanomas (21.3%, $n_{\pm}$=19) were detected in the initial stage II. In 18.0% of patients ($n_{\pm}$=16), melanoma was diagnosed in stage I, 20.2%, ($n_{\pm}$=18) was already in stage IV at the time of diagnosis and 7.9% ($n_{\pm}$=7) had no information on the stage at initial diagnosis. The majority of patients receiving active immunosuppression were initially diagnosed in stage III (n_{+}=14 / 34.14%), then stage II (n_{+}=10 / 24.4%) and I (n_{+}=9 / 22.0%). Fewest patients were directly diagnosed in stage IV (n_{+}=6 / 14.6%). (Figure 4)

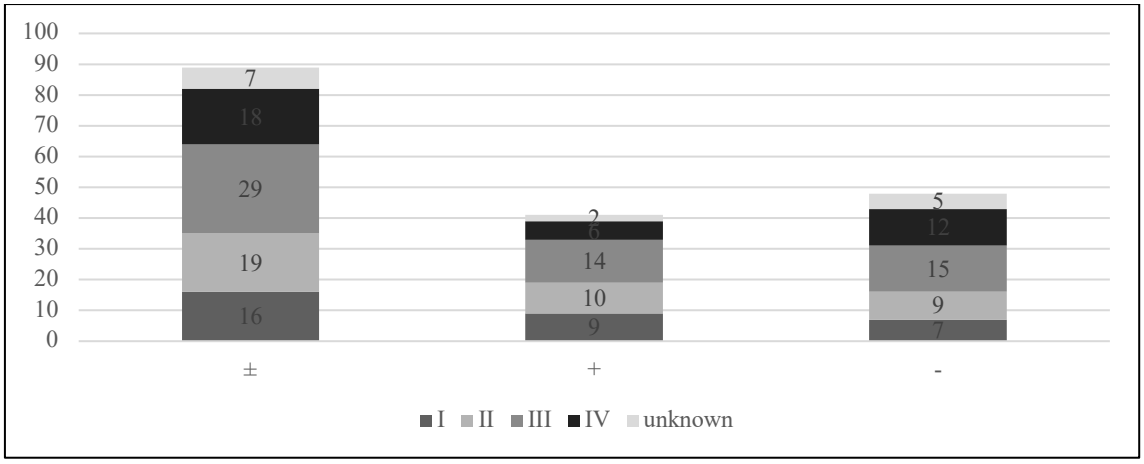

Figure 4: Stage at first diagnosis

3.2.2.2 Mutation status

In 6.0% ($n_{\pm}$=5) of the cases, information about any mutation was missing and these patients had to be further excluded from the analysis. In 6.0% ($n_{\pm}$=5) of the study population, BRAF and NRAS mutation status was missing, and in 52.8% (n=42) regarding cKIT mutation. One patient (1.1%) had both BRAF and cKIT mutation and another patient (1.1%) had BRAF and NRAS mutation.

In 39.3%, ($n_{\pm}$=33/84) of the patients had a BRAF mutation, 23.8% ($n_{\pm}$=20/84) were NRAS mutated and in 76.2% (n=64/84), an NRAS mutation could be excluded.

Two patients had a cKIT-mutated (4.3%, $n_{\pm}$=2/47) and 85.1% ($n_{\pm}$=40/47) were KIT wild-type. BRAF mutation in patients with active immunosuppression occurred in 46.3% (n_{+}=19). (Figure 5)

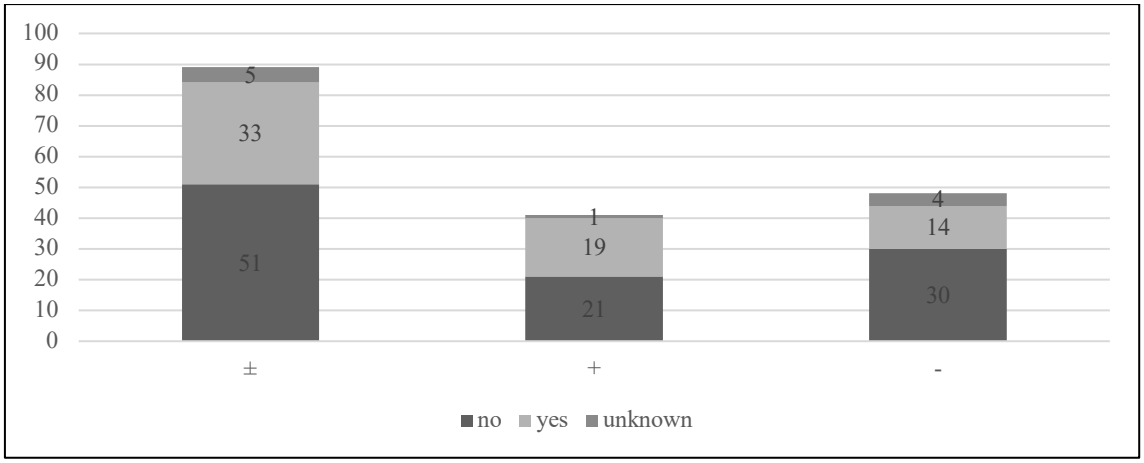

Figure 5: BRAF mutation status

3.2.2.3 Localisation of primary tumour

The localization of the primary tumour was unknown in 19.1% ($n_{\pm}$=17) and had therefore to be excluded from the study. In majority, primary tumour was described on the extremities (44.4%, $n_{\pm}$=32). Further locations included the torso (31.9%, $n_{\pm}$=32) and head and neck (23.6%, $n_{\pm}$=17). Numbers differed in patients with active immunosuppression. Primary tumor was found on the head/neck in 22.0% (n_{+}=9), on the torso in 24.4% (n_{+}=10) and on the extremities in 36.6% of the cases (n_{+}=15) (Figure 6)

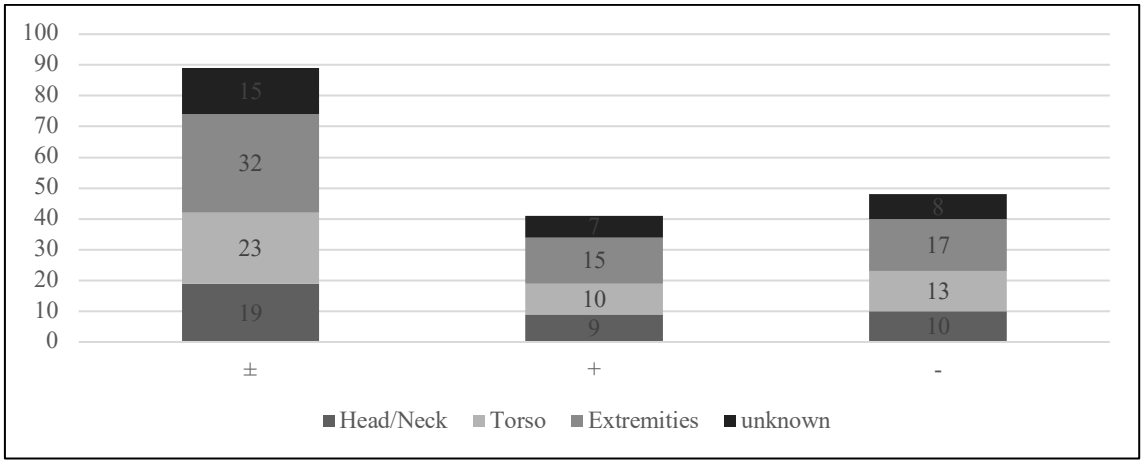

Figure 6: Localisation of primary tumour

3.2.2.4 Histological subtypes

In this analysis, most frequent histological subtype was SSM, the second most frequent type was NM. SSM was diagnosed in 27.0% of patients ($n_{\pm}$=24), NM in 21.3% ($n_{\pm}$=11), LMM in 6.7% ($n_{\pm}$=6), ALM in 4.5% of the cases ($n_{\pm}$=4). Other histological subtypes (nevus associated, mucosal, choroidal were observed in 20 patients overall – 22.5%)). In 27.0% ($n_{\pm}$=24) of melanoma patients, histological subtype was not specified and therefore could not be included in any category. In patients under active immunosuppression, SSM and NM were also most frequent (n_{+}=15 / 36.6% and n_{+}=8 / 19.5%). (Figure 7)

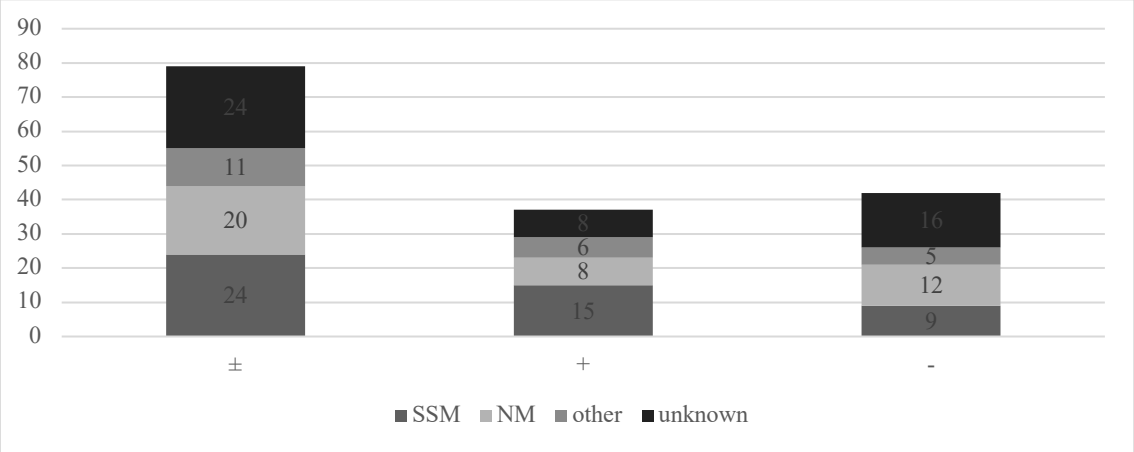

Figure 7: Histological subtypes

3.2.3 Laboratory parameters

3.2.3.1 LDH

In 46% of the cases ($n_{\pm}$=41) LDH levels were elevated, while in 48.3% ($n_{\pm}$=43) a normal LDH level was detected in the blood. When assessing LDH, 5.7% ($n_{\pm}$=5) of patients had to be excluded due to lack of information. Patients with active immunosuppression had elevated LDH levels in 51.2% (n_{+}=21) and normal LDH levels in 46,3% (n_{+}=19) (Figure 8)

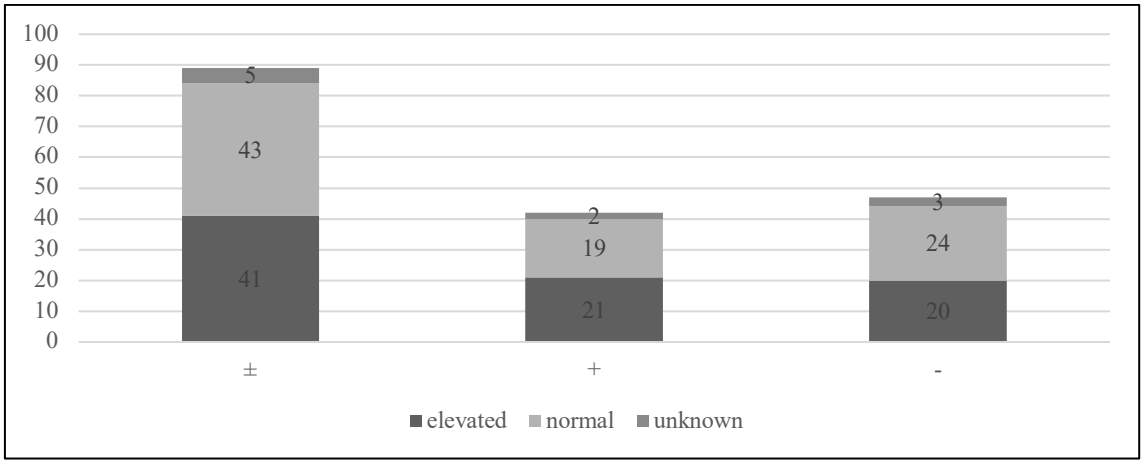

Figure 8: LDH

3.2.3.2 S100

Elevated and normal S100 levels were seen in the same proportion of patients - 47.1% ($n_{\pm}$=42). S100 level was unknown in 5.7% ($n_{\pm}$=5) of patients and these were therefore excluded. Patients with active immunosuppression had elevated S100 levels in 46.3% (n_{+}=19) and normal S100 levels in 53.7% (n_{+}=22) (Figure 9)

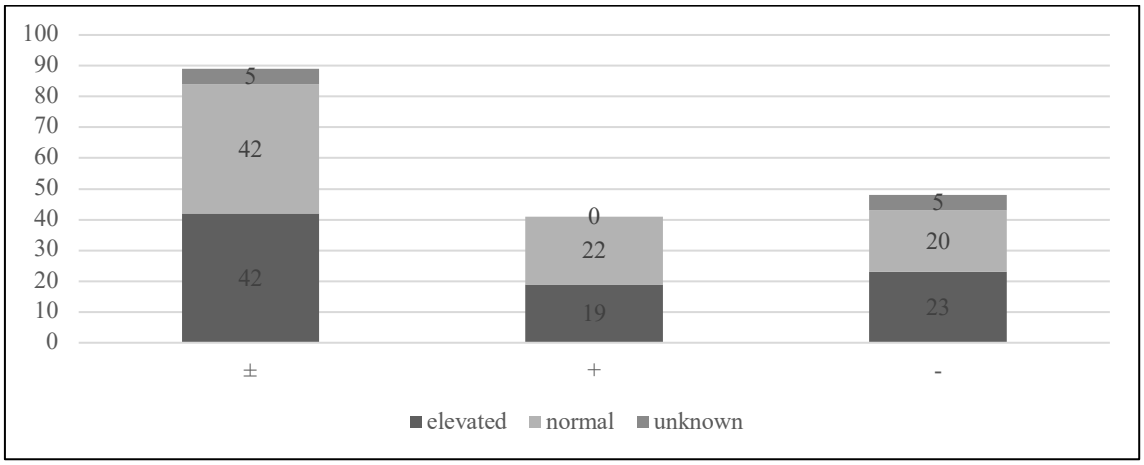

Figure 9: S100

3.2.3.3 Pre-existing autoimmune diseases (PAD)

Rheumatologic PADs were present in 48.3% of patients ($n_{\pm}$=43: rheumatoid arthritis ($n_{\pm}$=24); polymyalgia rheumatica ($n_{\pm}$=6); sarcoidosis ($n_{\pm}$=5) ankylosing spondylitis

($n_{\pm}$=3); dermatomyositis; limited cutaneous systemic scleroderma, sharp syndrome; Sjogren's syndrome each ($n_{\pm}$=1)).

Patients with gastrointestinal PAD were represented in 22.5% of cases ($n_{\pm}$=20: ulcerative colitis ($n_{\pm}$=11); Crohn's disease ($n_{\pm}$=9)). Dermatologic PAD was seen in 16.9% ($n_{\pm}$=15: psoriasis vulgaris ($n_{\pm}$=15), vitiligo ($n_{\pm}$=2) and bullous pemphigoid ($n_{\pm}$=1)). Patients with endocrine PAD came next with 6.7 % ($n_{\pm}$=6: Hashimoto thyroiditis ($n_{\pm}$=3)); diabetes mellitus type I ($n_{\pm}$=2); Graves' disease ($n_{\pm}$=2)). Respectively 2.2% of the study population had either hematologic ($n_{\pm}$=2: familial mediterranean fever ($n_{\pm}$=1); autoimmune haemolytic anaemia (each $n_{\pm}$=1) or neurologic (multiple sclerosis, $n_{\pm}$=2) PADs. 1.1% were categorized as other (Morbus Ormond ($n_{\pm}$=1)). (Table 9 and Figure 10)

Two patients (2.3%) were diagnosed with two different PADs. One patient had Rheumatoid arthritis and Psoriasis vulgaris and the other one ulcerative colitis and Grave's disease.

Table 9: Pre-existing autoimmune diseases

Rheumatologic	**43**	48.3%
Rheumatoid arthritis	24	
Polymyalgia rheumatica	6	
Sarcoidosis	5	
Ankylosing spondylitis	3	
Dermatomyositis	1	
Limited cutaneous systemic scleroderma	1	
Lupus erythematosus	1	
Sharp syndrome	1	
Sjogren's syndrome	1	
Gastrointestinal	**20**	22.5%
Ulcerative colitis	11	
Crohn's disease	9	
Dermatologic	**15**	16.9%
Psoriasis vulgaris	12	
Vitiligo	2	
Bullous pemphigoid	1	
Endocrine	**6**	6.7%
Hashimoto thyroiditis	3	
Diabetes mellitus Type I	2	
Graves' disease	2	
Haematologic	**2**	2.2%
Autoimmune haemolytic anaemia	1	

Familial Mediterranean Fever	1	
Neurologic	**2**	2.2%
Multiple sclerosis	2	
other	**1**	1.1%
Morbus Ormond	1	
Total	**89**	**100.00%**

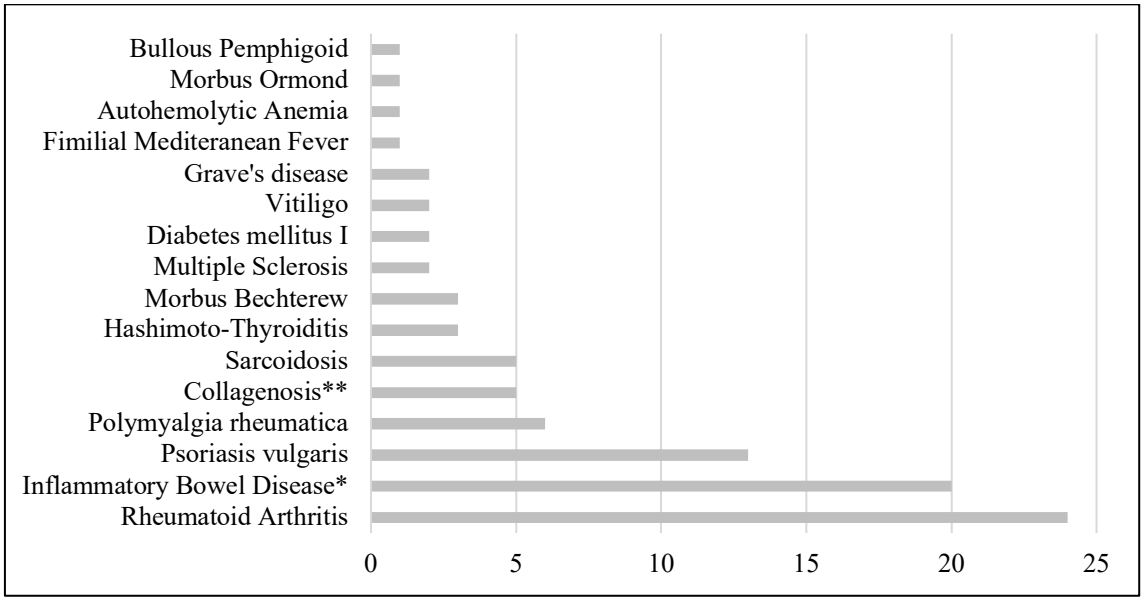

Figure 10: Autoimmune diseases

47 (53.4%) patients did not receive any immunosuppressive agents to treat their PAD, 26 patients received one (29.5%), 11 patients received two (12.5%) and 4 patients received three (4.5%). More than one immunosuppressant was necessary mostly when patients had IBD or rheumatoid arthritis. (Figure 10)

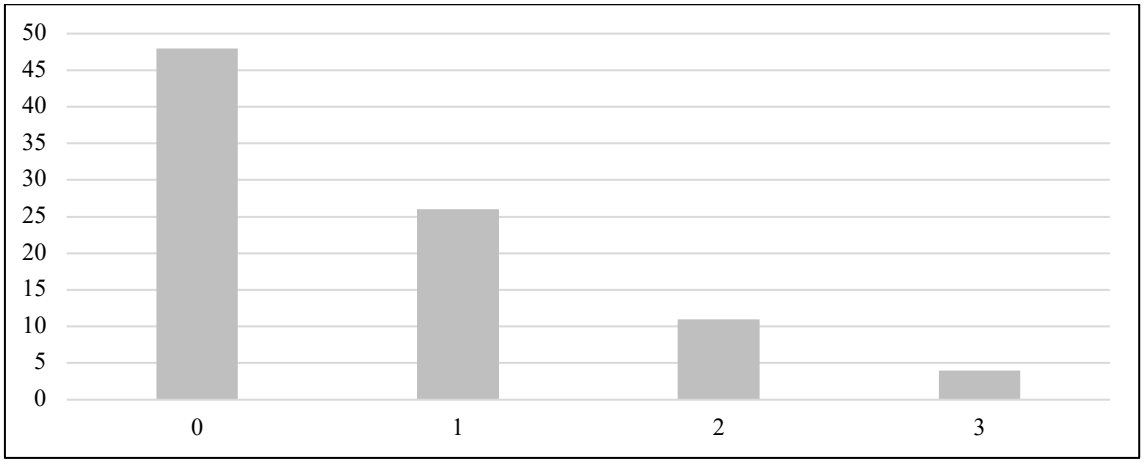

Figure 11: Number of immunosuppressive agents

Steroids were used most frequently ($n_{\pm}$=29; 48.3%), followed by MTX ($n_{\pm}$=13; 21.7%) and 5-ASA (Mesalamine/Sulfasalazine) ($n_{\pm}$=9; 15.0%). Vedolizumab was used in 5.0% of cases ($n_{\pm}$=3), Hydroxychloroquine and Adalimumab in 3.3% each ($n_{\pm}$=2) and Azathioprine and Tocilizumab in 1.7% respectively ($n_{\pm}$=1). (Figure 11)

When receiving multiple immunosuppressants, steroids were involved in 15 of 16 cases.

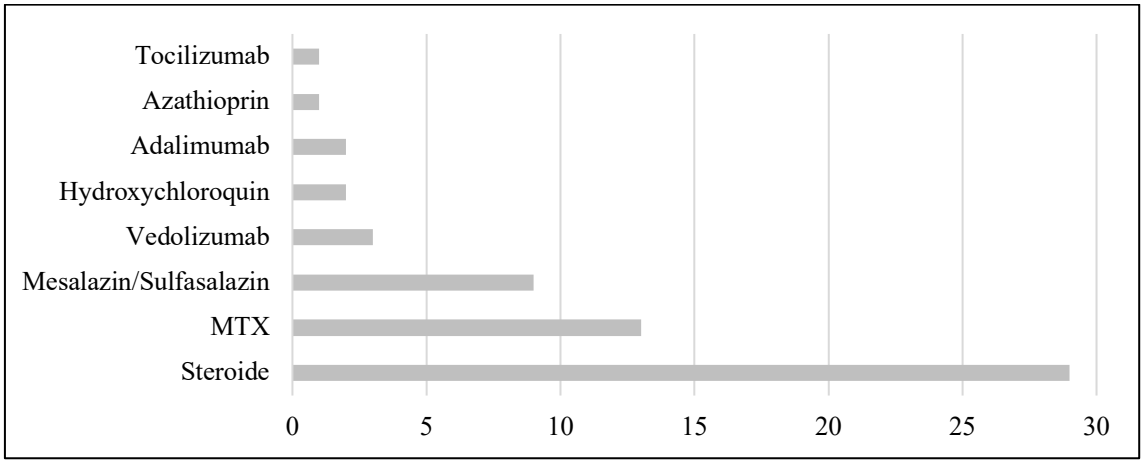

Figure 12: Immunosuppressive agents

3.2.4 Prognostic factors

3.2.4.1 Number of organ metastases

In 83.1% ($n_{\pm}$=74) of the patients, 1-3 organs were affected with metastases. 16.9% ($n_{\pm}$=15) of the total collective had metastases in more than 3 organs. Patients with active immunosuppression had up to 3 organs with metastasis in 75.6% (n_{+}=31) and more in 24.4% of cases (n_{+}=10). (Figure 13)

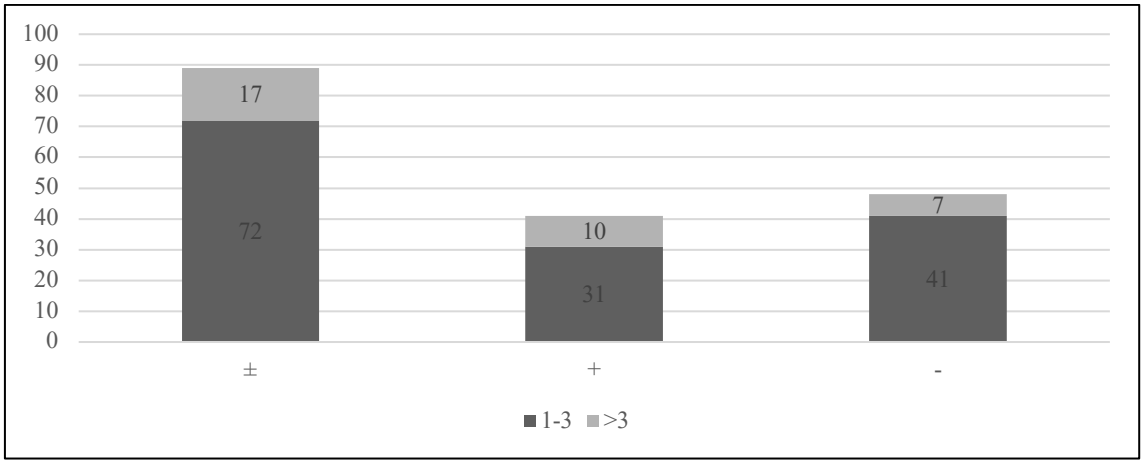

Figure 13: Number of metastatic organs

3.2.4.2 Brain and liver metastases

37.1% ($n_{\pm}$=33) had brain metastases and 62.9% ($n_{\pm}$=56) of PAD didn't. 36.0% had liver metastases ($n_{\pm}$=32) while 64.0% ($n_{\pm}$=57) did not. Finally, 13.5% of patients ($n_{\pm}$=12) had both brain and liver metastases. Patients under active immunosuppression had brain metastases in 34.1% (n_{+}=14) and liver metastases in 36.6% of cases (n_{+}=15), 14.6% (n_{+}=6) had both. (Figures 14 and 15)

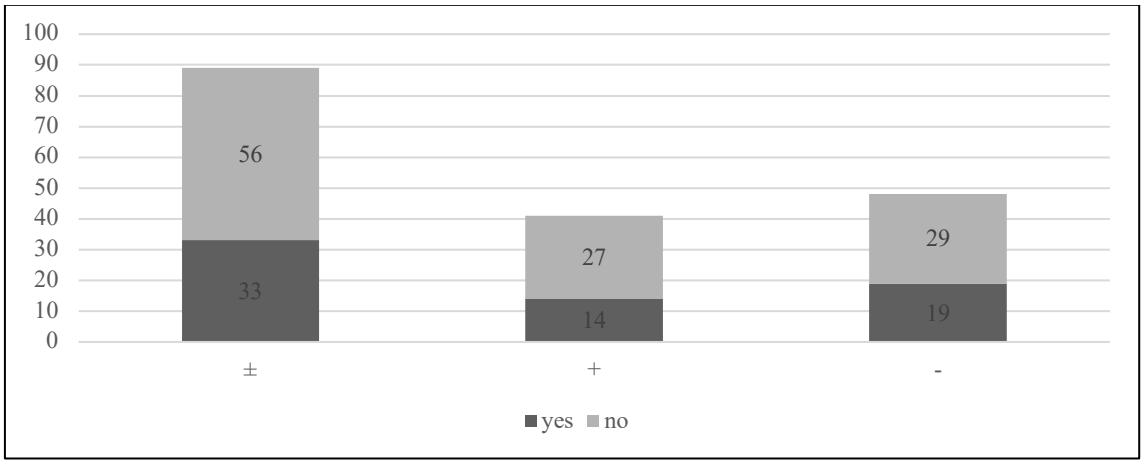

Figure 14: Brain metastases

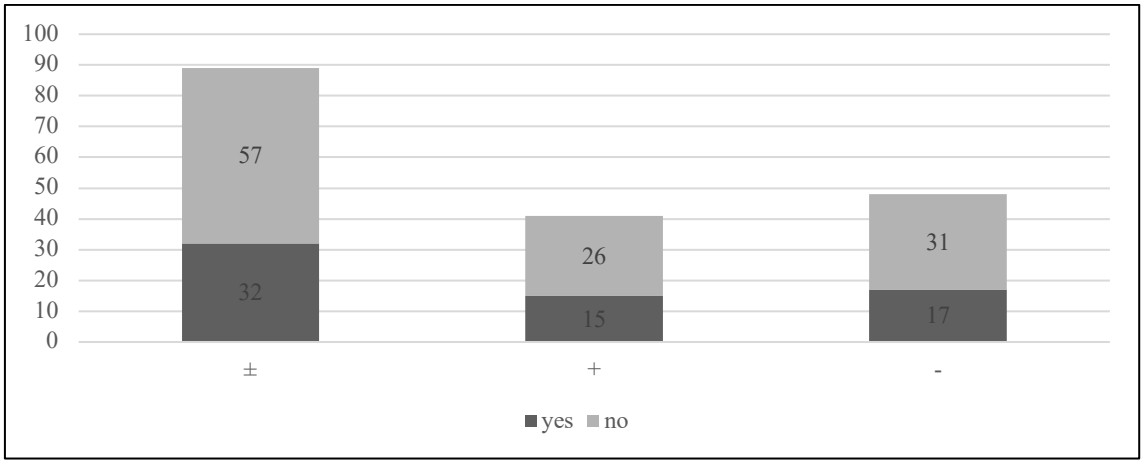

Figure 15: Liver metastases

3.2.5 Therapy regimen

In total 87.6% ($n_{\pm}$=78) received systemic therapy during study observation. 48.3% (n=43) received combined immune checkpoint, 29.2% ($n_{\pm}$=26) had PD-1 monotherapy. Patients under active immunosuppression received systemic therapy in 90.2% (n_{+}=37), combined immunotherapy in 46.3% (n_{+}=19) and PD-1 monotherapy in 31.7% of cases (n_{+}=13). (Figure 16)

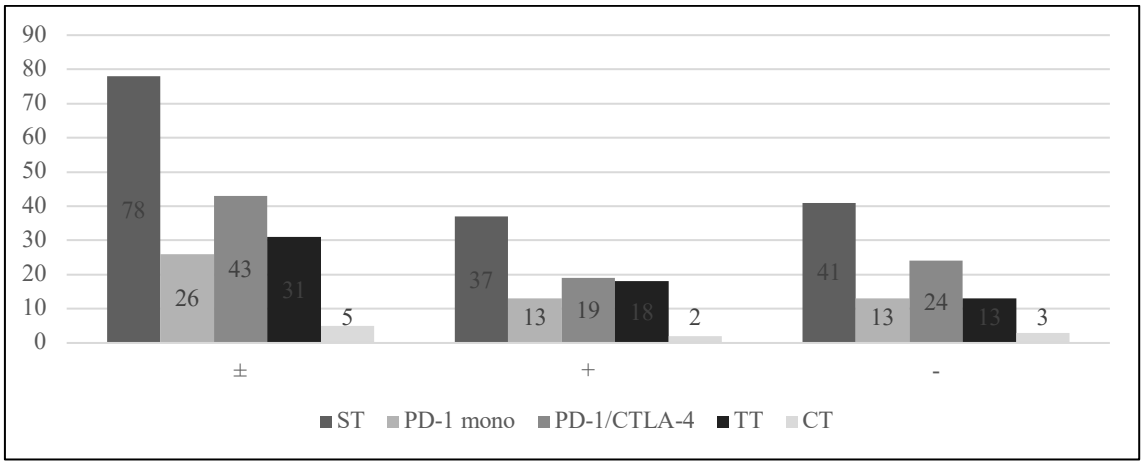

Figure 16: systemic therapies

3.2.5.1 First-line therapy

12.4% of patients never received any systemic therapy ($n_{\pm}$=11/89). First-line, 42.3% of patients ($n_{\pm}$=33/78) received combined immunotherapy; 24.4% ($n_{\pm}$=19/78) were given PD-1 monotherapy. Targeted therapy was administered in 30.8% of patients ($n_{\pm}$=24/78)

and CTLA-4 monotherapy in 2.6% of patients ($n_{\pm}$=2/78). Nobody received chemotherapy as first-line.

Regarding patients who have immunosuppressive therapy, 9.76% patients never received systemic therapy ($n_{\pm}$=4/41). 35.1% ($n_{\pm}$=13/37) received combined immunotherapy; 24.3% ($n_{\pm}$=9/37) were given PD-1 monotherapy. Targeted therapy was administered in 37.8% of patients ($n_{\pm}$=14/37) and CTLA-4 monotherapy in 2.7% of patients ($n_{\pm}$=1/37). Overall, 59.5% ($n_{\pm}$=22/37) of patients received PD-1 immune checkpoint inhibitors in some form.

Overall, 53.8% ($n_{\pm}$=42/78) of all PAD patients and 51.4% (n_{+}=19/37) of patients with immunosuppressive therapy had progressive disease. (Table 10)

Table 10: First-line systemic therapy

First-line ST	**All**		**Immunosuppression**	
	n	**%**	**n**	**%**
PD-1 Mono	19	24.4%	9	24.3%
PD-1/CTLA-4	33	42.3%	13	35.1%
TT	24	30.8%	14	37.8%
CTLA-4 Mono	2	2.6%	1	2.7%
∑	78	100.0%	37	100.0%

3.2.5.2 Second-line therapy

57.14% ($n_{\pm}$=24/42) had second-line therapy. 29.2% of patients ($n_{\pm}$=7/24) received combined immunotherapy; 16.7% ($n_{\pm}$=4/24) were given PD-1 monotherapy. Targeted therapy was administered in 37.5% of patients ($n_{\pm}$=9/24) and chemotherapy in 12.5% of patients ($n_{\pm}$=3/24). Others include combined therapy of Nivolumab, Trametinib and Dabrafenib ($n_{\pm}$=1/24. 4.2%). Nobody received CTLA-4 monotherapy as second-line. All in all, 50.0% of patients received PD-1 therapy (either mono or combined immune checkpoint inhibition) (Table 11).

Table 11: Second-line systemic therapy

Second-line ST	All		Immunosuppression	
	n	%	n	%
PD-1 Mono	4	16.7%	3	21.4%
PD-1/CTLA-4	7	29.2%	4	28.6%
TT	9	37.5%	6	42.9%
CT	3	12.5%	0	0.0%
other	1	4.2%	1	7.1%
∑	24	100.0%	14	100.0%

3.2.6 Immune related adverse events (irAEs)

Out of 89 patients, 12.4% ($n_{\pm}$=11) never received any systemic therapy. Further 15.7% ($n_{\pm}$=14) of the study population never received PD-1 therapy (PD-1 monotherapy or PD-1/CTLA-4 combined immunotherapy). In conclusion, 64 patients received PD1 therapy. 54.7 % ($n_{\pm}$=35/64) of them experienced a total of 69 irAEs. 18.8% ($n_{\pm}$=12/64) had flare ups of their PAD. 51.4% of patients had 1 ($n_{\pm}$=18/35), 31.4% ($n_{\pm}$=11/35) had 2, 11.47% ($n_{\pm}$=4/35) had 3 and 5.7% ($n_{\pm}$=2/35) had 4 irAEs. 29.0% ($n_{\pm}$=20/69) of irAEs were mild, 43.5% ($n_{\pm}$=30/69) were moderate, 21.7% ($n_{\pm}$=15/69) were severe and 5.8% ($n_{\pm}$=4/69) were life threatening. (Figure 17)

58.9% of patients with IBD ($n_{\pm}$=9) and 40.0% of patients with thyroiditis had flare-ups. Out of 41 patients with active immunosuppression, 7.3% (n_{+}=3/41) never received ICI. In conclusion, 38 patients received ICI. 39.5% (n_{+}=15/38) of them experienced a total of 30 irAEs. 21.1% (n_{+}=8/38) had flare ups of their PAD. 46.7% of patients had 1 (n_{+}=7/15), 33.3% (n_{+}=5/15) had 2, 13.3% (n_{+}=2/15) had 3 and 6.7% (n_{+}=1/15) had 4 irAEs. 33.3% (n_{+}=10/30) of irAEs were mild, 36.7% (n_{+}=11/30) were moderate, 16.7% (n_{+}=5/30) were severe and 13.3% (n_{+}=4/30) were life-threatening.

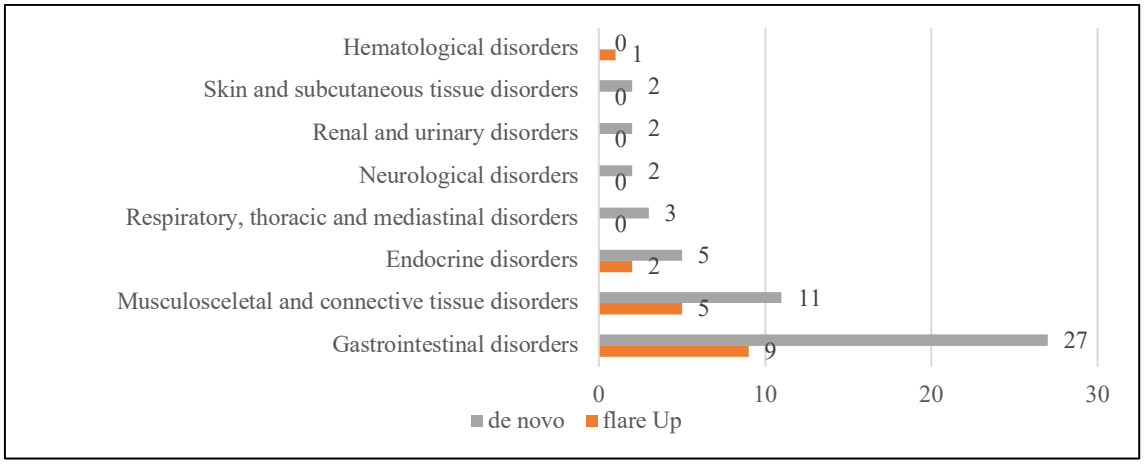

Figure 17: irAEs under PD-1 therapy ± PAD

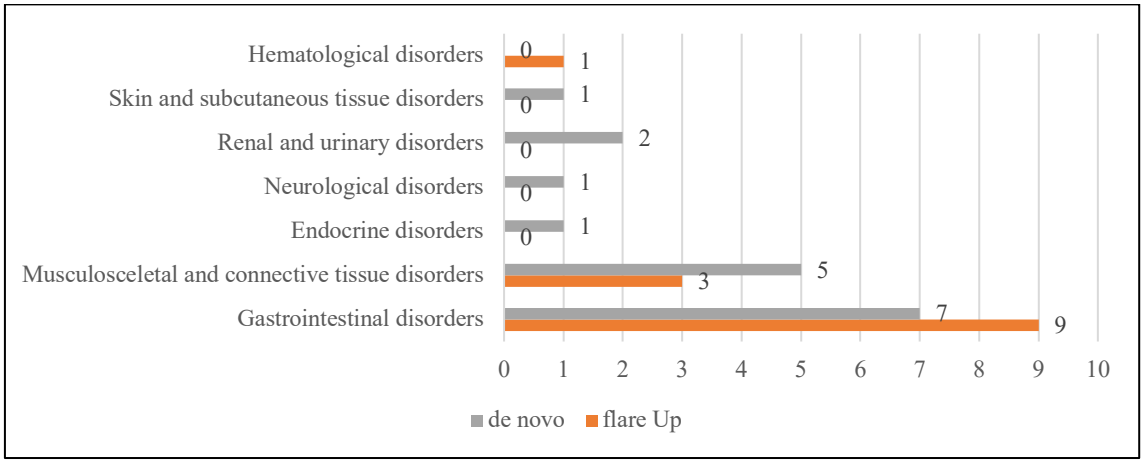

Figure 18: irAEs under PD-1 therapy + PAD

Patients with pre-existing sarcoidosis, autoimmune haemolytic anaemia had no irAEs during PD-1 based therapy in this study (16.9%, $n_{\pm}$=15). Patients with Multiple Sclerosis or Vitiligo never had PD-1 based therapy.

3.3 Best and Overall Response Rate (BOR) according to RECIST

BOR were assessed using RECIST 1.1 criteria (1 = complete response (CR), 2 = partial response (PR), 3 = stable disease (SD), 4 = progressive disease (PD)). (Eisenhauer et al., 2009)

Patients with PAD and presence of stage IV malignant melanoma, 29.2% ($n_{\pm}$=26/89) of had complete remission (CR), 19.1% ($n_{\pm}$=17/89) had partial remission (PR) and 7.9% ($n_{\pm}$=7/89) had stable findings (SD) on imaging. Progression (PD) of the disease was detected in 24.7% (n=22/89). In 18.0% ($n_{\pm}$=16/89), no usable data was available for this purpose and therefore had to be excluded from the assessment.
Under second-line treatment, 4.5% ($n_{\pm}$=4/89) of patients achieved CR, 4.5% ($n_{\pm}$=4/89) PR and 2.2% ($n_{\pm}$=2/89) SD. 12.4% ($n_{\pm}$=16/89) of patients had PD. In 71.0% ($n_{\pm}$=63/89) had no usable data and therefore had to be excluded from the assessment.

Table 12: BOR (RECIST) PAD ± immunosuppression

±	First-line therapy $n_{\pm}$=78, missing $n_{\pm}$=11		Second-line therapy $n_{\pm}$=26, missing $n_{\pm}$=63	
CR	29.2%	$n_{\pm}$=26/89	4.5%	$n_{\pm}$=4/89
PR	19.1%	$n_{\pm}$=17/89	4.5%	$n_{\pm}$=4/89
SD	7.9%	$n_{\pm}$=7/89	2.2%	$n_{\pm}$=2/89
PD	24.7%	$n_{\pm}$=22/89	12.4%	$n_{\pm}$=11/89
ORR	48.3%	$n_{\pm}$=43/89	9.0%	$n_{\pm}$=8/89

Patients with PAD and active immunosuppression in presence of malignant melanoma in stage IV malignant melanoma, 34.1% (n_{+}=14/41) of patients had a CR, 24.4% (n_{+}=10/41) had PR and 7.3% (n_{+}=3/41) had SD on imaging. Progression detected in 19.5% (n_{+}=8/41). (n_{+}=22/41). In 14.6% (n_{+}=6/41), no usable data was available for this purpose and therefore had to be excluded from the assessment.
Under second-line treatment, 4.9% (n_{+}=2/41) of patients achieved CR, 4.9% (n_{+}=2/41) PR and 0.0% (n_{+}=0/41) SD. 17.1% (n_{+}=7/41) of patients had PD. In 36.6% (n+=15/41) had no usable data and therefore had to be excluded from the assessment.

Table 13: BOR (RECIST) PAD + immunosuppression

+	First-line therapy n_{+}=35, missing n_{+}=6		Second-line therapy n_{+}=26, missing n_{+}=15	
CR	34.1%	n_{+}=14/41	4.9%	n_{+}=2/41

PR	24.4%	n_{+}=10/41	4.9%	n_{+}=2/41
SD	7.3%	n_{+}=3/41	0.0%	n_{+}=0/41
PD	19.5%	n_{+}=8/41	17.1%	n_{+}=7/41
ORR	58.5%	n_{+}=24/41	9.8%	n_{+}=4/41

3.3.1 BOR according to RECIST and therapy regimen

3.3.1.1 First-line

Regarding first-line therapy in patients with PAD, 24.4% ($n_{\pm}$=19) received PD-1 monotherapy, 42.3% ($n_{\pm}$=33) received PD-1/CTLA-4 combined immunotherapy and 33.3% ($n_{\pm}$=26) received other therapies (TT and CTLA-4 monotherapy). In every group, there were two patients with missing response and had therefore to be excluded.

In first-line treatment with PD-1 monotherapy, 52.9 % ($n_{\pm}$=9/17) of patients had a complete response, 11.8% ($n_{\pm}$=2/17) a partial response and 5.9% ($n_{\pm}$=1/17) stable disease. Progression occurred in 29.4% ($n_{\pm}$=5/17) of patients.

In first-line treatment with PD-1/CTLA-4 combined immunotherapy, 38.7% ($n_{\pm}$=12/31) of patients had a complete remission, 16.1% ($n_{\pm}$=5/31) a partial remission and 16.1% ($n_{\pm}$=5/31) a proven disease stabilisation. A progression occurred in 29.0% ($n_{\pm}$=9/31) of patients.

In first-line treatment with other therapies, 20.8% ($n_{\pm}$=5/24) of patients had a complete remission and 41.7% ($n_{\pm}$=10/24) had a partial remission. Stable disease occurred in 4.2% ($n_{\pm}$=1/24). Progressive disease was found in 33.3% ($n_{\pm}$=8/24). ORR for PD-1 monotherapy was 22.9% ($n_{\pm}$=(9+2)/48) and for PD-1/CTLA-4 35.4% ($n_{\pm}$=(12+5)/48) (Table 14)

Table 14: BOR (RECIST) first-line PAD ± immunosuppression

± $n_{\pm}$=78	PD-1 $n_{\pm}$=17		PD-1/CTLA-4 $n_{\pm}$=31		other $n_{\pm}$=24	
CR n=26	52.9%	$n_{\pm}$=9	38.7%	$n_{\pm}$=12	20.8%	$n_{\pm}$=5
PR n=17	11.8%	$n_{\pm}$=2	16.1%	$n_{\pm}$=5	41.7%	$n_{\pm}$=10
SD n=7	5.9%	$n_{\pm}$=1	16.1%	$n_{\pm}$=5	4.2%	$n_{\pm}$=1
PD n=22	29.4%	$n_{\pm}$=5	29.0%	$n_{\pm}$=9	33.3%	$n_{\pm}$=8

ORR	64.7%	$n_{\pm}$=11	54.8%	$n_{\pm}$=17	62.5%	$n_{\pm}$=15

Out of first-line therapy in patients with PAD and active immunosuppression 7 received PD-1 monotherapy, 33 received PD-1/CTLA-4 combined immunotherapy and 26 received other therapies (TT and CTLA-4 monotherapy). In every group, there were two patients with missing response.

In first-line treatment with PD-1 monotherapy, 85.7% (n_{+}=6/7) of patients had a complete remission, 0.0% (n_{+}=0/7) a partial remission and 14.3% (n_{+}=1/7) a stable disease course. Progression occurred in 0.0% (n_{+}=0/0) of patients.

In first-line treatment with PD-1/CTLA-4 combined immunotherapy, 38.5% (n_{+}=5/13) of patients had a complete remission, 15.4% (n_{+}=2/15) a partial remission and 7.7% (n_{+}=1/13) a proven disease stabilisation. A progression occurred in 38.5% (n_{+}=5/13) of patients.

In first-line treatment with other therapies, 20.0% (n_{+}=3/15) of patients had a complete remission and 53.3% (n_{+}=8/15) had a partial remission. Stable disease happened in 6.7% (n_{+}=3/15). Progression did occur in 20.0% of patients (20.0%, n_{+}=3/15). ORR for PD-1 monotherapy was 30.0% (n_{+}=(6+0)/20) and for PD-1/CTLA-4 35.0% (n_{+}=(5+2)/20). (Table 15)

Table 15: BOR (RECIST) first-line PAD + immunosuppression

+ n=37	PD-1 n_{+}=7		PD-1/CTLA-4 n_{+}=13		other n_{+}=15	
CR n_{+}=14	85.7%	n_{+}=6	38.5%	n_{+}=5	20.0%	n_{+}=3
PR n_{+}=10	0.0%	n_{+}=0	15.4%	n_{+}=2	53.3%	n_{+}=8
SD n_{+}=3	14.3%	n_{+}=1	7.7%	n_{+}=1	6.7%	n_{+}=1
PD n_{+}=8	0.0%	n_{+}=0	38.5%	n_{+}=5	20.0%	n_{+}=3
ORR	85.7%	n_{+}=6	53.9%	n_{+}=7	73.3%	n_{+}=11

3.3.1.2 Second-line

Regarding second-line therapy in patients with PAD 3 received PD-1 monotherapy (2 missing), 7 received PD-1/CTLA-4 combined immunotherapy (1 missing) and 13 received other therapies (2 missing).

In second-line treatment with PD-1 monotherapy, all patients had stable disease (2/2). No patient had a complete remission, a partial remission or stable disease. Progression occurred in 100.0% ($n_{\pm}$=2/2) of patients.

In second-line treatment with PD-1/CTLA-4 combined immunotherapy, 33.3% ($n_{\pm}$=2/6) of patients had a complete remission, 16.7% ($n_{\pm}$=1/6) a partial remission and 0.0% ($n_{\pm}$=0/6) a proven disease stabilisation. A progression occurred in 50.0% ($n_{\pm}$=3/6) of patients.

In second-line treatment with other therapies,15.4% ($n_{\pm}$=2/13) of patients had a complete remission and 23.1% ($n_{\pm}$=3/13) had a partial remission. Stable disease occurred in 15.4% ($n_{\pm}$=2/13). Progressive disease was found in 46.2% ($n_{\pm}$=3/13). ORR for PD-1 monotherapy was 0.0% and for PD-1/CTLA-4 50.0% ($n_{\pm}$=(2+1)/6). (Table 16)

Table 16: BOR (RECIST) second-line PAD ± immunosuppression

±	PD-1 $n_{\pm}$=2		PD-1/CTLA-4 $n_{\pm}$=6		other $n_{\pm}$=13	
CR $n_{\pm}$=4	0.0%	n=0	33.3%	$n_{\pm}$=2	15.4%	$n_{\pm}$=2
PR $n_{\pm}$=4	0.0%	n=0	16.7%	$n_{\pm}$=1	23.1%	$n_{\pm}$=3
SD $n_{\pm}$=4	0.0%	n=0	0.0%	$n_{\pm}$=0	15.4%	$n_{\pm}$=2
PD $n_{\pm}$=9	100.0%	n=2	50.0%	$n_{\pm}$=3	46.2%	$n_{\pm}$=6
ORR	0.0%	n=0	50.0%	$n_{\pm}$=3	38.5%	$n_{\pm}$=5

Out of second-line therapy in patients with PAD and active immunotherapy 2 received PD-1 monotherapy (1 missing), 4 received PD-1/CTLA-4 combined immunotherapy (1 missing) and 6 received other therapies (1 missing).

In second-line treatment with PD-1 monotherapy under active immunosuppression, no patient had neither complete remission, partial remission, or stable disease. Progressive was observed in 100.0% (n_{+}=2/2) of cases.

In second-line treatment with PD-1/CTLA-4 combined immunotherapy, 0.0% (n_+=0/3) of patients had a complete remission or stable disease, 33.3% (n_+=1/3) a partial remission and 7.7% (n_+=1/13) a proven disease stabilisation. A progression occurred in 66.7% (n_+=2/3) of patients.

In second-line treatment with other therapies, 33.3% (n_+=2/6) of patients had a complete remission and 16.7% (n_+=1/6) had a partial remission. Stable disease happened in 0.0% (n_+=0/6). Progression did occur in 50.0% of patients (20.0%, n_+=3/6). ORR for PD-1 monotherapy was 0.0% and for PD-1/CTLA-4 33.3% (n_+=(0+1)/3). (Table 17)

Table 17: BOR (RECIST) second-line PAD + immunosuppression

+	PD-1 n_+=2		PD-1/CTLA-4 n_+=3		other n_+=6	
CR n_+=2	0.0%	n_+=0	0.0%	n_+=0	33.3%	n_+=2
PR n_+=2	0.0%	n_+=0	33.3%	n_+=1	16.7%	n_+=1
SD n_+=2	0.0%	n_+=0	0.0%	n_+=0	0.0%	n_+=0
PD n_+=5	100.0%	n_+=2	66.7%	n_+=2	50.0%	n_+=3
ORR	0.0%	n_+=0	33.3%	n_+=1	50.0%	n_+=3

3.4 Survival analysis

Kaplan-Meier curves were used to assess the influence of several factors on patient overall survival.

We examined patient characteristics (age distribution and sex), characteristics of the primary tumour (tumour location, histological subtype), prognostic factors (number of organ metastases, presence of brain and liver metastases), laboratory parameters (LDH and S100 levels) and existence of PAD with or without active immunosuppression.

3.4.1 Age

There was no statistically significant difference regarding the different age groups (p-value 0.433). Median overall survival was not reached in patients < 65 years old, between

65 and 75 years mOS was 30.5 months (95% CI: 10.7-50.4) and >75 years old 26.2 months (95% CI: 22.3-53.8). (Figure 19)

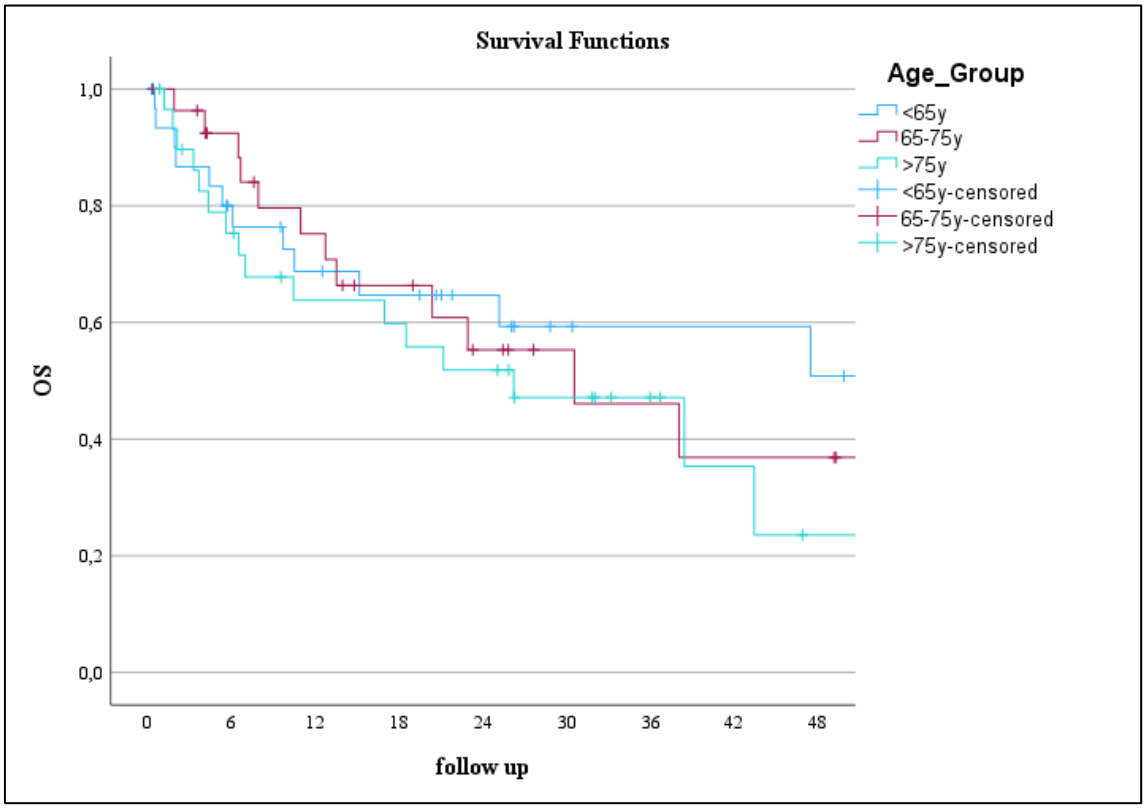

Figure 19: mOS age group – PAD ± immunosuppression

No statistical significance (p=0.267) was found in patients with immunosuppression. Median overall survival was not reached in patients < 65 years old, between 65 and 75 years mOS was 38.0 months (95% CI: 9.4-66.7) and >75 years old 38.4 months (95% CI: 15.4-61.4). (Figure 20)

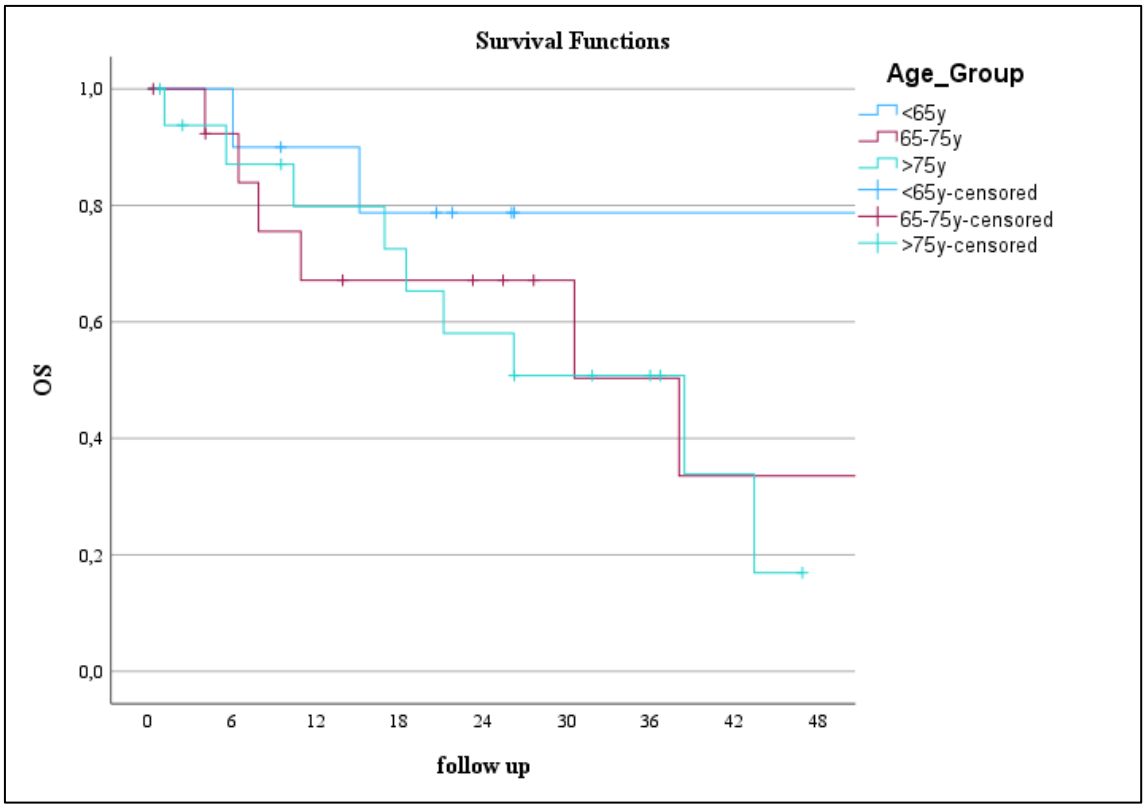

Figure 20: mOS age group – PAD + immunosuppression

3.4.2 Sex

There is no significant difference between sexes in mOS (p=0.877). The median OS for men was 30.5 months (95% CI: 5.1-52.9) and for women 38.0 months (95% CI: 13.6-62.4). (Figure 21)

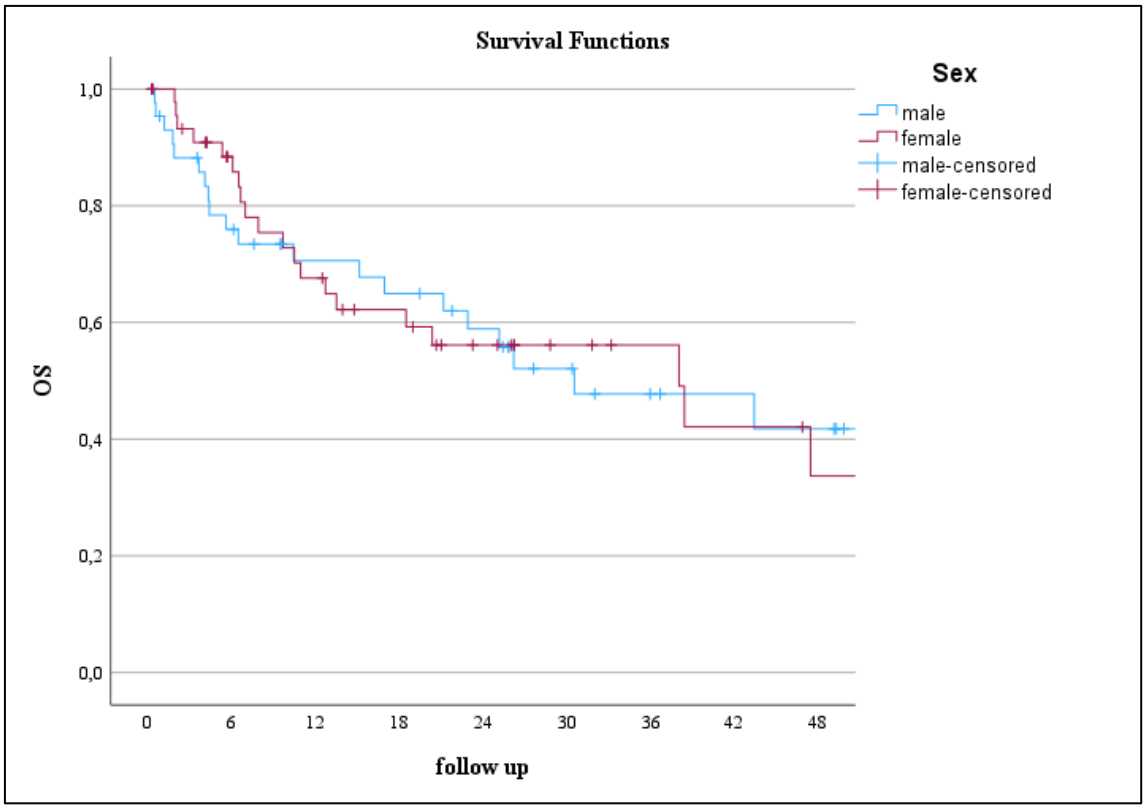

Figure 21: mOS sex – PAD ± immunosuppression

There is also no significant difference between sexes in mOS (p=0.315) if patients receive immunosuppressive therapy. The median OS for men was 30.5 months (95% CI: 9.6-51.5) and women 38.4 months (95% CI: 37.5-39.3). (Figure 22)

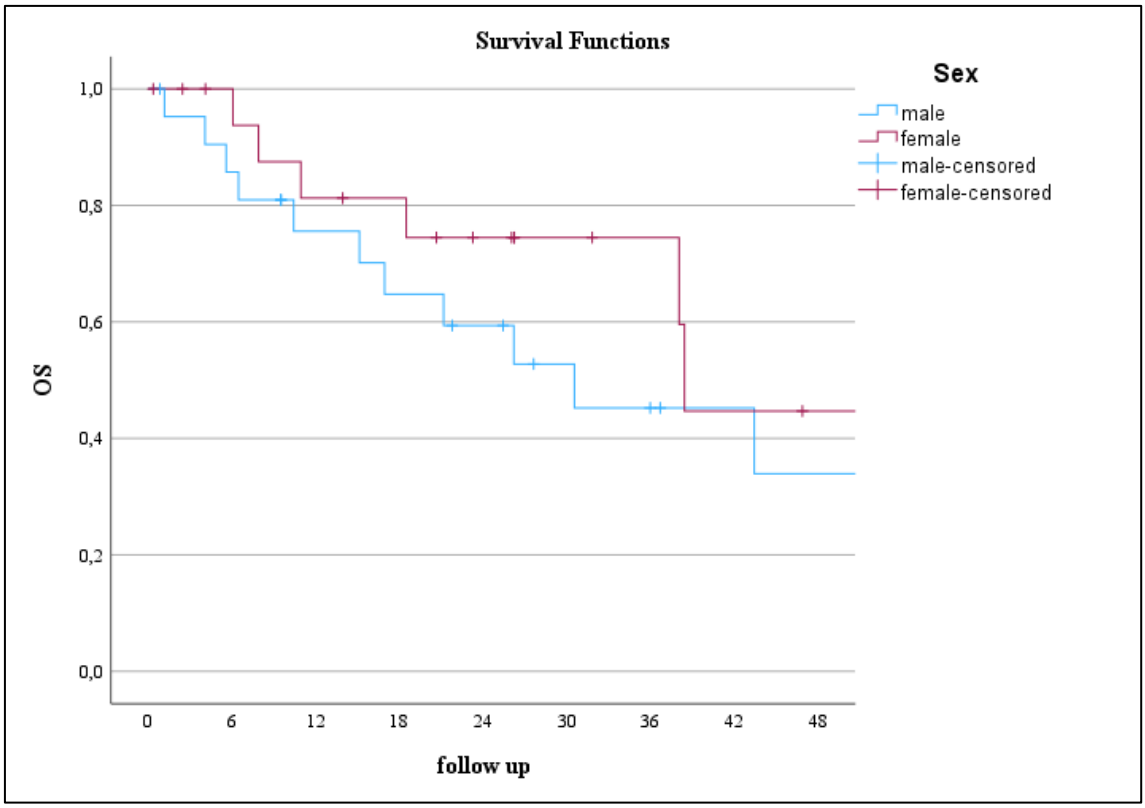

Figure 22: mOS sex – PAD + immunosuppression

3.4.3 Stage at initial diagnosis

Different stages of malignant melanoma at initial diagnosis showed no significant results (p=0.639) regarding mOS: Stage I was not reached, for stage II mOS was 30.5 months (95% CI: 13.0-48.1), for stage III mOS was 10.5 months (95% CI: 0.0-50.5) and for stage IV mOS was 38.4 months (95% CI: 17.8-59.0). (Figure 23)

In patients with active immunosuppression there was no significant difference (p=0.155) in survival. For patients with initial stage I or III, median was not reached. For stage II mOS was 30.5 months (95% CI: 14.6-46.4) and for stage IV mOS was 36.8 months (95% CI: 0.0-33.9). (Figure 24)

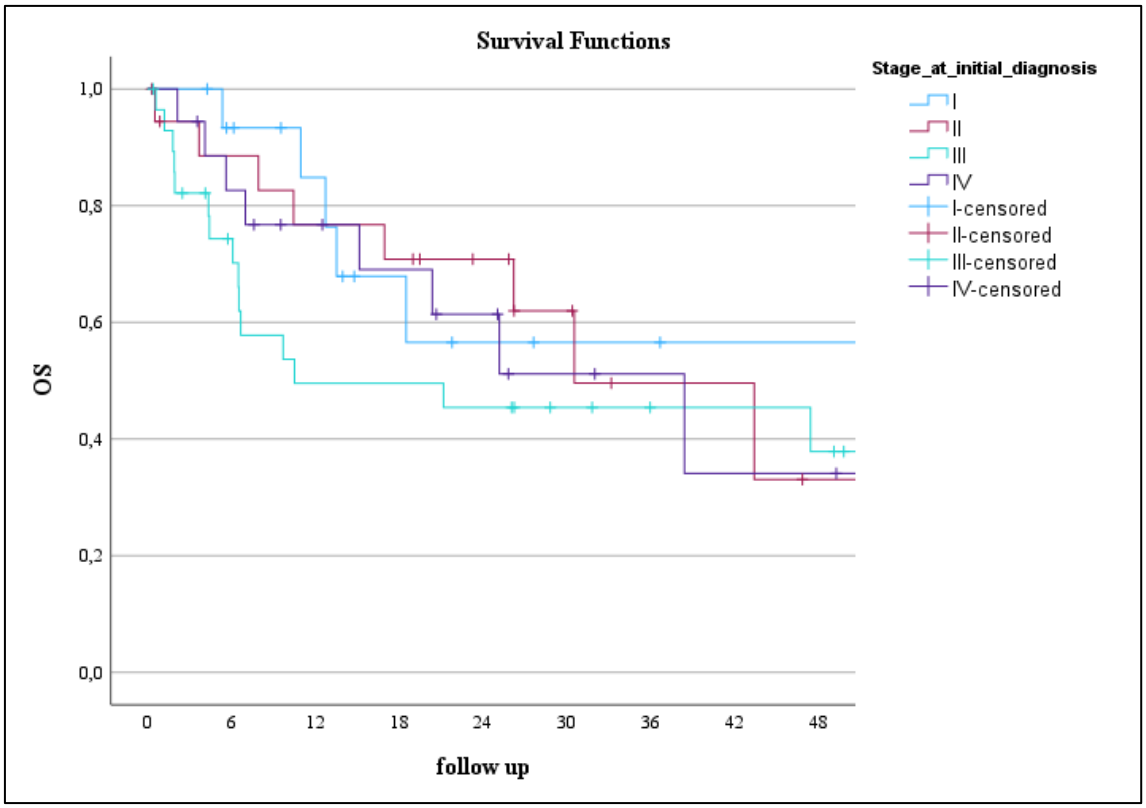

Figure 23: mOS stage at initial diagnosis – PAD ± immunosuppression

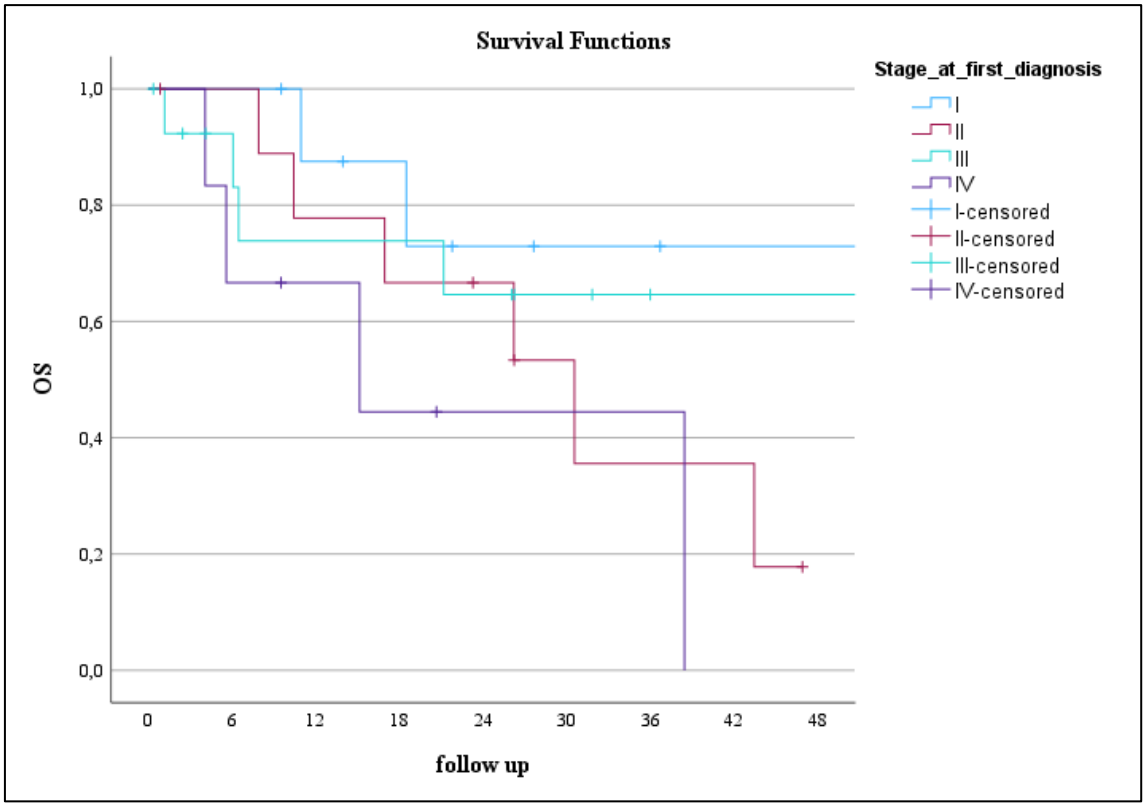

Figure 24: mOS stage at initial diagnosis – PAD + immunosuppression

3.4.4 Mutation status

The presence of a BRAF mutation didn't show a statistically significant mOS (p = 0.848). If BRAF mutation was present the mOS was 25.2 (95% CI: 0.0-53.6) and if it was not 38.0 (95% CI: 23.4-52.6). (Figure 25)

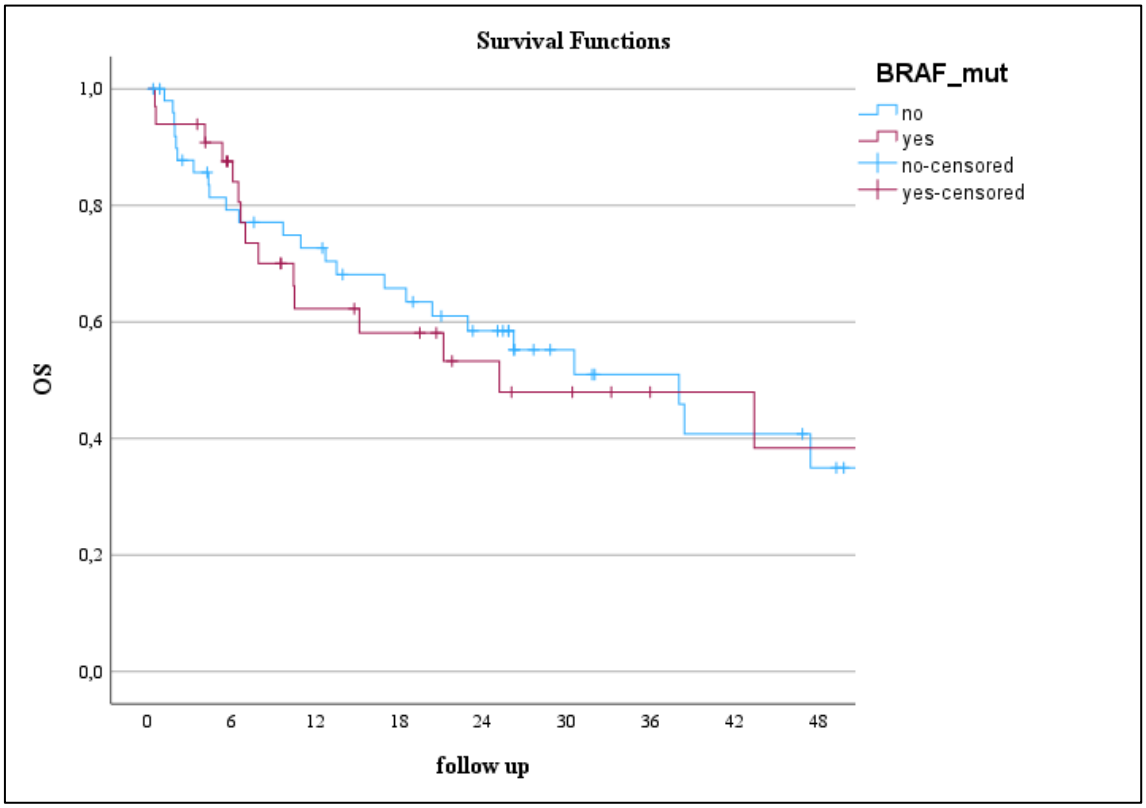

Figure 25: mOS BRAF mutation – PAD ± immunosuppression

There was no significant difference (p=0.862) in patients with PAD and immunosuppression and BRAF mutation. If BRAF was mutated mOS was not reached and if it was not 38.0 months (95% CI: 23.0-53.0). (Figure 26)

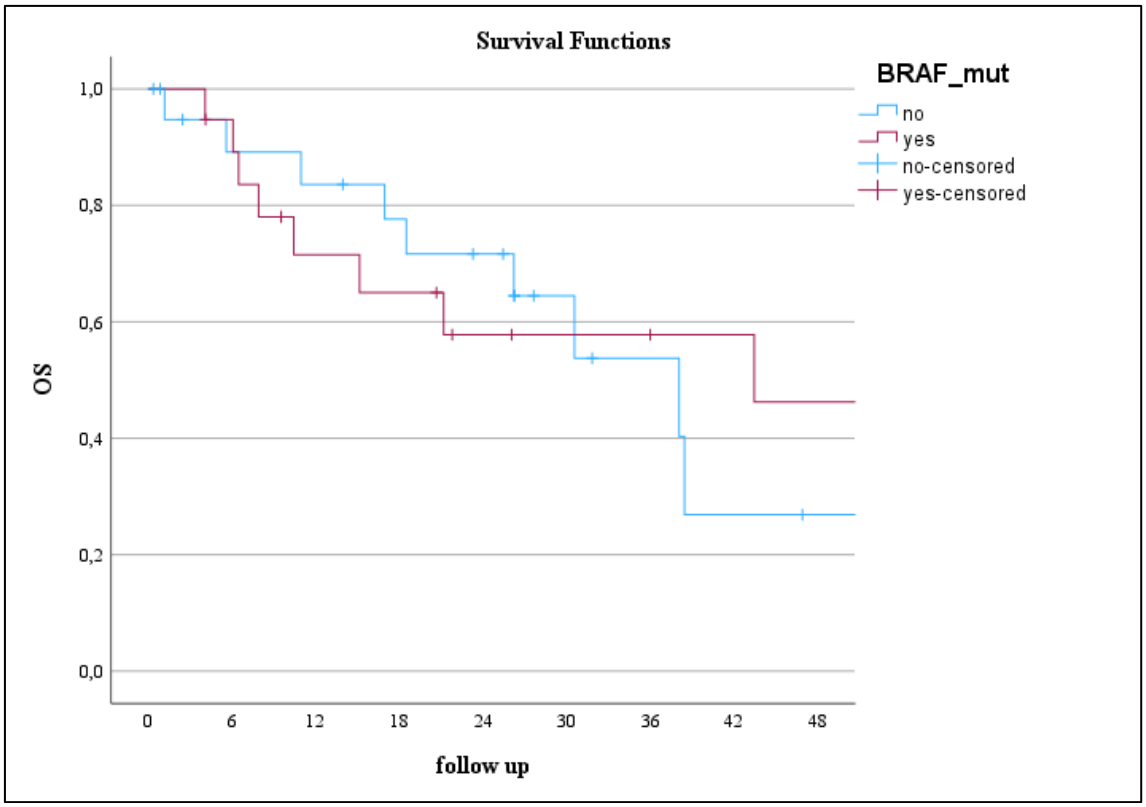

Figure 26: mOS BRAF mutation – PAD + immunosuppression

3.4.5 Location of primary tumour

Localization of primary tumour had no impact in mOS (p=0.204). Median OS with primary tumour in the head and neck region was 38.4 months (95% CI: 16.4-60.5), on the torso 30.5 (95% CI: 0.7-60.4) and on the extremities 10.5 (95% CI: 4.6-16.4). (Figure 27)

Localization of primary tumour in patients with PAD and immunosuppression had also no significance in mOS (p=0.947). Median OS with primary tumour in the head and neck region was 38.4 months (95% CI: 21.9-55.0), on the torso 30.5 (95% CI: 8.5-52.5). On the extremities mOS was not reached. (Figure 28)

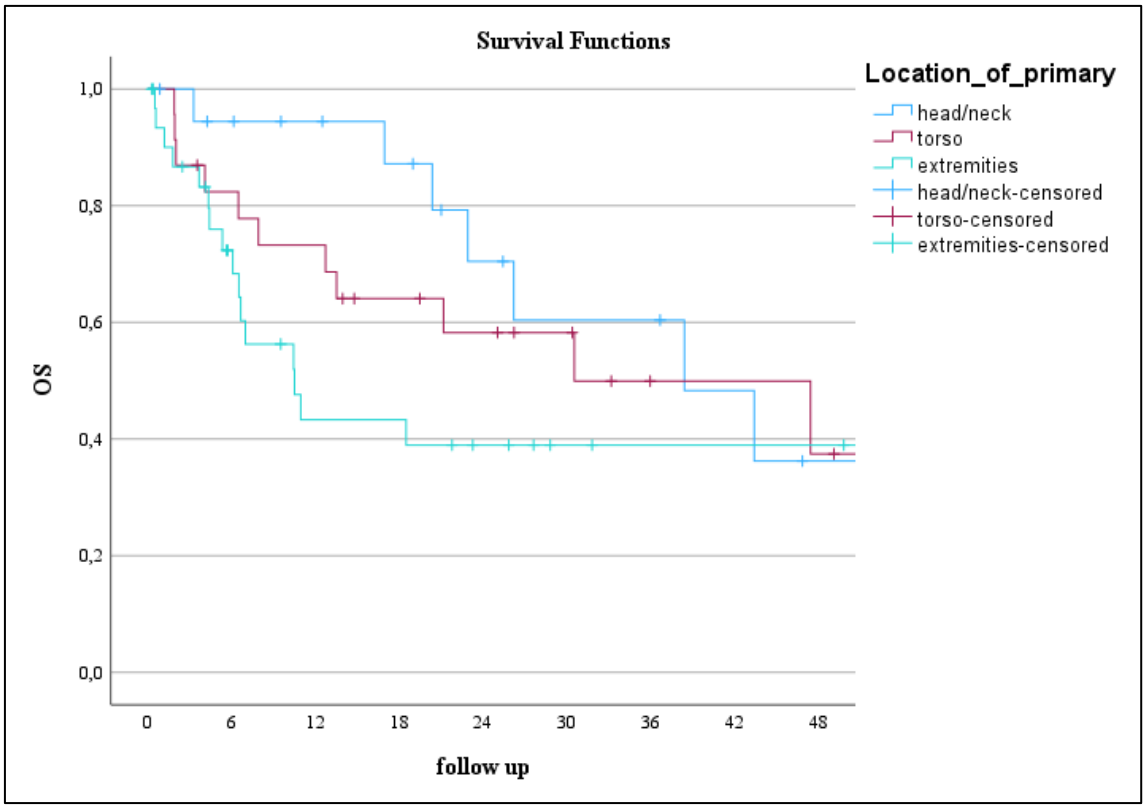

Figure 27: mOS location of primary tumour – PAD ± immunosuppression

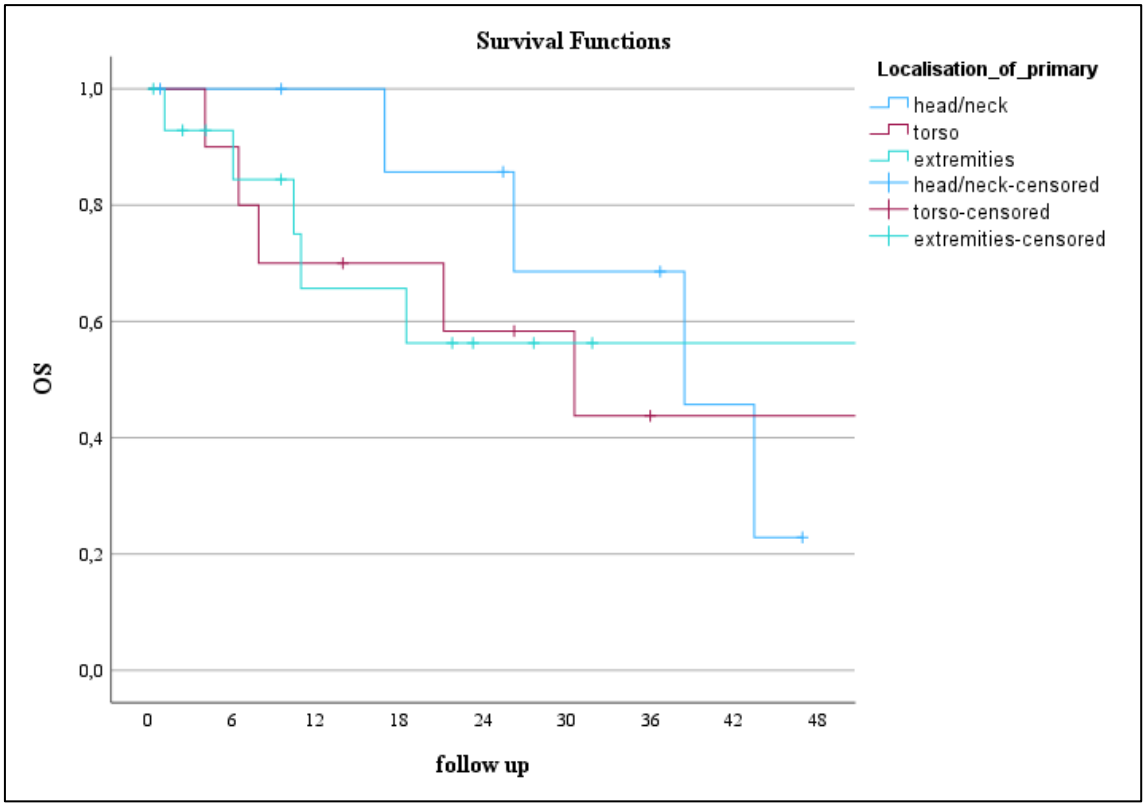

Figure 28: mOS location of primary tumour – PAD + immunosuppression

3.4.6 Histological subtype

We found insignificant differences (p=0.252) in terms of mOS considering histological subtypes: In SSM mOS was not reached. NM was 21.1 months (95% CI: 0.0-43.5) and other (LMM, ALM, MuM, OM, CM) 26.2 months (95% CI: 18.6-33.8). (Figure 29)

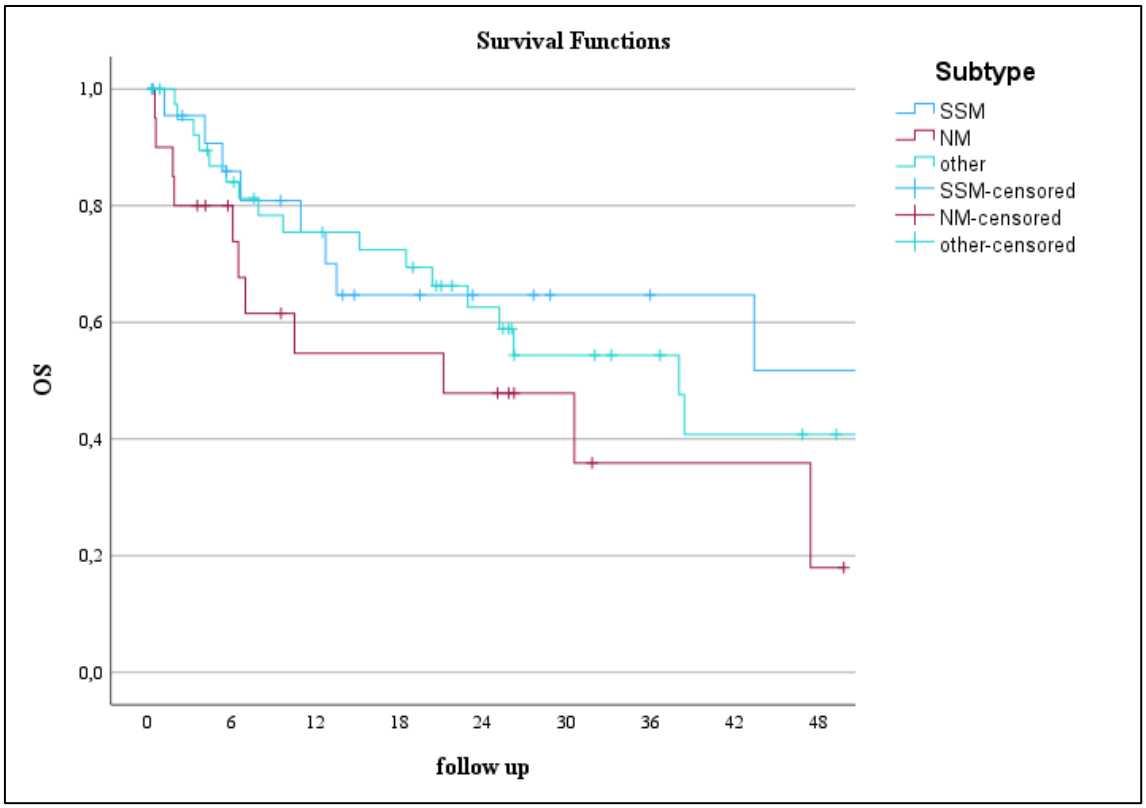

Figure 29: mOS histological subtype – PAD ± immunosuppression

We found insignificant differences (p=0.324) in terms of mOS considering histological subtypes: In SSM mOS was not reached. NM was 30.5 months (95% CI: 7.8-53.2) and other (LMM, ALM, MuM) 38.4 months (95% CI: 19.5-57.4). (Figure 30)

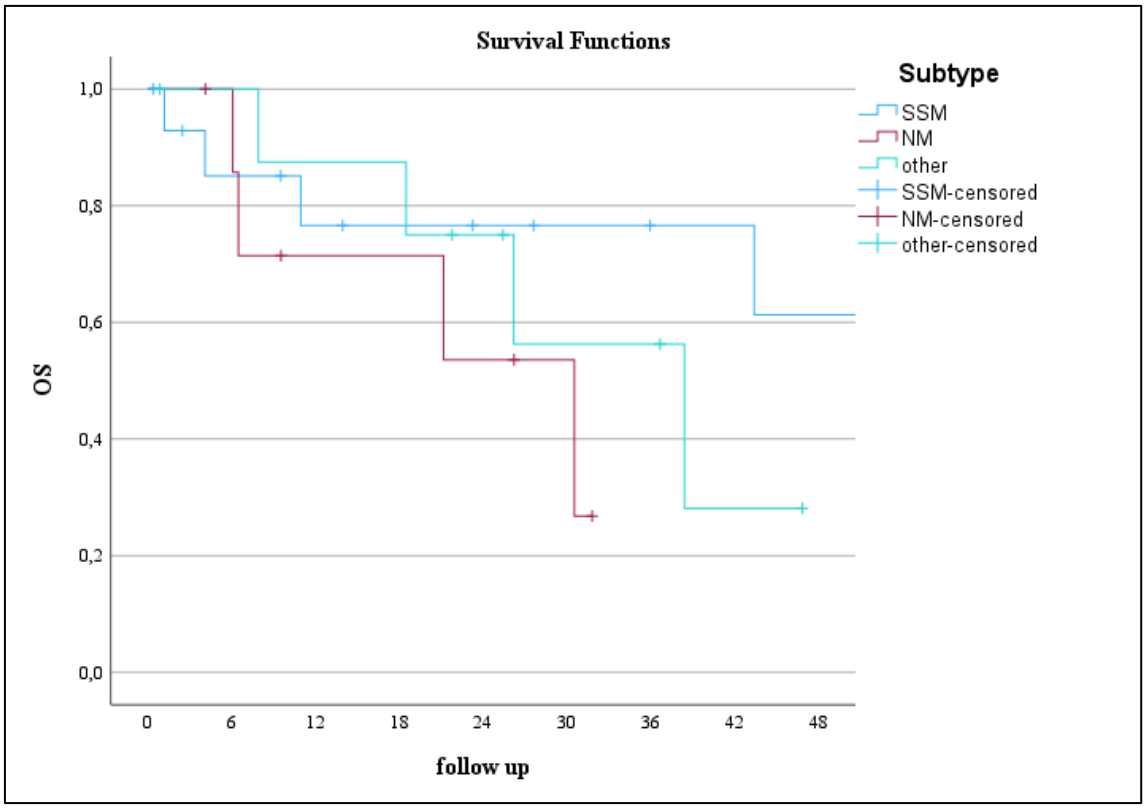

Figure 30: mOS histological subtype – PAD + immunosuppression

3.4.7 Laboratory parameters

3.4.7.1 LDH

As for LDH levels, significant differences could not be determined (p=0.150). If blood levels were normal, mOS was 43.4 months (95% CI: 24.1-62.8) and if elevated 22.9 (95% CI: 8.3-37.5). (Figure 31)

For patients with under active immunosuppression results were also insignificant regarding mOS (p=0.920). mOS for normal blood level was 38.0 months (95% CI: 21.5-54.6) and if elevated 38.4 (95% CI: 0.0-79.9). (Figure 32)

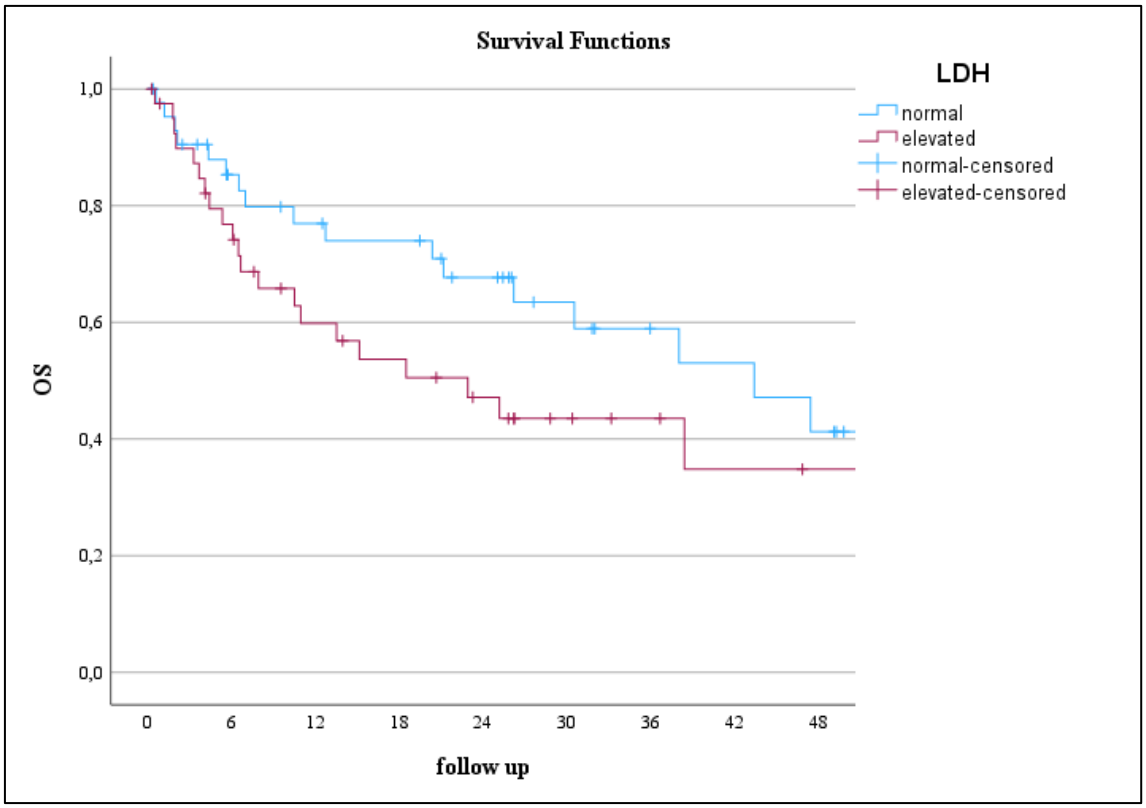

Figure 31: mOS LDH – PAD ± immunosuppression

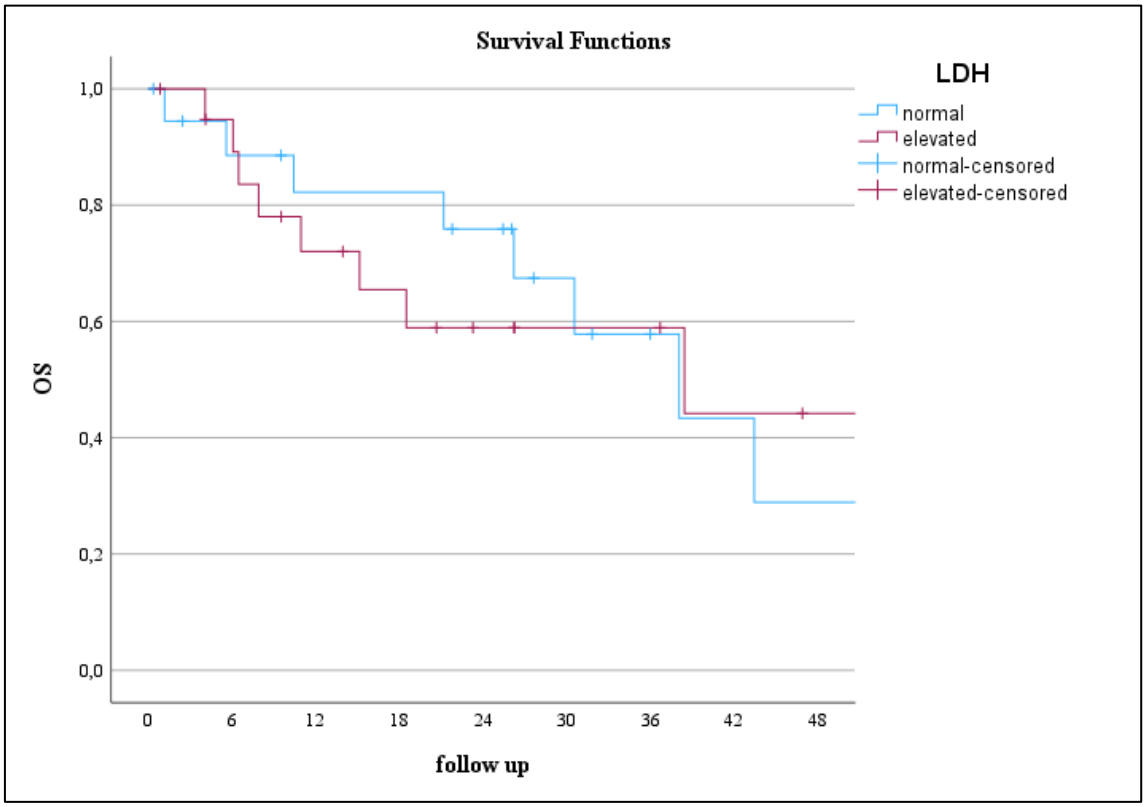

Figure 32: mOS LDH – PAD + immunosuppression

3.4.7.2 S100

The same goes for S100 levels (p=0.138). If S100 was normal, median overall survival time was 43.4 months (95% CI: 16.8-70.0) and if elevated 25.2 months (95% CI: 0.0-54.7). (Figure 33) In patients with active immunosuppression mOS was 43.4 months (95% CI: 21.7-65.1) if S100 levels were normal and 38.4 months (95% CI: 7.6-69.2) if S100 levels were elevated (p=0.989). (Figure 34)

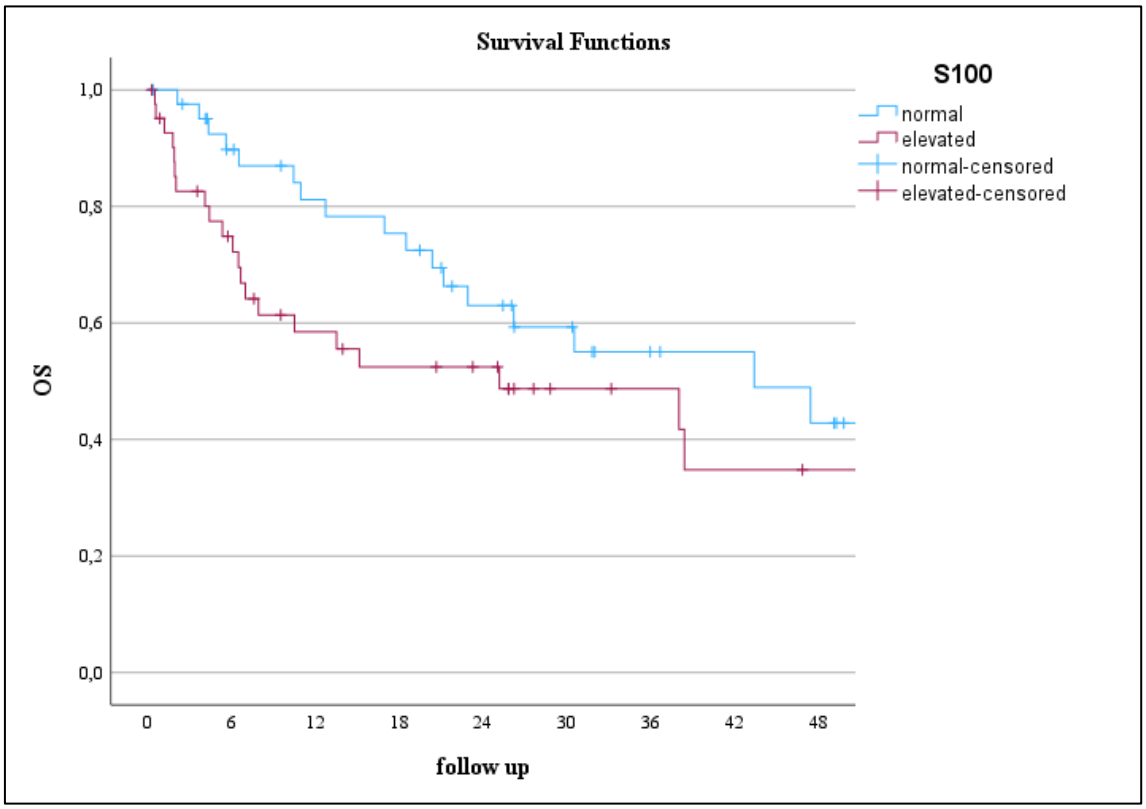

Figure 33: mOS S100 – PAD ± immunosuppression

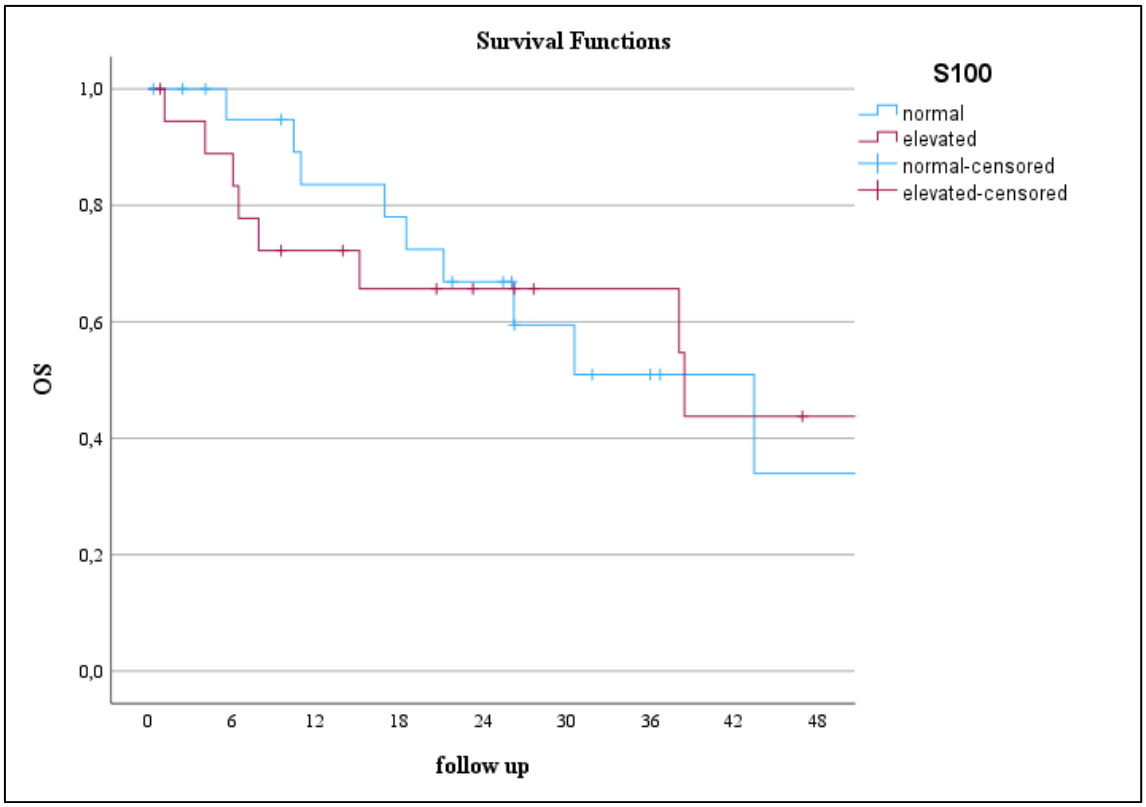

Figure 34: mOS S100 – PAD + immunosuppression

3.4.8 Pre-existing autoimmune disease

Median overall survival of all 89 patients with PAD was 38.0 months (95% CI: 22.3-53.8). (Figure 35)

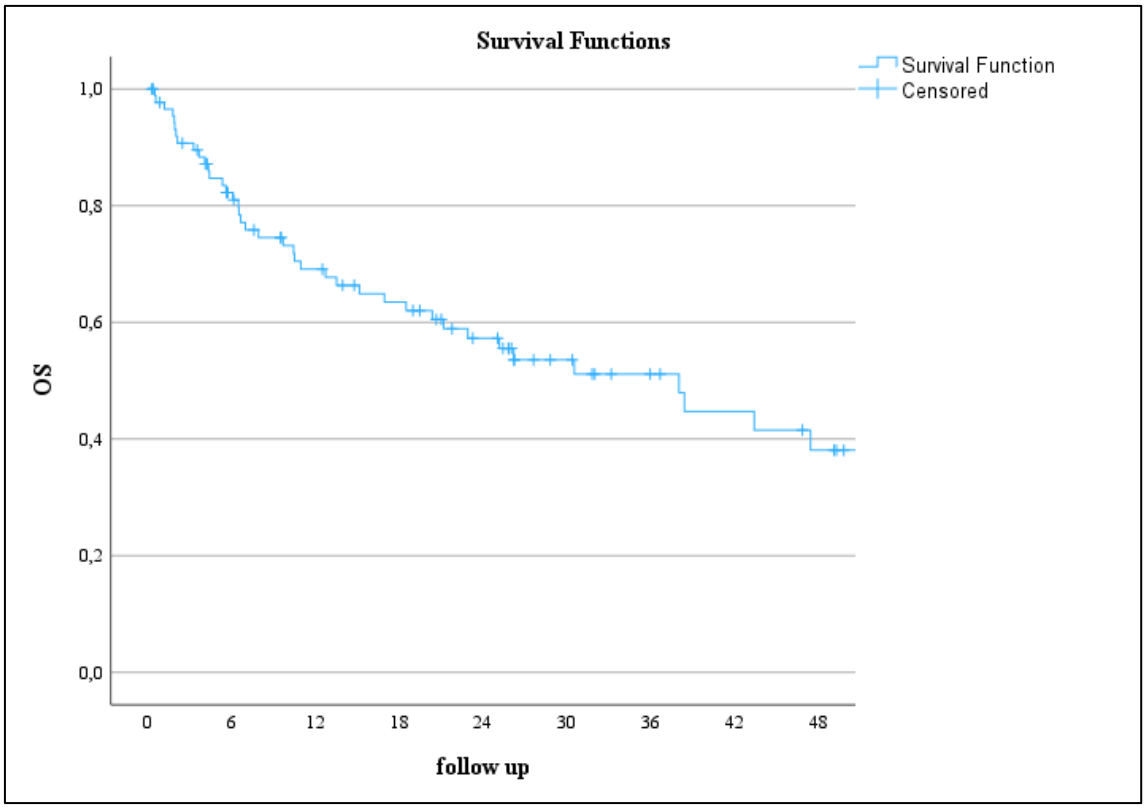

Figure 35: mOS – PAD ± immunosuppression

3.4.9 Immunosuppressive therapy

With a p-value of 0.232 there is no significant difference in mOS regarding active immunosuppressive therapy of PAD. Patients with baseline immunosuppressive therapy had median overall survival of 38.4 (95% CI: 25.5-51.3) and patients without 22.9 months (95% CI: 0.0-55.1). (Figure 36)

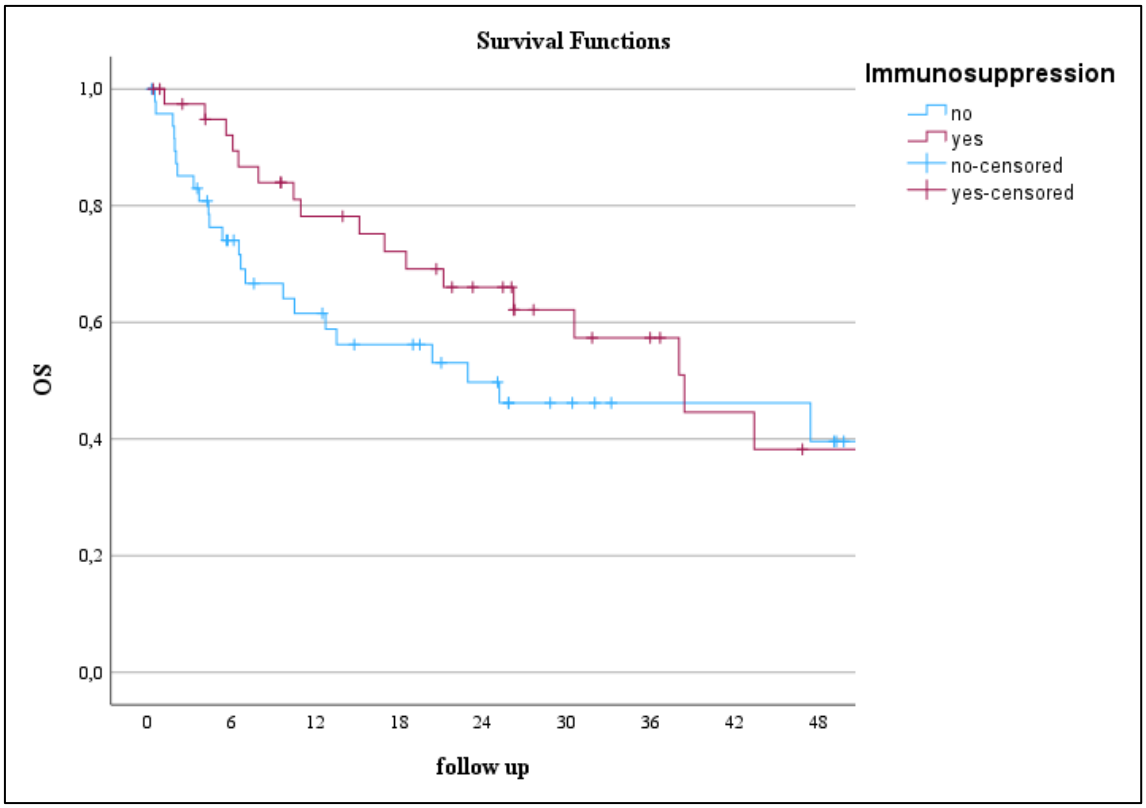

Figure 36: mOS immunosuppressive therapy – PAD ± immunosuppression

3.4.10 Prognostic factors

3.4.10.1 Number of metastatic organs

Number of distant metastases had no impact in median overall survival (p=0.565). If patients had up to 3 metastatic organs mOS was 38.0 (95% CI: 21.9-54.2) and if more 25.2 (95% CI: 2.4-47.9). (Figure 37)

Similar results (p=0.765) can be seen in patients with active immunosuppression. mOS for 1-3 affected organs was 38.4 (95% CI: 27.0-49.9) if more median was not reached. (Figure 38)

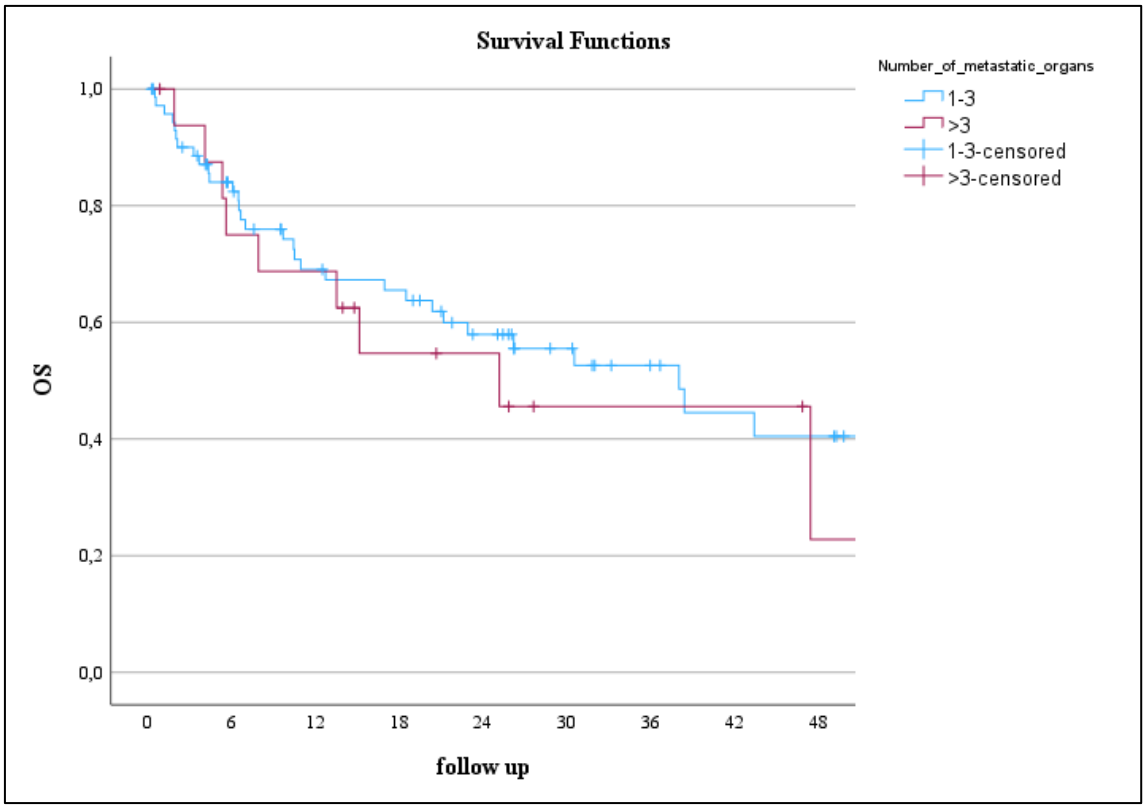

Figure 37: mOS number of metastatic organs – PAD ± immunosuppression

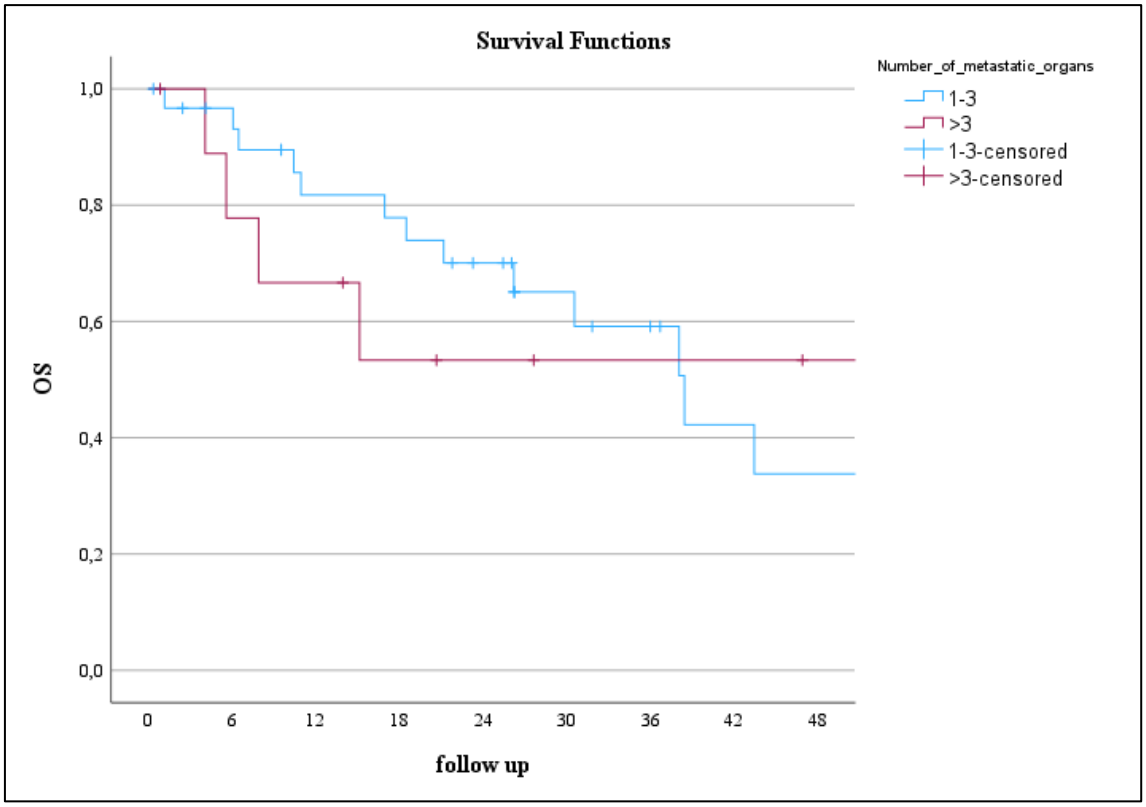

Figure 38: mOS number of metastatic organs – PAD + immunosuppression

3.4.10.2 Brain metastases

Existence of brain metastases had no significant difference regarding mOS (p=0.727). If patients had brain metastases mOS was 47.5 months (95% CI: 1.6-93.3), if not 38.0 months (95% CI: 23.2-52.9). (Figure 39)

If patients with active immunosuppression had no brain metastases, mOS was 38.4 months (95% CI: 24.6-52.2). If they had brain metastases, median was not reached (p=0.560) (Figure 40)

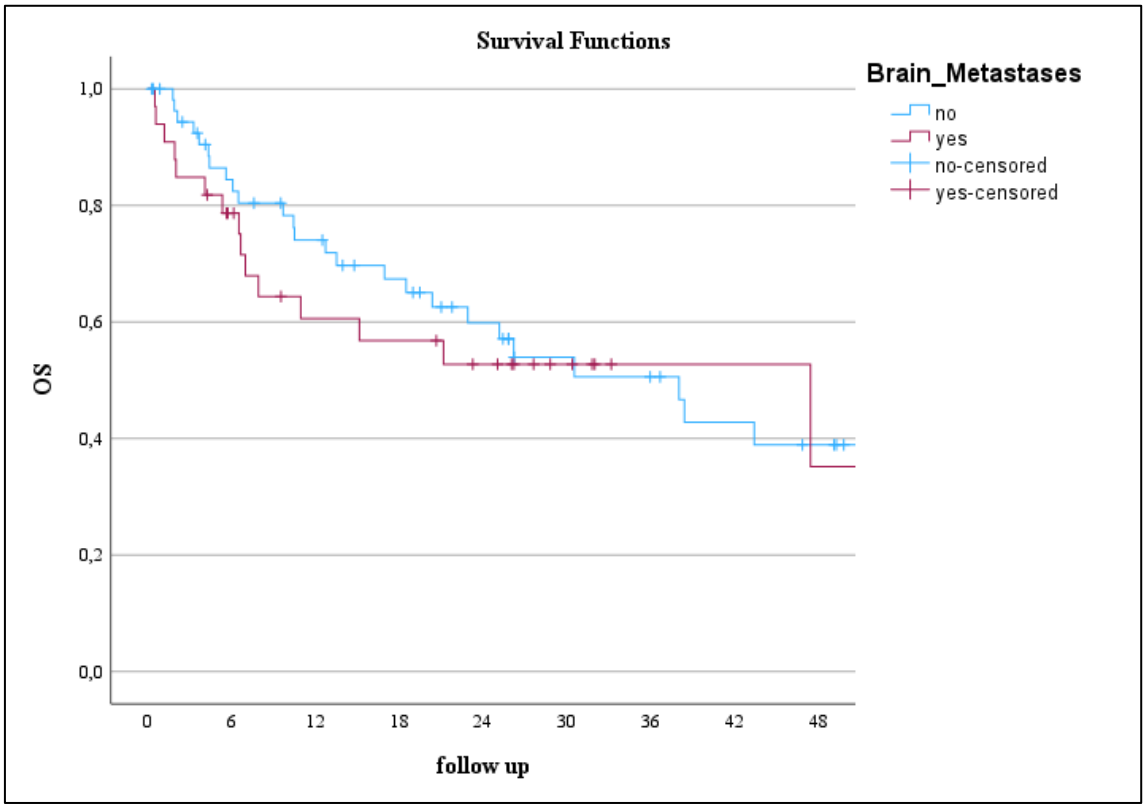

Figure 39: mOS brain metastases – PAD ± immunosuppression

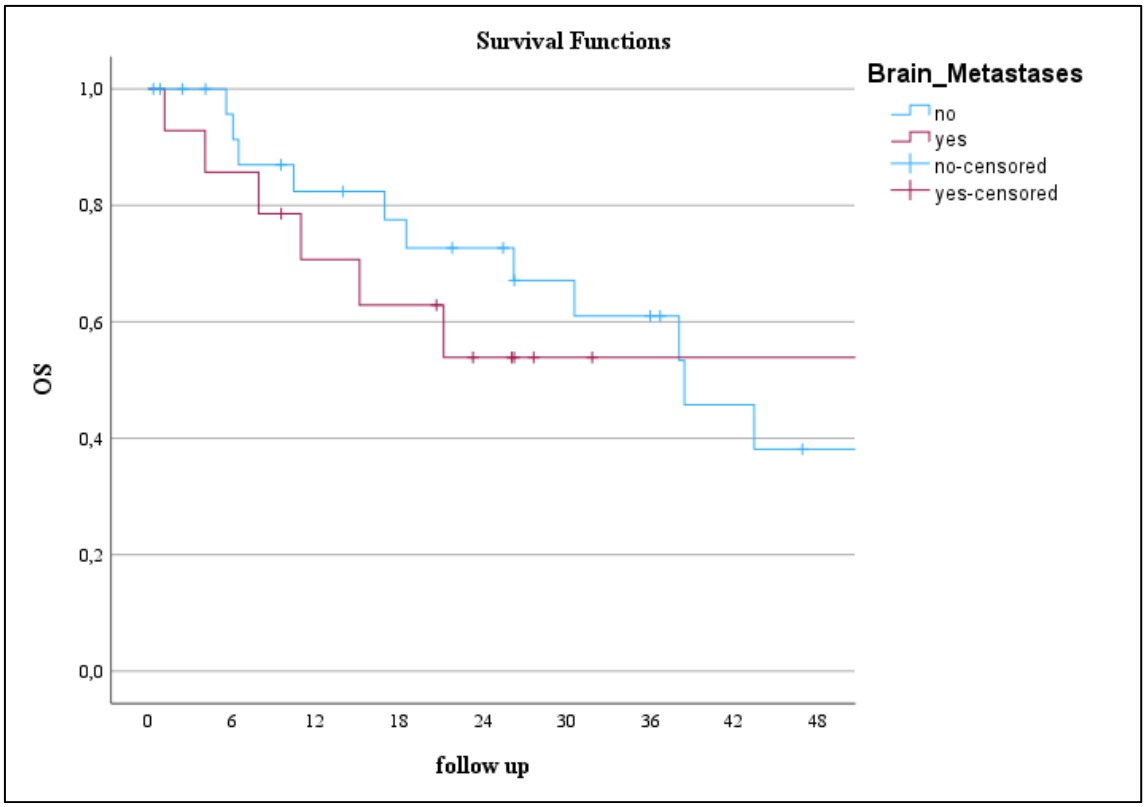

Figure 40: mOS brain metastases – PAD + immunosuppression

3.4.10.3 Liver metastases

If patients had liver metastases there was no significant difference regarding mOS (p=0.970). If yes, mOS was 38.4 months (95% CI: 15.8-61.0) and if not 30.5 months (95% CI: 7.5-53.5). (Figure 41)

Patients with active immunosuppression also had insignificant differences in mOS (p=0.463). If yes, mOS was not reached and if not 38.54 months (95% CI: 11.2-64.9). (Figure 42)

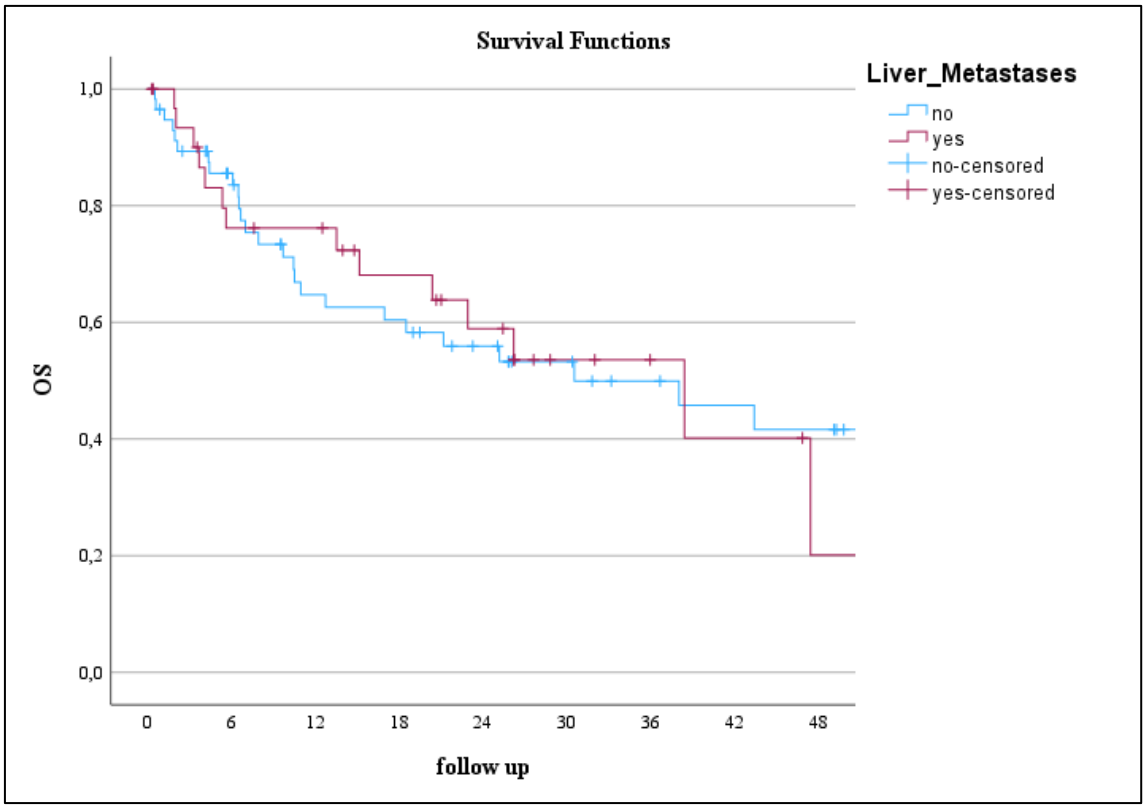

Figure 41: mOS liver metastases – PAD ± immunosuppression

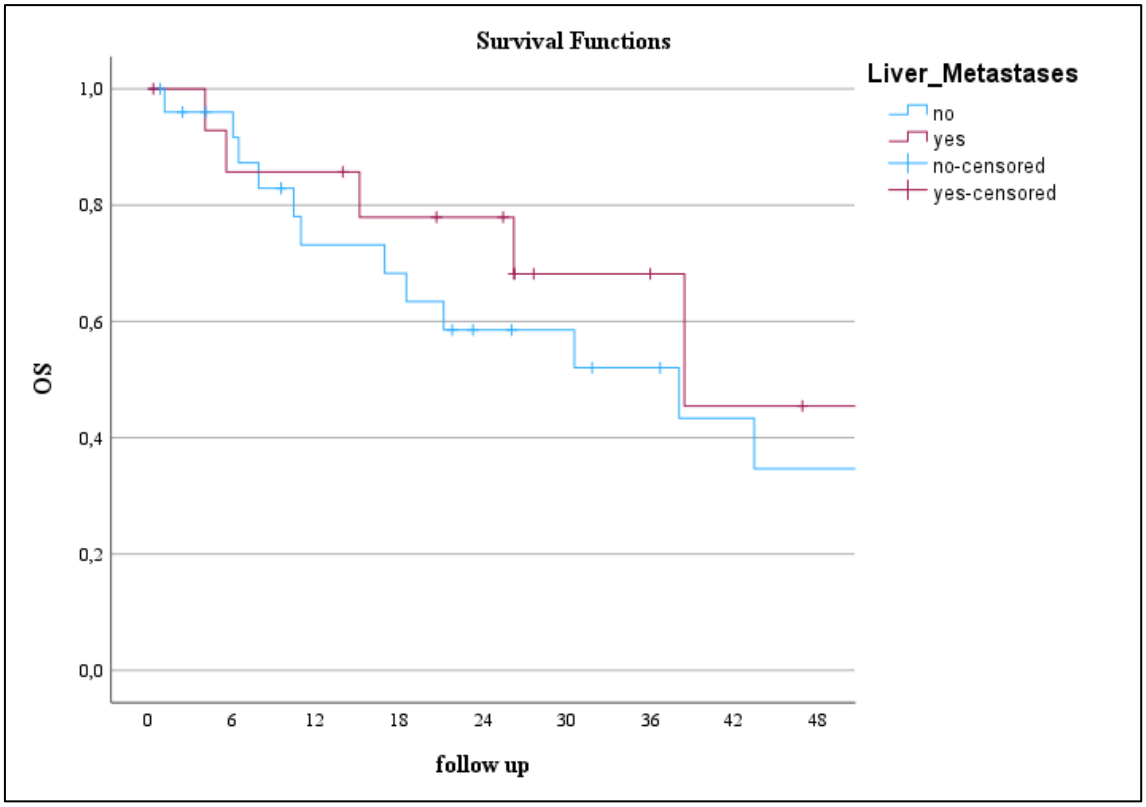

Figure 42: mOS liver metastases – PAD + immunosuppression

3.5 Influence of systemic therapies on overall survival

3.5.1 Therapy regimen

3.5.1.1 Systemic therapy

87.6 % of patients (n=78) received any systemic therapy. Differences in mOS were insignificant (p=0.084). If patients ever had systemic therapy, mOS was 38.4 months (95% CI: 19.2-57.7), if not 6.5 (95% CI: 2.1-10.9). (Figure 43)

If patients received active immunosuppression because of PAD, differences in mOS were also insignificant (p=0.460). If patients ever had systemic therapy, mOS was 38.4 months (95% CI: 24.7-52.1), if not median was not reached.

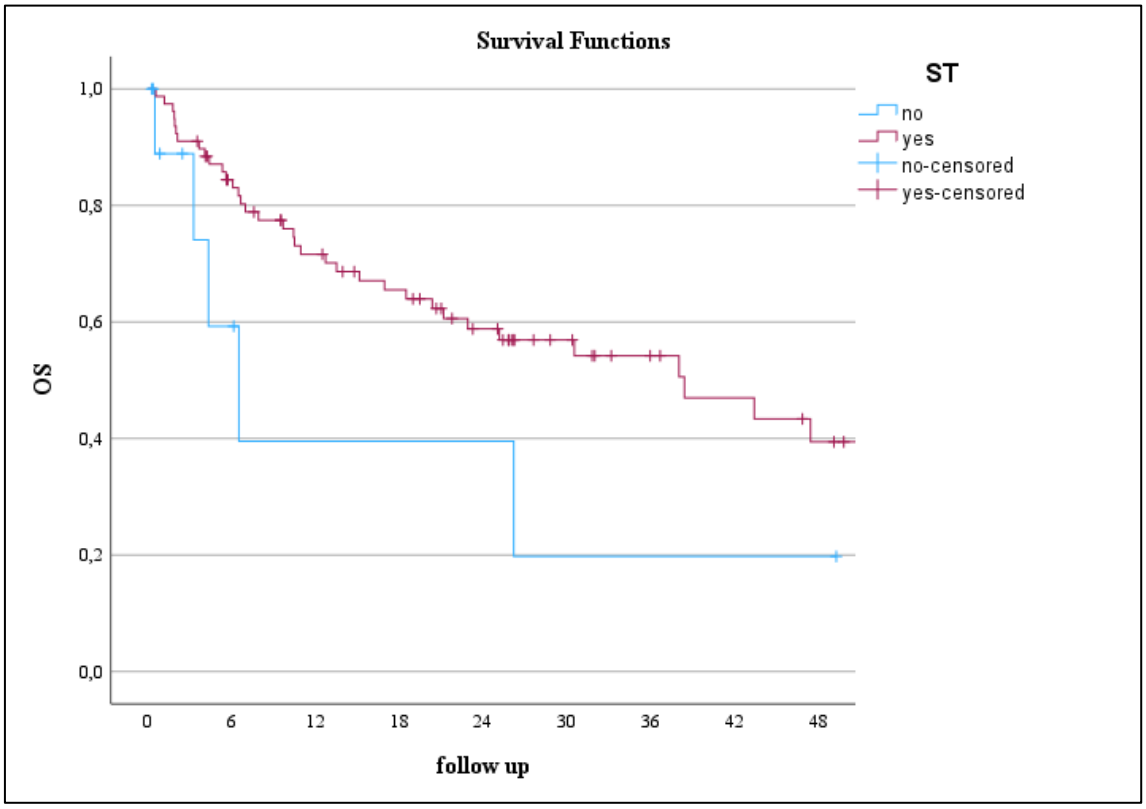

Figure 43: mOS systemic therapy – PAD ± immunosuppression

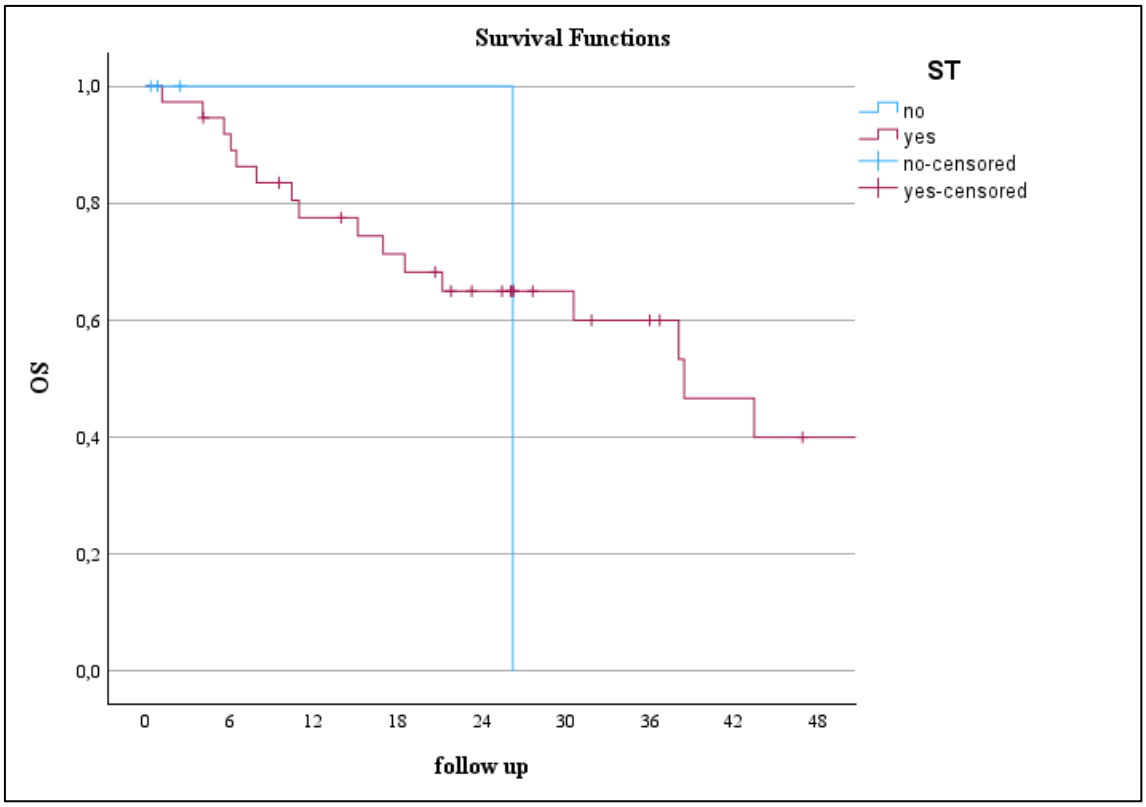

Figure 44: mOS systemic therapy – PAD + immunosuppression

3.5.1.2 PD-1 monotherapy

If patients received PD-1 monotherapy we were not able to find significant differences in survival rates (p=0.314). If patients received PD-1 monotherapy at some point mOS was 43.4 months (95% CI: 11.3-75.5) and if not 30.5 months (95% CI: 14.3-46.7). (Figure 45) There were also no significant differences in mOS regarding active immunosuppression (p=0.847). mOS with PD-1 monotherapy was 38.4 months (95% CI: 6.1-70.8) and without 38.0 months (95% CI: 22.7-53.4). (Figure 46)

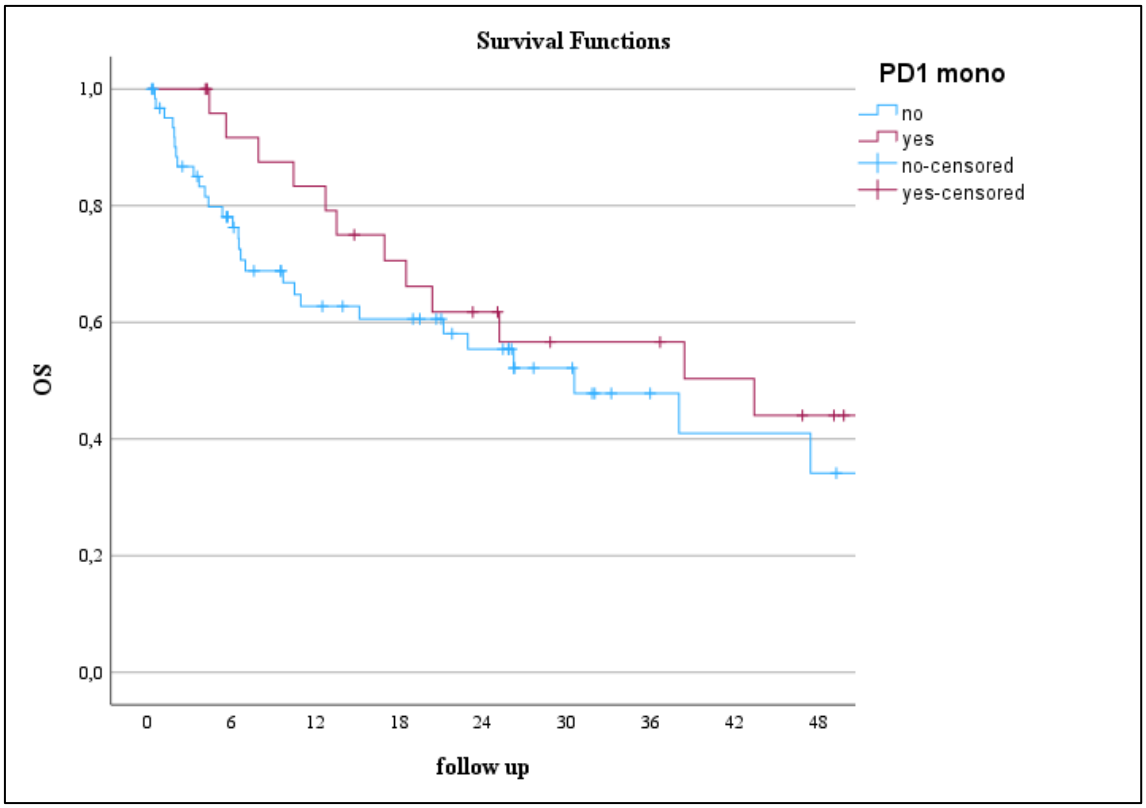

Figure 45: mOS PD-1 monotherapy – PAD ± immunosuppression

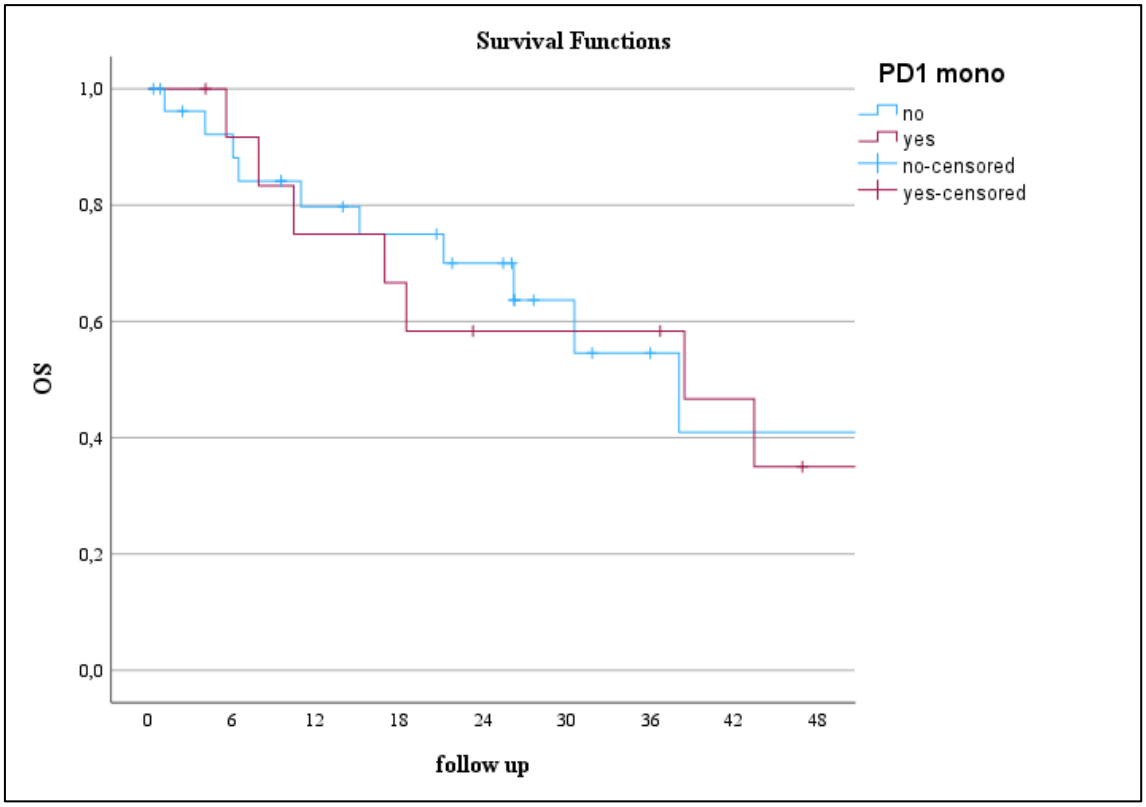

Figure 46: mOS PD-1 monotherapy – PAD + immunosuppression

3.5.1.3 PD-1/CTLA-4

We found no significant evidence in median overall survival when combined immunotherapy (PD-1/CTLA-4) was administered (p=0.381). Patients receiving combined immune checkpoint inhibition mOS was 38.0 (95% CI: 19.8-56.3) and if they did not 26.2 months (95% CI: 0.0-53.9). (Figure 47)

We could not find significant differences (p=0.870) if patients received active immunosuppression. mOS with combined ICI was 38.0 months (95% CI: 21.4-54.7) and without 38.4 months (95% CI: 9.2-67.7). (Figure 48)

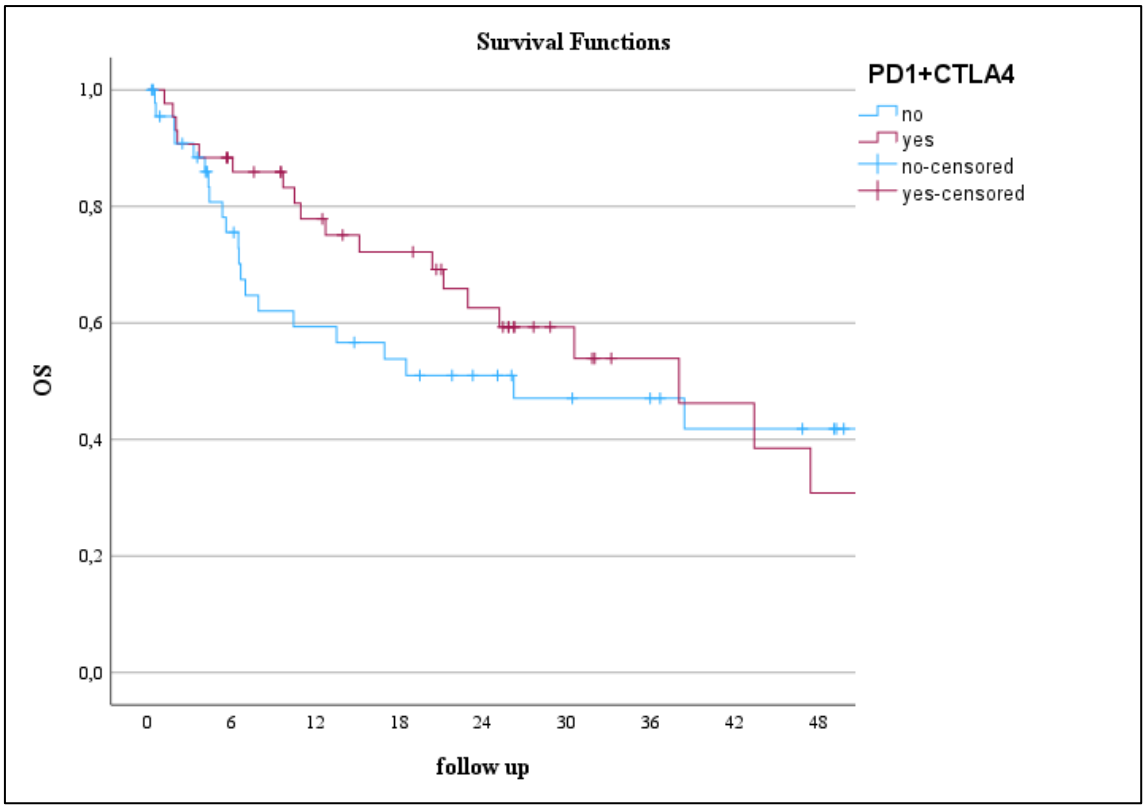

Figure 47: mOS PD-1/CTLA-4 – PAD ± immunosuppression

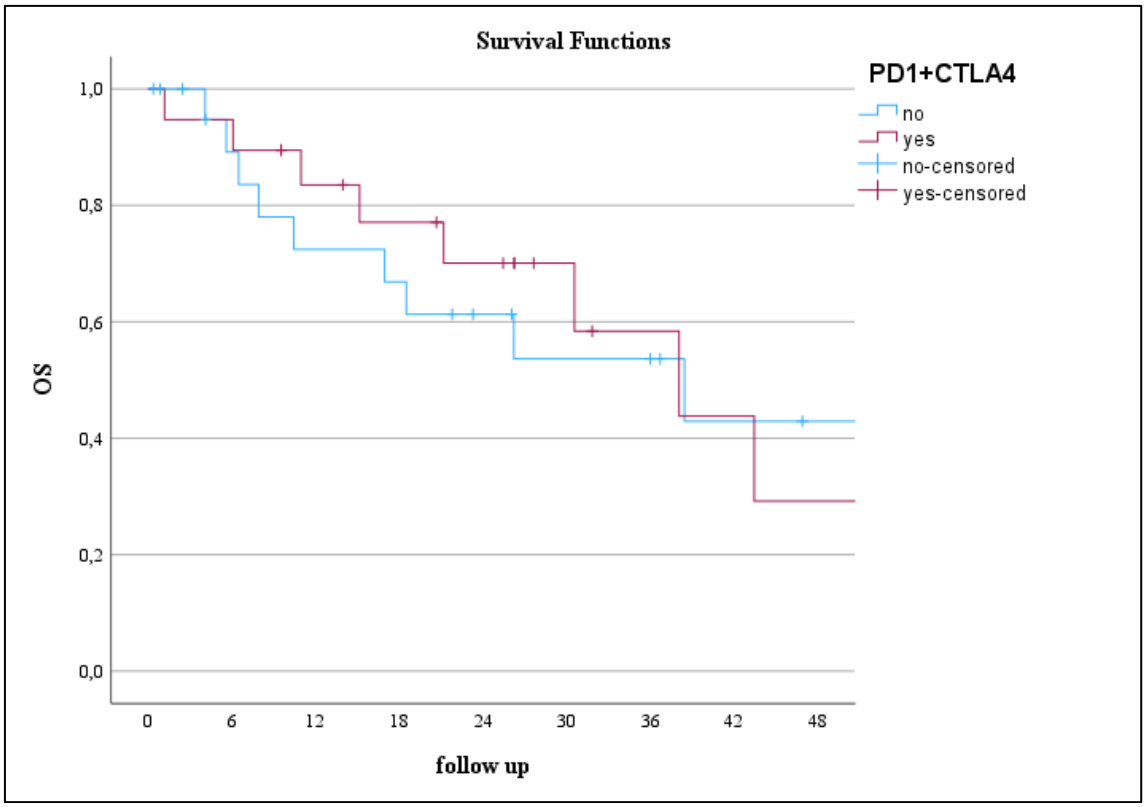

Figure 48: mOS PD-1/CTLA-4 – PAD + immunosuppression

3.5.2 First-line vs second-line therapy

We can see a significant differences (p=0.01) in survival between type of used therapy regimens as first-line therapy. mOS for PD-1 monotherapy was 79.5 months (95% CI: 20.1-138.8), 38.0 months (95% CI: 18.9-57.2) for PD-1/CTLA-4 combined immunotherapy, 6.0 months (95% CI: 0.0-22.3) for other (TT, CTLA-4 monotherapy or other combinations). (Figure 49)

For patients undergoing active immunosuppression, there were no significant results (p=0.094). Median for mOS in PD-1 monotherapy and PD-1/CTLA-4 combined immunotherapy was not reached, mOS for other therapies was 18.5 months (95% CI: 8.2-28.8) (Figure 50)

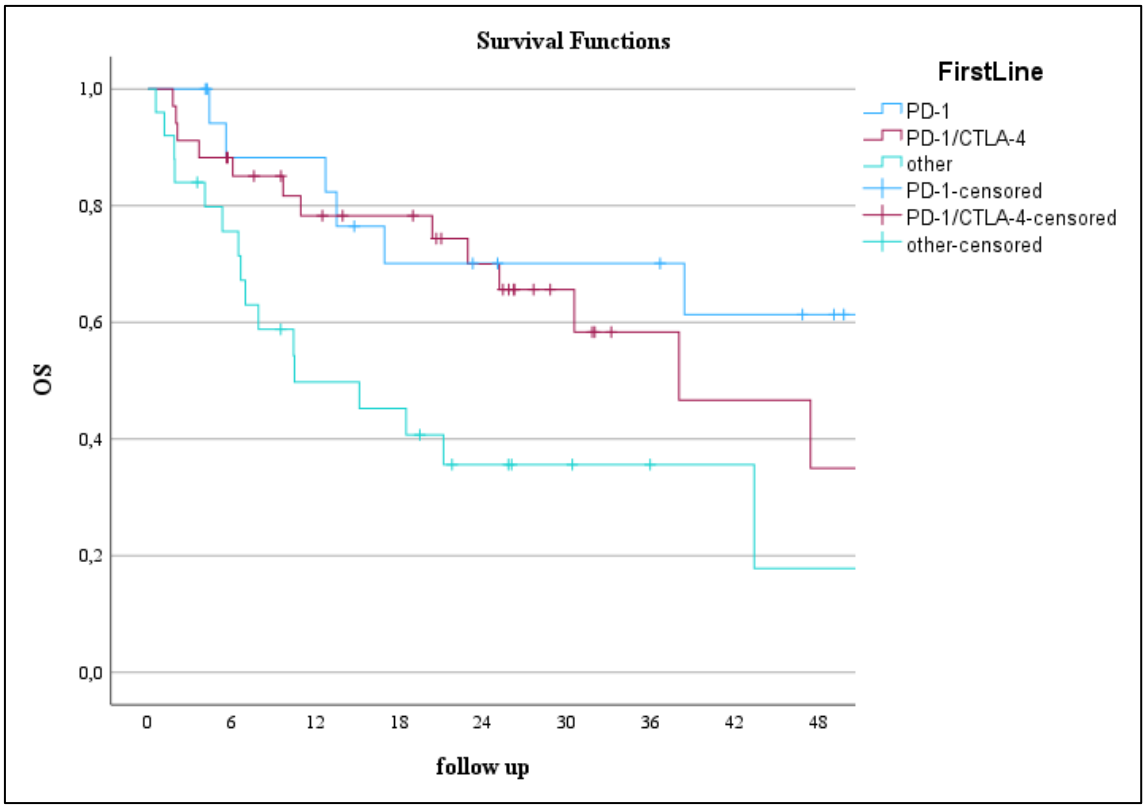

Figure 49: mOS first-line therapy – PAD ± immunosuppression

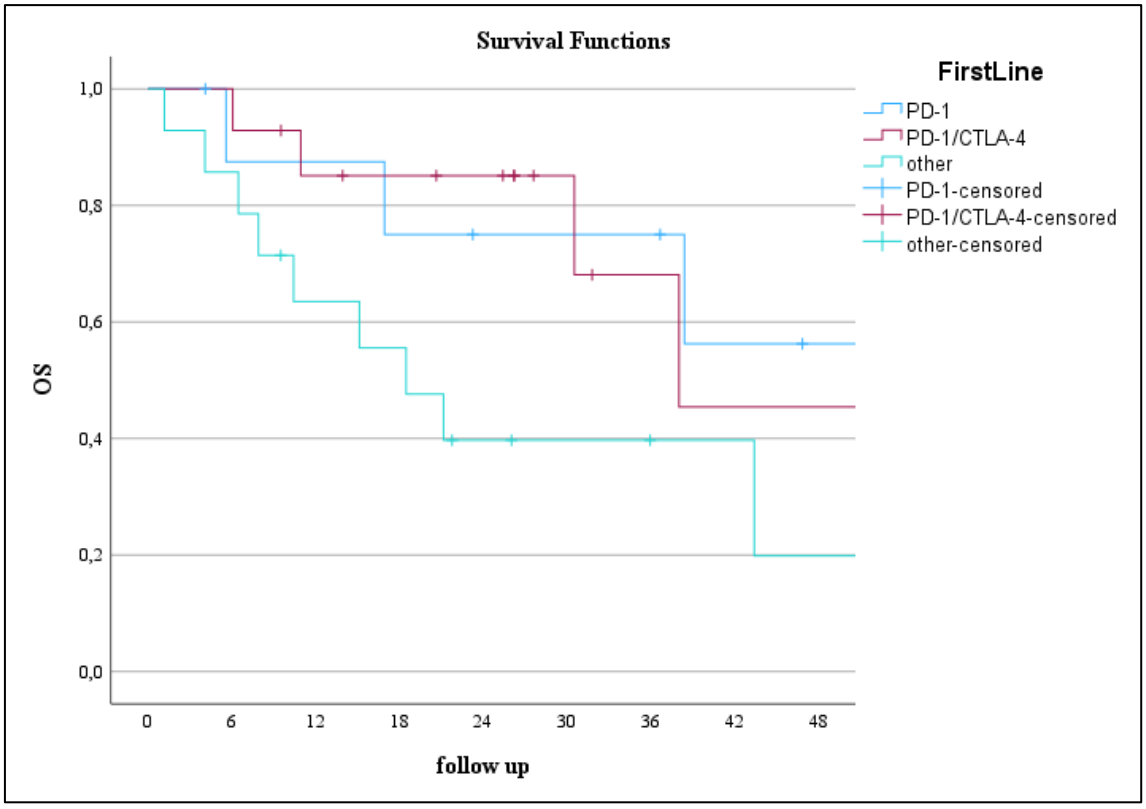

Figure 50: mOS first-line therapy – PAD + immunosuppression

In contrast, we cannot see significant differences in second-line therapy for all patients with PAD (p=0.933). mOS for patients receiving PD-1 based therapy was 21.2 months (95% CI: 17.2-26.2) and for other therapy regimen 15.1 months (95% CI: 2.9-27.4). (Figure 51)

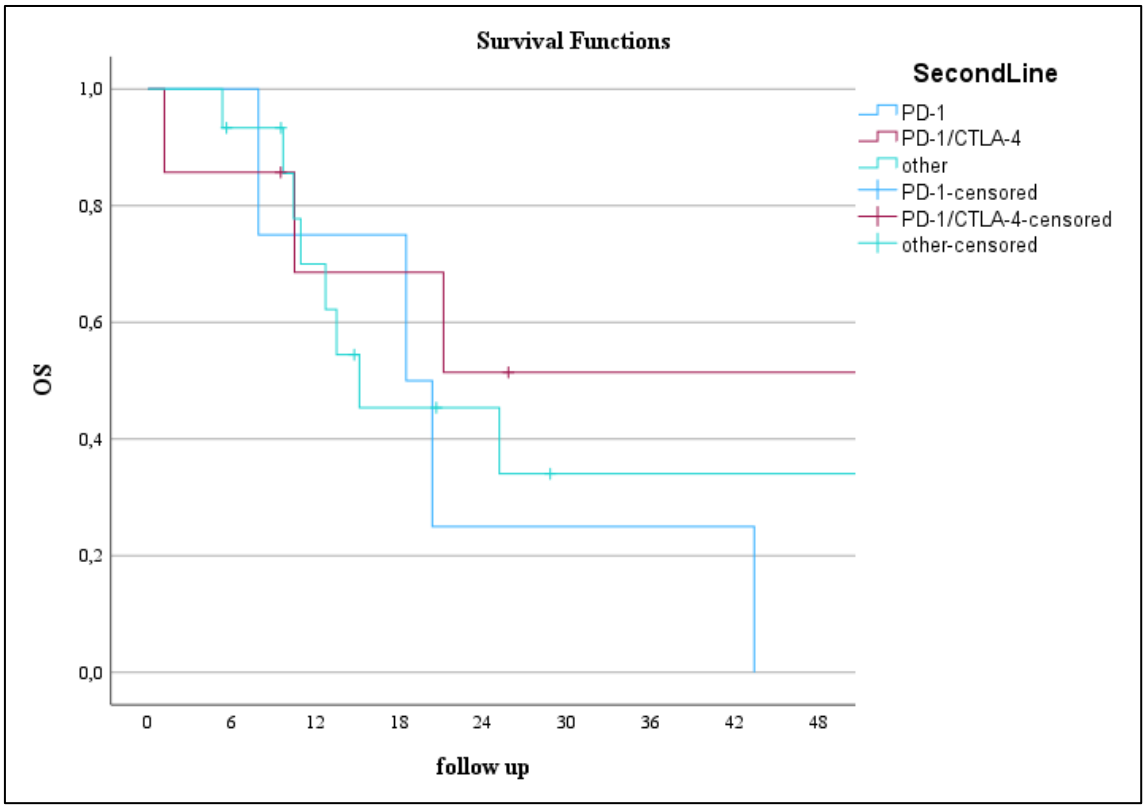

Figure 51: mOS second-line therapy – PAD ± immunosuppression

When receiving active immunosuppression, significant differences could also not be found (p=0.612). mOS for PD1 monotherapy was 18.5 months (95% CI: 1.5-35.4), for PD-1/CTLA-4 combined ICI 15.3 months ((95% CI: 0.0-51.1). mOS for other therapies was not reached.

3.5.3 Progression Free Survival (PFS) under active immunosuppression

PFS1 is defined as the time interval between the start of first systemic therapy and the date of disease progression. PFS2 is defined as the time interval between the start of first systemic therapy and the date of second disease progression.

In total 38 patients had 1, 25 had 2, 8 had 3, 4 had 5, 2 had 6 and 1 had 7 different systemic therapy regimens.

Median PFS1 was 3.7 months for all PAD patients (95% CI: 2.0-5.4) (Figure 51). Median duration of ST1 was 5.8 months and median time to BOR1 was 3.1 months. (Figure 53) Median PFS1 for PAD + immunosuppression was 4.1 months (95% CI: 1.6-6.6). Median duration of ST1 8.2 months and median time to BOR1 was 3.2 months. (Figure 54)

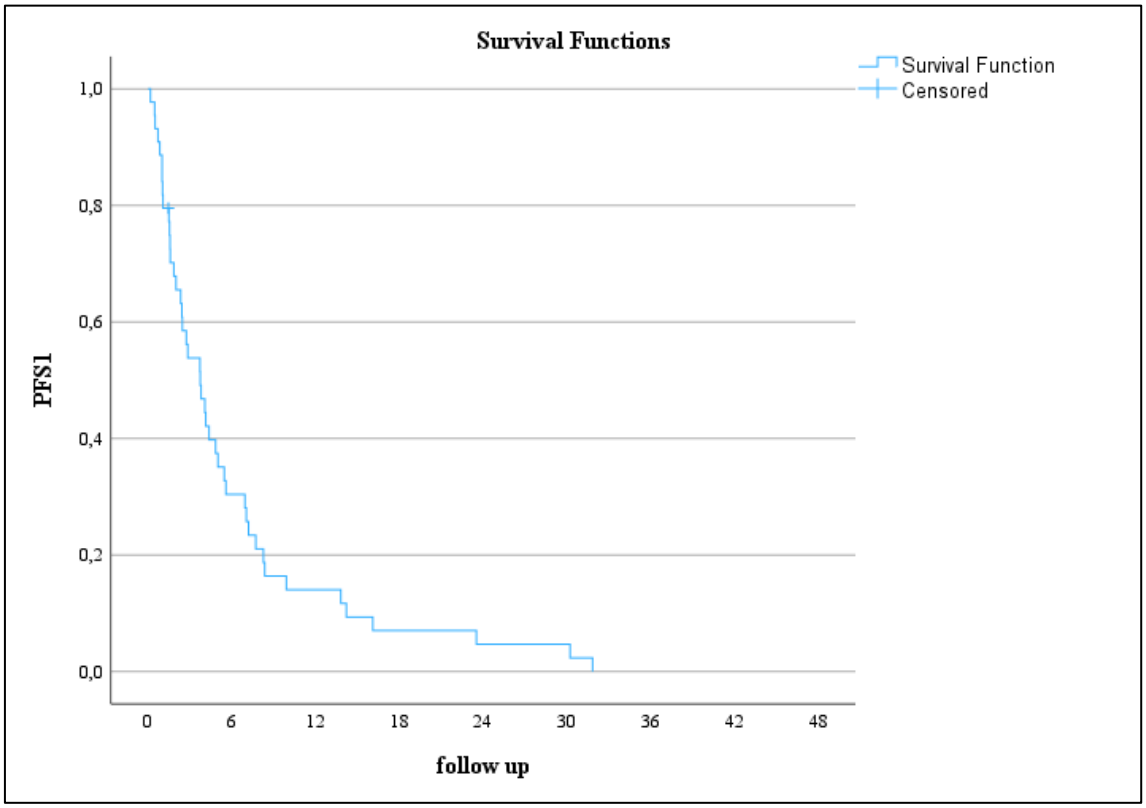

Figure 52: PFS1 – PAD ± immunosuppression

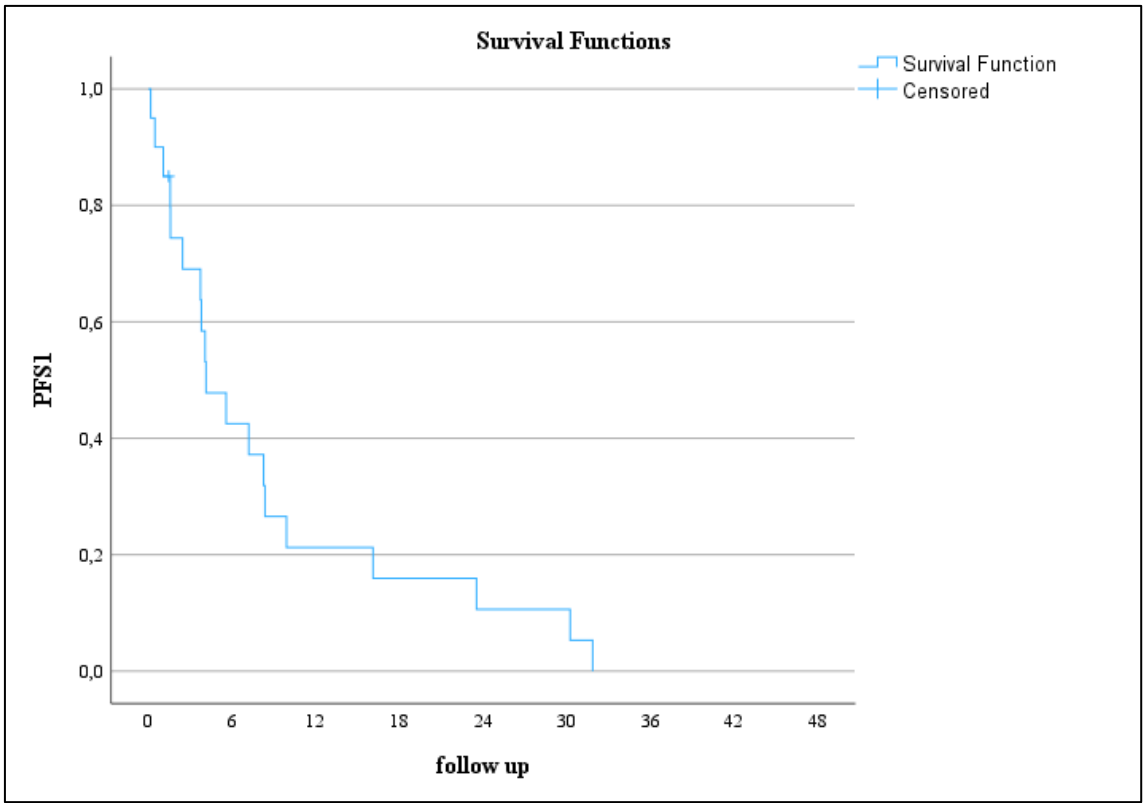

Figure 53: PFS1 – PAD + immunosuppression

We found significant differences (p=0.028) in PFS1 regarding active immunosuppression. If patients received any immunosuppression because of PAD, PFS1 was 4.1 months (95% CI: 1.6-6.6) and if not 2.4 months (95% CI: 1.4-3.4). (Figure 55)

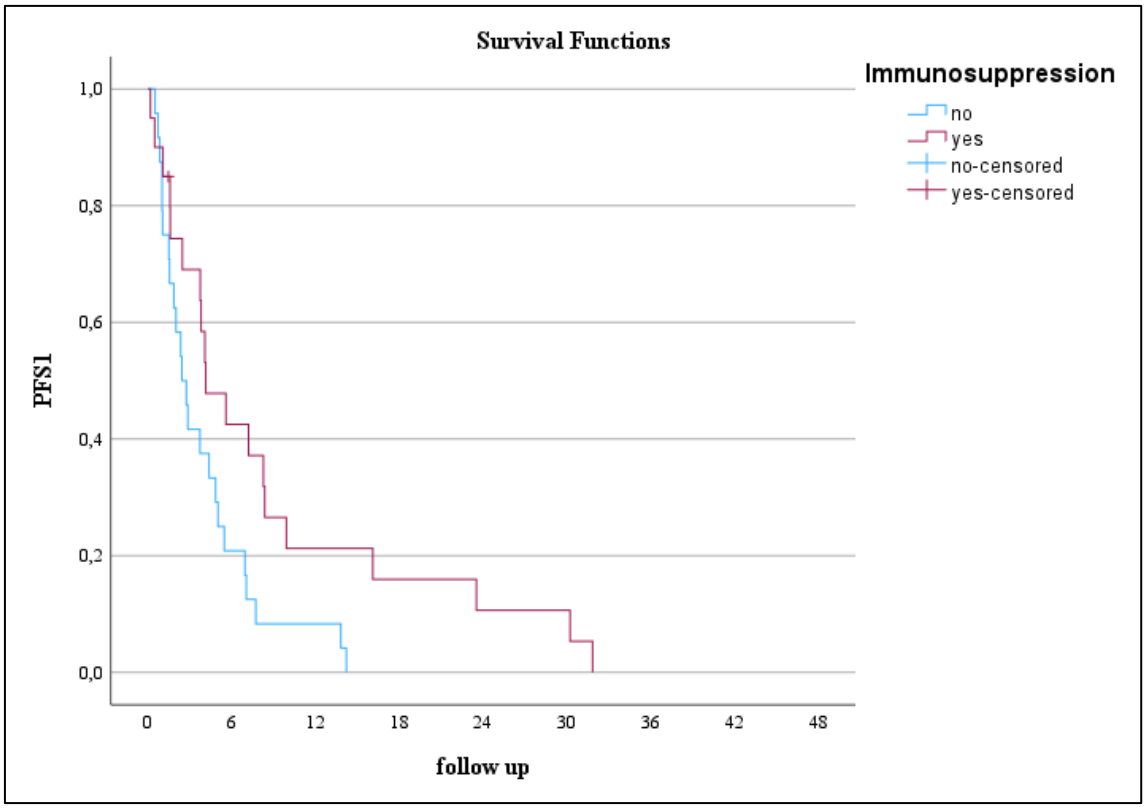

Figure 54: PFS1 PAD ± immunosuppression

Median PFS2 was 10.3 months (95% CI: 7.7-13.0) for all patients and 9.4 months (95% CI: 1.9-16.8) for patients with immunosuppression. (Figures 56, 57)

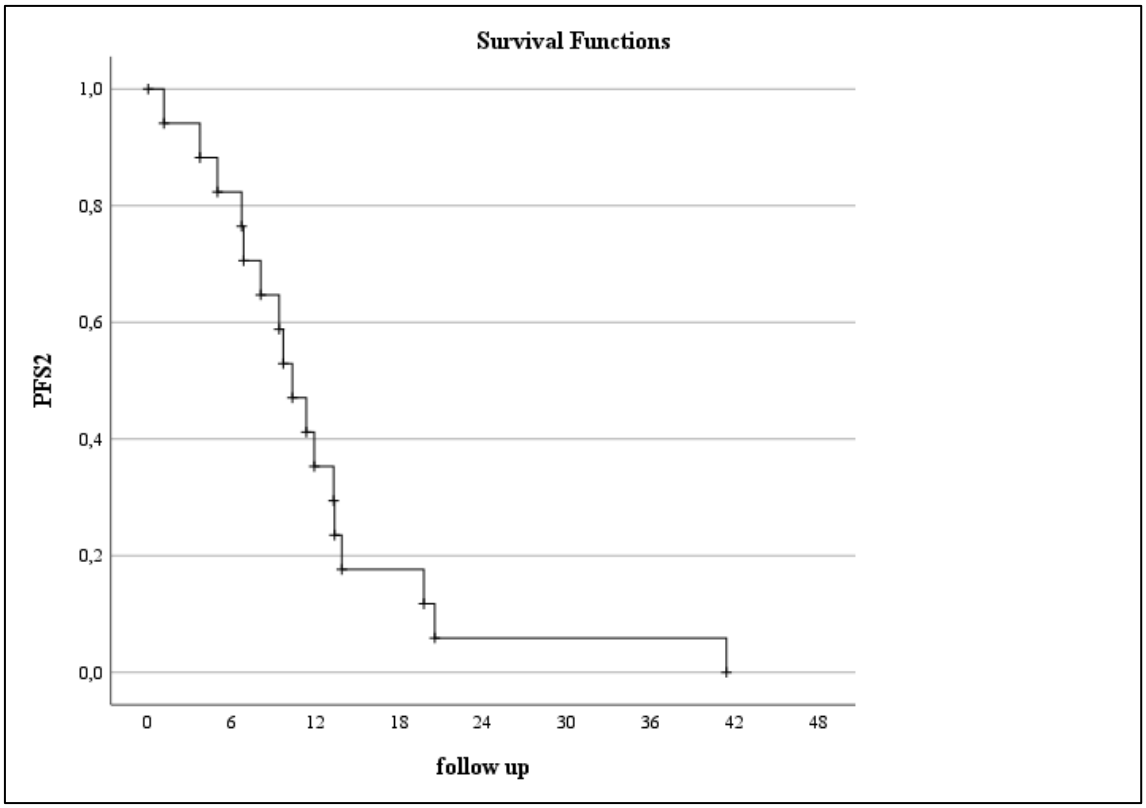

Figure 55: PFS2 – PAD ± immunosuppression

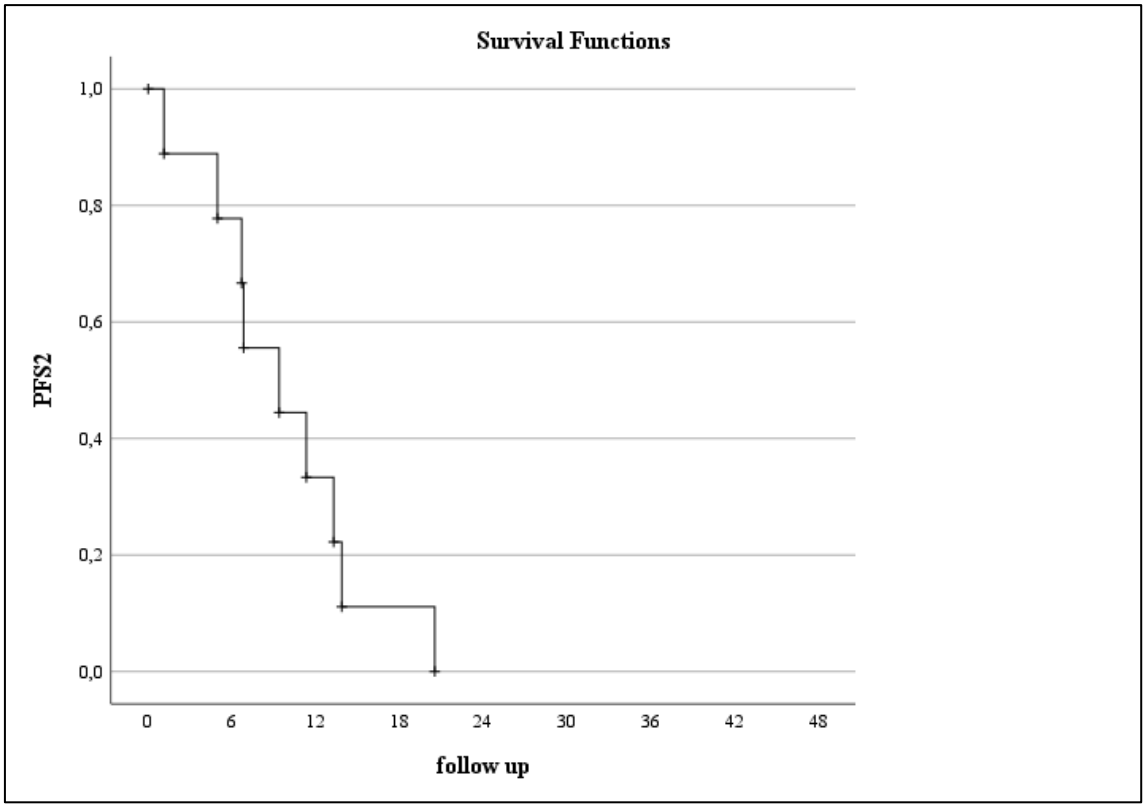

Figure 56: PFS2 – PAD + immunosuppression

There was no significant difference in PFS2 concerning active immunosuppression (p=0.420). If yes, PFS2 was 9.4 months (95% CI: 1.9-16.8), if no 10.3 months (95% CI: 7.2-13.4). (Figure 58) Median ST2 was 4.1 months and median BOR2 time was 2.6 months.

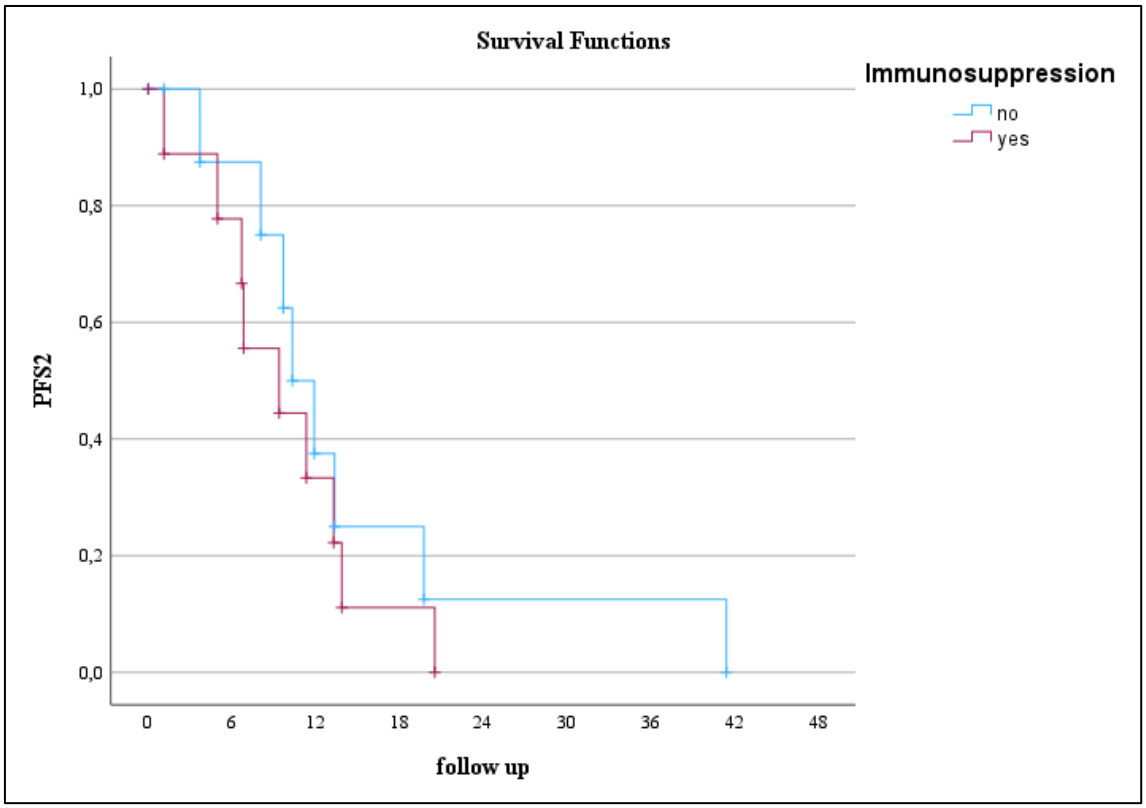

Figure 57: PFS2 PAD ± immunosuppression

3.5.4 Progression Free Survival per first or second-line therapy

PFS1 per first-line therapy showed insignificant results (p=0.725). PFS1 for PD-1 mono 2.3 months (95% CI: 0.0-4.7), for PD-1/CTLA-4 combined immunotherapy 4.4 months (95% CI: 1.2-7.5) and for other therapies 3.7 months (95% CI: 2.0-5.4) (Figure 59). If under active immunosuppressive therapy with PD-1 monotherapy (p_+=0.382) median was not reached, PD-1/CTLA-4 was 5.6 months (95% CI: 0.9-10.2) and other therapies 3.8 months (95% CI: 1.2-6.4) (Figure 60)

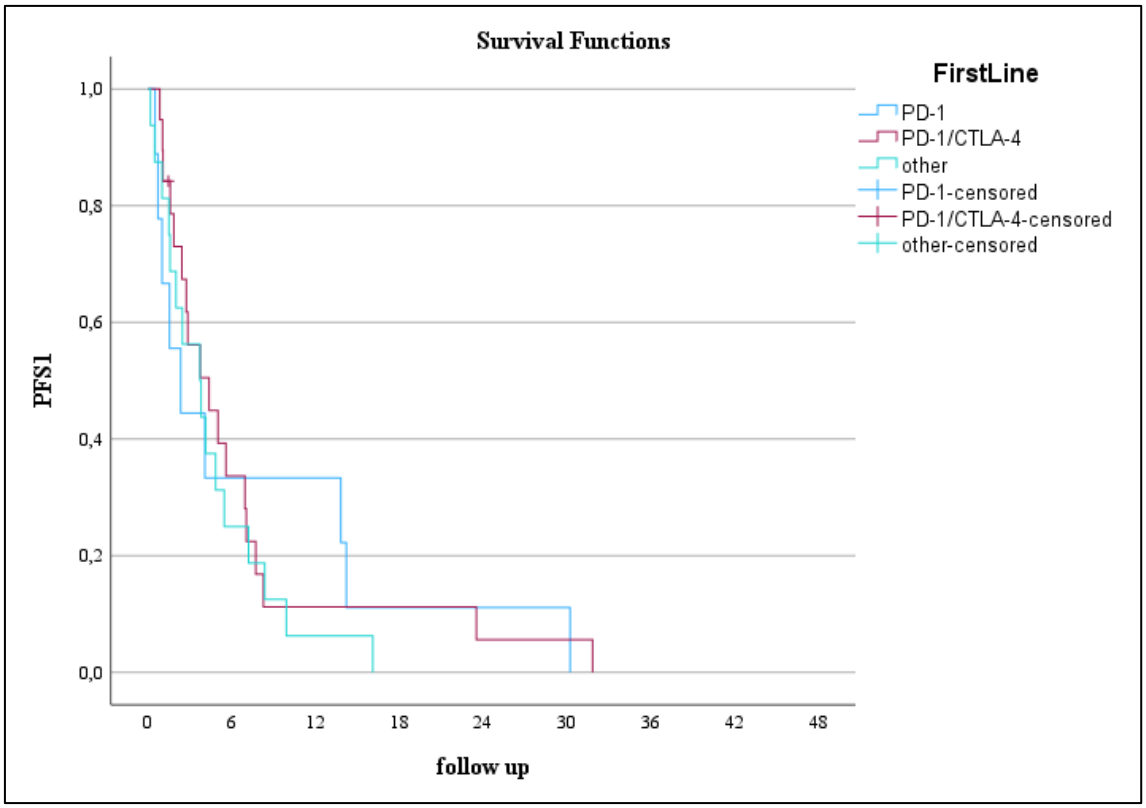

Figure 58: PFS1 per first-line therapy – PAD ± immunosuppression

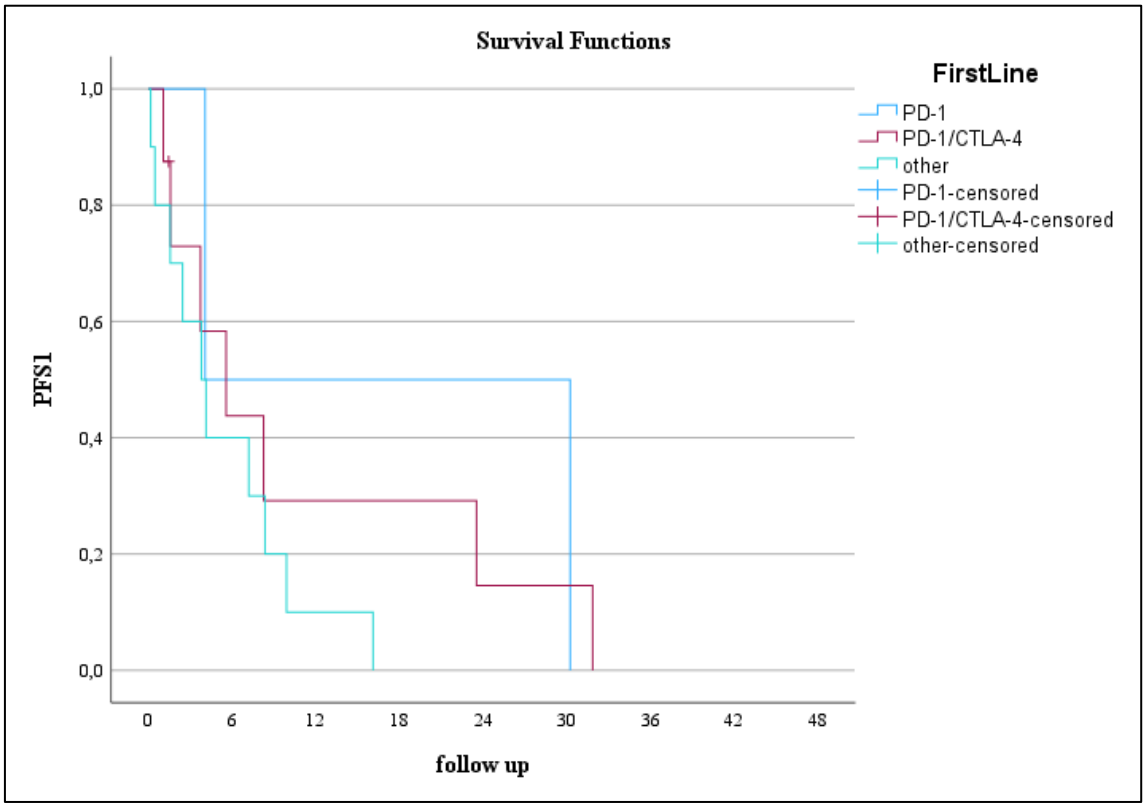

Figure 59: PFS1 per first-line therapy – PAD + immunosuppression

PFS1 second-line was insignificant ($p_{\pm}$=0.824), all cases were censored and median not reached. (Figure 61) PFS1 second-line for patients with active immunosuppression was also insignificant (p_{+}=0.079). PFS1 for PD-1 mono 4.1 months (95% CI: 1.4-6.8), for PD-1/CTLA-4 7.2 months (95% CI: 0.0-14.8) and for other 1.6 months (95% CI: 1.6-1.6) (Figure 62)

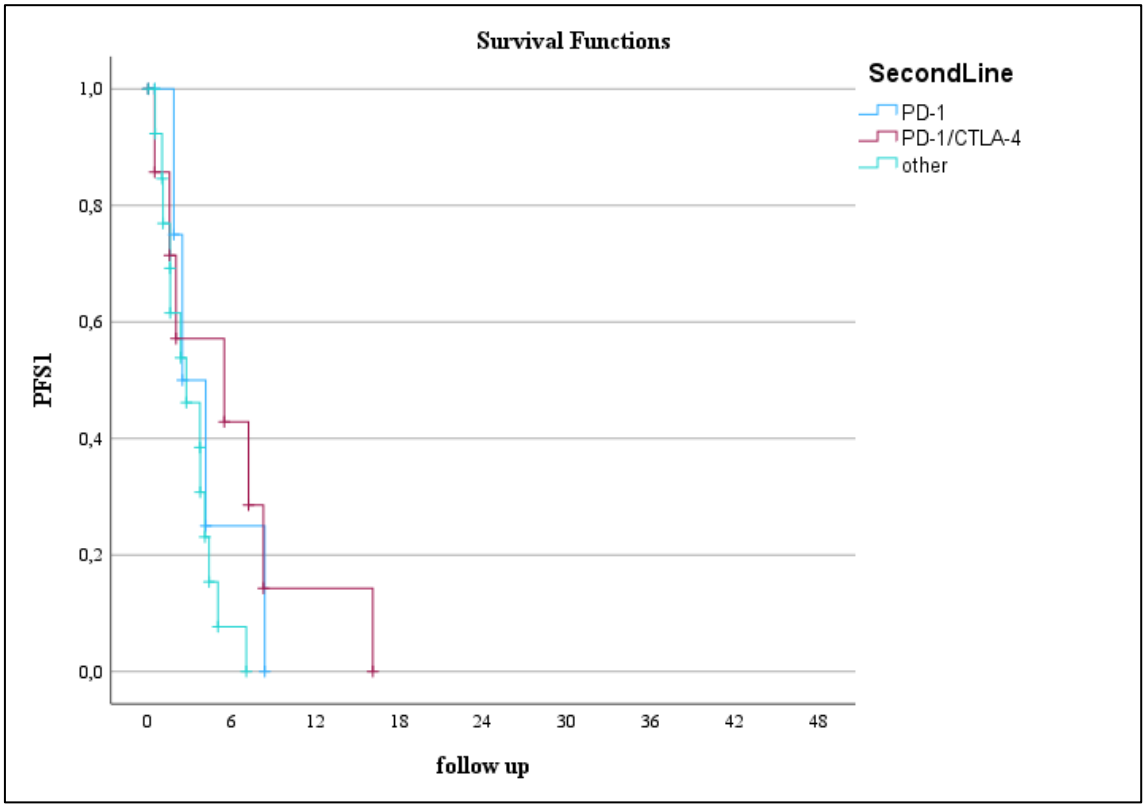

Figure 60: PFS1 per second-line therapy – PAD + immunosuppression

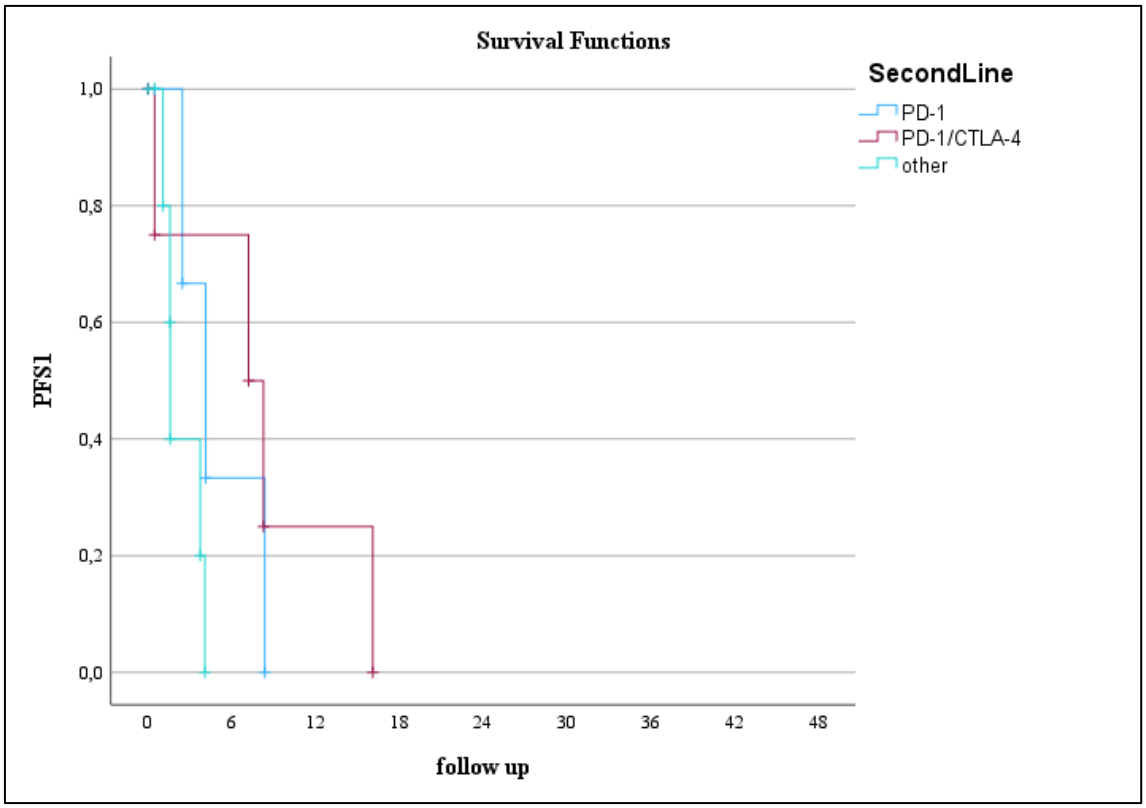

Figure 61: PFS1 per second-line therapy - PAD + immunosuppression

PFS2 also showed insignificant results (p=0.164) for first-line therapy. PD-1 monotherapy was 2.5 months (95% CI: 0.2-4.7), PD-1/CTLA-4 was 4.5 months (95% CI: 0.0-14.3) and other therapies 2.7 months (95% CI: 0.2-5.2) (Figure 63), if under immunosuppressive therapy PFS2 is only available for PD-1/CTLA-4 combined immunotherapy and other therapy. PFS2 for PD-1/CTLA-4 was 6.8 months (95% CI: 6.6-7.0) and for other 9.4 months (95% CI: 1.7-17.0), p=0.541) (Figure 64)

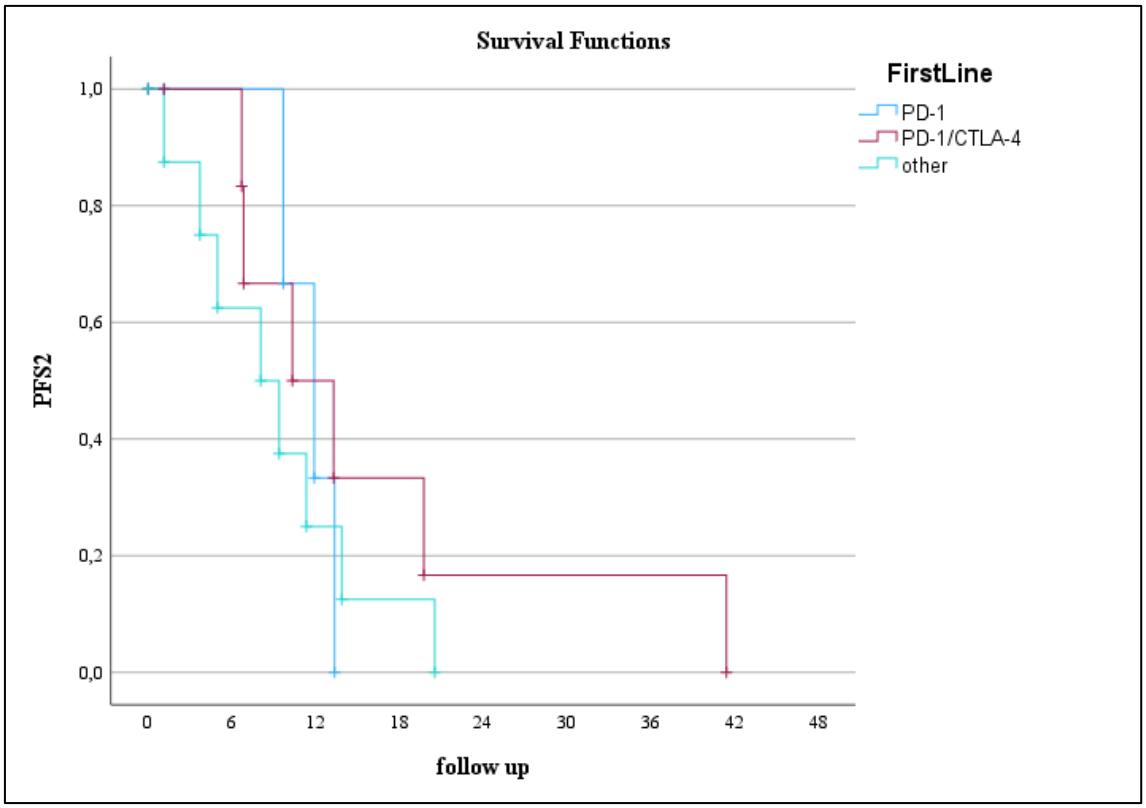

Figure 62: PFS2 per first-line therapy – PAD ± immunosuppression

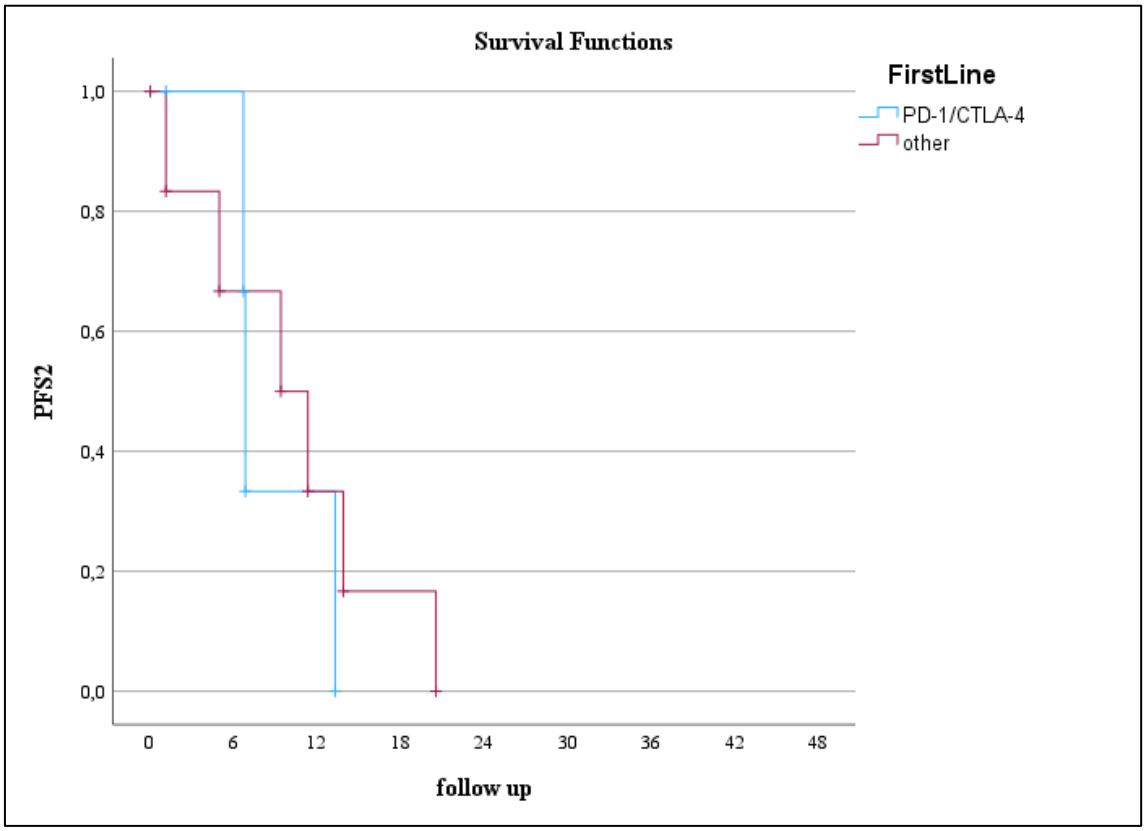

Figure 63: PFS2 per first-line therapy – PAD + immunosuppression

PFS2 second-line was insignificant (p=0.939). For PD-1 monotherapy median was not reached, PD-1/CTLA-4 was 9.4 months (95% CI: 6.5-12.2) and other was 9.7 months (95% CI: 4.3-15.1). (Figure 65)

If patients were under active immunosuppression (p=0.120) PFS2 for PD-1 monotherapy was also not reached. For PD-1/CTLA-4 9.4 months (95% CI: 0.0-21.3) and for other therapies 6.7 months (95% CI: 1.9-16.8).

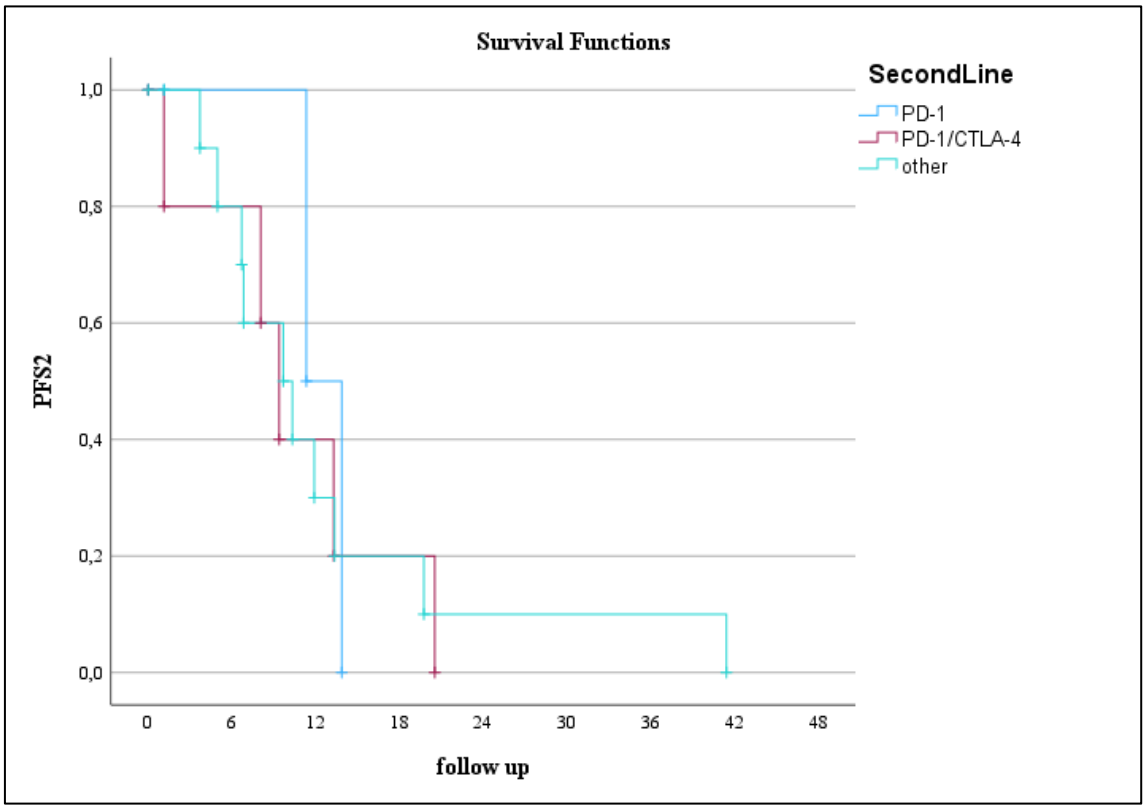

Figure 64: PFS2 per second-line therapy – PAD ± immunosuppression

4. Discussion

In this study, we examined 89 patients with stage IV malignant melanoma and pre-existing autoimmune disease with and without active immunosuppression regarding their response to PD-1 mono- or PD-1/CTLA-4 combined immunotherapy.

The collective analysed in the present study included enough patients with malignant melanoma to be able to assess prognostic factors and the effect of therapies. Corresponding retrospective studies in the literature include comparable patient collectives. The monocentric documentation of the present results analysis was carried out over a long-term period and is therefore quite extensive.

The objective was to evaluate if patients with PAD benefit from ICI, the same way as patients without PAD. This evaluation can only be made retrospectively, as most of the patients are excluded from clinical trials.

4.1 Patient characteristics

4.1.1 Age and sex

The patient population described and analysed in this paper has already been studied in other publications of the Universitäts-Hautklinik Tübingen. (Amaral et al., 2020; Chatziioannou et al., 2023)

A comparison of the epidemiological data from the literature with the data from the presented analysis shows both similarities and differences between the analysed parameters.

Data collection began before the start of the retrospective study. Percentage distribution of the two sexes was completely random. The aim was to reflect heterogeneous real-world treatment practice, ensuring good generalisability of study results to an actual treated patient population.

Of 89 patients, 43 were male (47,4%) and 46 were female (52,6%). The studies by Danlos et al., Tison et al. and Menzies et al show a similar gender distribution pattern (46.7% vs. 52.3%, 47.0% vs. 53.0%, 40% vs. 60%). (Danlos et al., 2018; Menzies et al., 2017; A. Tison et al., 2019)

Median age was 66.9 years (IQR 66.5-78.0. Gutzmer et al described a different and Abdel-Wahab et al described a similar age distribution in a systematic review including 123 patients in 49 publications (61.4 years). (Abdel-Wahab et al., 2018; Gutzmer et al., 2017)

4.2 Primary tumour characteristics

4.2.1 Location of primary tumour

Many patients had the primary tumour located on the upper and lower extremities (44.4%). Further localisations were found on the torso (31.9%) and on the head and neck (17%).

Regarding localisation, similar percentage distribution is reported in literature. (Amaral et al., 2020) Kraywinkel et al. also describe that cutaneous malignant melanoma occurs most frequently on the extremities (46.0%), the trunk (33.0%) and the head/neck region (21.0%). (Kraywinkel et al., 2014)

Between sexes, malignant melanoma appears on different parts of the body exposed to the sun. In women, the skin tumour is typically found on the extremities and in men on the back. Furthermore, the location of the primary tumour differs depending on the histological subtype. (Michielin et al., 2019; Rastrelli et al., 2014)

4.2.2 Histological subtype

Lee et al. describe that the BRAF mutation was most frequently detected in patients with SSM, followed by NM. In ALM, however, fewer patients carried a BRAF mutation. (Lee et al., 2011)

In our own analysis, the most common histological subtype was SSM (27.0%). NM could be diagnosed in 21.3%. OM was diagnosed in 19.5%. ALM was less frequent (4.5%). 22.0% of all patients had other melanomas, which are not further defined. Amaral et al. describe a frequency distribution very similar to our own findings excluding OM. (Amaral et al., 2020)

4.2.3 Laboratory parameters

4.2.3.1 LDH

Diem et al. carried out an analysis in which 51.5% of patients had elevated LDH levels at baseline. Results were a significantly shorter overall survival rate for those patients. (Diem et al., 2016b)

Prognostic value of LDH serum levels was documented in various studies in the past. Weide et al. found out first about LDH as a significant prognostic factor for long term survival in melanoma patients with distant metastasis ($p<0.001$). (Weide et al., 2012) Recent results of pooled analysis published by Long et al. and Schadendorf et al. verified that conclusion (Long et al., 2016. Schadendorf et al., 2017)

In this case 5.6% of patients had to be excluded because of unknown LDH levels. Patients with and without elevation of serum LDH were about even to other studies (46.21 % vs 48.3%) and a corresponding distribution is also described by Weide et al. (Weide et al., 2012)

In present analysis there was no significant difference ($p=0.171$) in median overall survival of patients with different LDH levels at baseline. Again, low number of patients that could be included or presence of PAD may be the reason.

4.2.3.2 S100

The S100 protein is a tissue specific tumour marker and is mostly expressed by glia cells of the brain and melanocytes. Most malignant melanomas have a strong expression of S100.

There are hints that S100 protein may takes a part in survival and proliferation of melanoma cells. (Donato, 2001; Hergovich et al., 2006)

Weide et al. examined a study population in which 40% of patients had elevated S100 levels. They had significantly lower survival rates compared to patients with normal S100 levels baseline ($p<0.001$). (Weide et al., 2012) Eigentler et al. also showed in a retrospective study with 691 patients and cerebral metastases from 1986 to 2007 that S100 was a significant negative prognostic factor in overall survival ($p<0.001$). (Eigentler et al., 2011)

In the present study we could not find a significant difference in overall survival ($p=0.123$); a comparable 47% of patients had elevated S100 levels at baseline. Differences may be caused by overall low number of patients included and additionally several patients without detectable data. Probably PADs are responsible for this unexpected outcome so further research and investigation is needed.

4.3 Prognostic factors

4.3.1 Metastases

In 83.1% of the patients, up to 3 organs were affected with metastases. 16.9% of the total collective had metastases in more than 3 organs. Number of organs metastases was not a significant prognostic factor for survival ($p=0.952$).
The Checkmate-067 study showed a similar distribution with one fifth of patients had metastases in more than 3 organs. (Hodi et al., 2018) Comparable percentages are also found in the study of Schadendorf et al. (Schadendorf et al., 2017)

More than one third of the investigated patient population had brain metastases with insignificant results ($p=0.827$) regarding overall survival. Tio et al. and other publications demonstrated that intracranial spread in stage IV melanoma is associated with a very unfavourable prognosis. (Eigentler et al., 2011; Staudt et al., 2010; Tio et al., 2018; Vosoughi et al., 2018) Patients diagnosed with a single cerebral lesion had a more

favourable prognosis than patients with multiple lesions or leptomeningeal spread (mOS 7 months vs. 4 months). (Eigentler et al., 2011)

In the present study, the liver was also involved in one third of the cases (n=32). A prognostic significance of liver metastases could not be proven significantly (p=0.839). This may be due to the low number of patients included in this study or the presence of PAD. Other studies implied highly significant results (p<0.0001) as presence of liver metastases is associated with lower mOS, PFS and risk of PD.

4.4 Survival analysis

The follow-up period is defined from the date of diagnosis of stage IV disease to the date of the last follow-up examination or death.
In the analysed population treated with targeted therapy, the median follow-up period was 16.9 months, which is considered informative enough to draw representative conclusions. conclusions can be drawn. Brown et all had similar follow-up time (14 months). (Brown et al., 2021) The studies of Danlos et al, Tison et al, Menzies et al report a shorter median follow-up period of 6.3 months, 8 months, 4.7 months respectively. (Danlos et al., 2018; Menzies et al., 2017; A. Tison et al., 2019) Large studies (Checkmate-067) without PAD patients had longer follow up times up to 46.9 months. (Hodi et al., 2018)

4.4.1 Analytic parameters

Overall survival in patients after diagnosis of distant metastasis was better with first-line ICI (PD-1 and PD-1/CTLA-4) ($n_{\pm}$=53) than with second-line ICI ($n_{\pm}$=11). Patients had a median OS of 47.5 months with first-line vs. 21.2 months with second-line. This also applies to patients under active immunosuppression. Their mOS was not reached first-line and 21.2 months second-line.

Patients survived a median of 47.5 months on first-line ICI and 10.5 months on chemo- or targeted therapy ($p_{\pm}$=0.003), ICIs appear superior to other therapies in the examined patient population. First-line ICI therapy was also superior in patients under active immunosuppression (p_{+}=0.019)

Schoenewolf et al. retrospectively analysed 310 melanoma patients in stage IV (AJCC 2009) for possible correlations between the occurrence of metastases and histological subtypes depending on their frequency. For all patients the time to distant metastasis, the distribution pattern of metastases and the associated mOS were analysed.
SSM and NM metastasised significantly more frequently to the brain than ALM (p=0.0012). (Schoenewolf et al., 2014) In this analysis, 27.0% of patients were diagnosed with SSM and 21.3% with NM.

37.1% / 34.1% of the patients had brain metastases. We could not find a significant correlation between presence of brain metastases and shorter mOS ($p_{\pm}$=0.727 / p_{+}=0.560). In contrast to other studies (Davies et al., 2011; Pedersen et al., 2022), patients with PAD might be not affected by brain or liver metastases.

Data analyses by Weide et al. showed that S100 is a meaningful prognostic marker for long-term overall survival. S100 protein is tissue-specific and is particularly expressed by melanocytes, cartilage cells and neuroglia. (Weide et al., 2012)
These findings are confirmed by the present results. Many of the study patients (47.1% / 46.3%) had elevated levels of S100. In this analysis, there was no significant correlation between elevated S100 levels and overall survival ($p_{\pm}$=0.138 / p_{+}=0.989).

Differences in the general state of health of the patients, for example due to comorbidities other than PAD, are possibly responsible for deviating p-values in the survival analyses. Due to the monocentric, retrospective collection of the data, a selection bias cannot be ruled out.

The localisation of melanoma in men and women is often found in different parts of the body. (Kraywinkel et al., 2014) There was neither a significant difference between the sexes ($p_{\pm}$=0.877 / p_{+}=0.315) regarding mOS nor based on the primary tumour location ($p_{\pm}$=0.204 / p_{+}=0.947). The treatment success appears to be independent of gender and tumour location.

Even though LDH is an important prognostic parameter for overall survival in malignant melanoma (Weide et al., 2012), in the present analysis no significant negative influence ($p_{\pm}$=0.150 / p_{+}=0.920) of elevated LDH levels could be determined.
We must keep in mind that LDH levels above the norm are also found in tother malignancies and non-cancerous, inflammatory diseases with cell damage. (Weide et al., 2012)

4.4.2 Active immunosuppression and PD-1 based therapy

46.1% of patients received anti-inflammatory therapy prior to melanoma therapy which corresponds with the patient population that Gutzmer et al examined. (Gutzmer et al., 2017)
19% experienced PAD flare-ups, considerably fewer than reported by Gutzmer et al. (40%) and Menzies et al. (38%). (Gutzmer et al., 2017; Menzies et al., 2017)

Gutzmer et al and Leonardi et al showed that the use of immunosuppressive agents at baseline do not influence efficacy of treatment. (Gutzmer et al., 2017; Leonardi et al., 2018) On the other hand various studies showed inferiority in treatment outcomes for patients with anti-inflammatory medication (Menzies et al p=0.033; Xie et al p>0.05). (Menzies et al., 2017; Xie et al., 2020)

In this study, objective response rate (ORR = CR or PR) for all patients with PAD using ICI was 22.9% for patients receiving PD-1 monotherapy and 35.4% for combined ICI therapy. Patients using immunosuppressive agents had 30.0 and 35.0% respectively.

Overall response rates for PD-1-based therapy in the present study were considerably higher than those reported by Menzies et al. and Gutzmer et al. (58.3% vs. 33.0% vs. 32.0%). (Gutzmer et al., 2017; Menzies et al., 2017) Even more, in patients receiving active immunosuppression (65.0%). Our data suggest a higher success rate with fewer risks. Higher percentages may be the result of including all PD-1-based therapies and the low number of patients receiving ICI therapy overall (53 patients with PAD and 37 patients with PAD and active immunosuppression).

4.4.3 PFS and active immunosuppression

Further we can report significantly better survival rates in mPFS1 with immunosuppression (5.8 months vs 2.7 months; p=0.028).

Other investigators like Tison et al. reported shorter mPFS for immunosuppressive therapy than without immunosuppressive agents in a study with 51 patients (3.8 versus 12 months, p=0.006), differences in mOS were not significant. (A. Tison et al., 2019)
Literature research report similar mPFS for PD-1 monotherapy, 5.1 months, and 6.9 months, respectively (95% CI: 3.5-10.8 and 5.1-10.2). (Hodi et al., 2018). The mPFS1 for combined immunotherapy (nivolumab plus ipilimumab) in the CheckMate-067 trial was 11.5 months, which was about double as long than in the present analysis (95% CI: 8.7-19.3). (Hodi et al., 2018; Wolchok et al., 2017)

Compared to the above-mentioned comparative study without PAD patients (Checkmate-067 study) in terms of overall survival and progression free survival. The following parameters offer a possible explanation: The number of patients in this study was comparatively lower (n=89 vs n=945). In addition, patients with poorer prognostic prerequisites were included in the study, e.g., patients with PAD.
The study cohorts of the cited publications differ significantly from the present number of patients and in terms of inclusion and exclusion criteria; they are therefore heterogeneous and not sufficiently comparable. In this retrospective monocentric study, such differences in endpoints are inherent to the study design. There may also have been a selection bias in the choice of treatment.

4.4.4 irAEs

In our study, 54.7% of patients with PAD and 39.5% patients with PAD under immunosuppression receiving PD-1 therapy experienced irAEs. Similar studies in the past came to different results. In contrast Placais et al. showed in a case-controlled study that PAD patients in fact had higher risk of irAEs and flare ups and that immunosuppression does not lower that risk. (Placais et al., 2022)

Lower numbers in this study may be caused by incomplete documentation. irAEs concerning the skin and thyroid seem underrepresented. Other studies suggest that thyroid and skin related side effects are among the most common (Cortellini et al., 2019; Eigentler et al., 2016; Hofmann et al., 2016) and not the least common.

Severe irAEs (grade ≥ 3) in this study were seen in 27.5% of all PAD patients. These numbers are lower than what Placais et al reported (57.0%). (Placais et al., 2022) Again, this could be affected by inconsistent documentation or if patients continued therapy in another facility.

4.5 Conclusions

1. We could only find significant results when comparing PD-1 therapies (either mono or combined therapy) altogether and not separately. That could be the result of the small sample size of each individual therapy regimen (PD-1 monotherapy first-line = 19 cases, combined immunotherapy = 33 cases). Insignificant result regarding non-therapeutic parameters may be the result of presence of PAD.
2. Consequently, it is difficult to draw meaningful comparisons with other publications or make therapy-relevant conclusions. Insignificant results may be attributable to the small sample size within individual ICI regimen subgroups.
3. Regarding mPFS, there were no significant differences in the type of therapy regimen in both first-line and second-line therapy. Present study demonstrates worse outcomes regarding mOS and mPFS compared to other studies without patients facing PAD (Checkmate-067 study), that includes findings for all patients with PAD and the subgroup receiving active immunosuppression. One possible explanation is the comparatively small number of patients in our own study (n=89 vs. n=945); furthermore, it is possible that patients with poorer prognostic conditions were included.
4. irAEs occur less often than in previous studies including patients with PAD and without. These results include irAEs in general and severe irAEs (CTCAE ≥ 3). Some irAEs are underrepresented to most of other studies (e.g., thyroid and cutaneous), this may lead to the assumption that documentation was incomplete.

4.6 Performance and Limitation

Advantages of the present study the large patient population (n=89) with diagnosed stage IV malignant melanoma and pre-existing autoimmune diseases between January 2015 and December 2021.

The median follow-up time of 16.9 months is long enough to draw meaningful conclusions.

Patients received first-line PD-1 based systemic therapy for a median duration of 5.8 months. Second-line systemic therapy with PD-1 had a median duration of 2.4 months. The duration of therapy was long enough for possible immune related adverse events to develop.

The collective includes both patients who were included in clinical trials and patients who received PD-1 based therapy as part of standard therapy. Conclusions can be drawn with general validity.

Therapy decisions were discussed in a multidisciplinary setting, and the best individual therapy selection was made for all patients.

On the other hand, this is a monocentric, retrospective study, so that a selection bias exists.

Some patients were not treated exclusively at the Universitäts-Hautklinik Tübingen, but also at other institutions or abroad. Due to new laws on the exchange of clinical information (Datenschutzgrundverordnung, DGVSO), it was difficult in a few cases to obtain a complete overview of the therapies received. Likewise, some therapy continuations or discontinuations could not be followed up. Few death data could not be verified. Local therapies, such as surgery or radiotherapy, were not included. Other prognostic factors that influence survival, e.g., ECOG status or tumour burden, were also not documented in this analysis.

5. Summary

In this study, we retrospectively examined 89 patients with stage IV malignant melanoma and pre-existing autoimmune disease with and without active immunosuppression regarding their response to PD-1 based immunotherapy.

In this univariate analysis, the type of first-line therapy was significantly associated with longer overall survival (PD-1 monotherapy: mOS 79.5 months; p=0.010). Active immunosuppression was significantly associated with longer progression-free survival (PFS1 with immunosuppression: 4.1 months vs. 2.4 months without; p=0.028). Interestingly, established indicators of poor prognosis — elevated LDH and S100 serum levels and the presence of liver and brain metastases — did not show a significant impact on survival in PAD patients.

Systemic treatment of metastatic melanomas with mono- or combined ICI therapy seems to be a viable and safe option for patients with PAD. Immune related adverse events did not generally occur more often or more severely than in patients without PAD.

Current data suggest that immune checkpoint inhibitors can be used safely and effectively in patients with PAD, achieving response rates comparable to those reported in studies of patients without PAD. Further prospective studies should be conducted and clinical guidelines adapted accordingly.

In dieser Studie untersuchten wir retrospektiv 89 Patienten mit malignem Melanom im Stadium IV und vorbestehender Autoimmunerkrankung mit und ohne aktive Immunsuppression hinsichtlich ihres Ansprechens auf eine PD-1-basierte Immuntherapie.

In der univariaten Analyse zeigte der Typ der Erstlinientherapie einen signifikanten Zusammenhang mit einem verlängerten Gesamtüberleben (PD-1-Monotherapie: mOS 79,5 Monate; p=0,010). Aktive Immunsuppression war signifikant mit einem längeren progressionsfreien Überleben assoziiert (PFS1 mit Immunsuppression: 4,1 Monate vs. 2,4 Monate ohne; p=0,028). Interessanterweise zeigten häufig als ungünstig geltende

Prognoseparameter — erhöhte LDH- und S100-Spiegel sowie Leber- und Hirnmetastasen — bei PAD-Patienten keinen signifikanten Einfluss auf das Gesamtüberleben.

Die systemische Behandlung von metastasierten Melanomen mit einer Mono- oder Kombinationstherapie mit ICI scheint eine praktikable und sichere Option für Patienten mit PAD zu sein. Immunbedingte unerwünschte Ereignisse traten im Allgemeinen nicht häufiger oder schwerer auf als bei Patienten ohne PAD.

Die aktuellen Daten deuten darauf hin, dass Immun-Checkpoint-Inhibitoren bei Patienten mit pAVK sicher und wirksam eingesetzt werden können, und zwar mit etwa der gleichen Ansprechrate wie in Studien, die nur Patienten ohne pAVK einschlossen. Es sollten weitere Studien durchgeführt und die Leitlinien entsprechend angepasst werden.

6. Bibliography

Abdel-Wahab, N., Shah, M., Lopez-Olivo, M. A., & Suarez-Almazor, M. E. (2018, 2018). Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Annals of Internal Medicine, 168*(2), 121–130.

Amaral, T., Seeber, O., Mersi, E., Sanchez, S., Thomas, I., Meiwes, A., Forschner, A., Leiter, U., Eigentler, T., Keim, U., & Garbe, C. (2020, Apr 22). Primary Resistance to PD-1-Based Immunotherapy-A Study in 319 Patients with Stage IV Melanoma. *Cancers (Basel), 12*(4). https://doi.org/10.3390/cancers12041027

BAnz AT 04.02.2016 B5, (2016).

BAnz AT 11.01.2017 B4, (2016).

BAnz AT 13.03.2016 B3, (2016).

Baumeister, S. H., Freeman, G. J., Dranoff, G., & Sharpe, A. H. (2016, 2016-05-20). Coinhibitory Pathways in Immunotherapy for Cancer. *Annual Review of Immunology, 34*(1), 539-573. https://doi.org/10.1146/annurev-immunol-032414-112049

Blank, C. U., Haining, W. N., Held, W., Hogan, P. G., Kallies, A., Lugli, E., Lynn, R. C., Philip, M., Rao, A., Restifo, N. P., Schietinger, A., Schumacher, T. N., Schwartzberg, P. L., Sharpe, A. H., Speiser, D. E., Wherry, E. J., Youngblood, B. A., & Zehn, D. (2019, 2019-11). Defining 'T cell exhaustion'. *Nature Reviews. Immunology, 19*(11), 665-674. https://doi.org/10.1038/s41577-019-0221-9

Boon, T., Coulie, P. G., Van den Eynde, B. J., & van der Bruggen, P. (2006). Human T cell responses against melanoma. *Annu Rev Immunol, 24*, 175-208. https://doi.org/10.1146/annurev.immunol.24.021605.090733

Brahmer, J. R., Tykodi, S. S., Chow, L. Q. M., Hwu, W.-J., Topalian, S. L., Hwu, P., Drake, C. G., Camacho, L. H., Kauh, J., Odunsi, K., Pitot, H. C., Hamid, O., Bhatia, S., Martins, R., Eaton, K., Chen, S., Salay, T. M., Alaparthy, S., Grosso, J. F., Korman, A. J., Parker, S. M., Agrawal, S., Goldberg, S. M., Pardoll, D. M., Gupta, A., & Wigginton, J. M. (2012, 2012-06-28). Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. *New England Journal of Medicine, 366*(26), 2455-2465. https://doi.org/10.1056/NEJMoa1200694

Brown, L. J., Weppler, A., Bhave, P., Allayous, C., Patrinely, J. R., Jr., Ott, P., Sandhu, S., Haydon, A., Lebbe, C., Johnson, D. B., Long, G. V., Menzies, A. A., & Carlino, M. S. (2021, May). Combination anti-PD1 and ipilimumab therapy in patients with advanced melanoma and pre-existing autoimmune disorders. *J Immunother Cancer, 9*(5). https://doi.org/10.1136/jitc-2020-002121

Calabrese, L., & Velcheti, V. (2017, 2017-01). Checkpoint immunotherapy: good for cancer therapy, bad for rheumatic diseases. *Annals of the Rheumatic Diseases, 76*(1), 1-3. https://doi.org/10.1136/annrheumdis-2016-209782

Chatziioannou, E., Leiter, U., Thomas, I., Keim, U., Seeber, O., Meiwes, A., Boessenecker, I., Gonzalez, S. S., Torres, F. M., Niessner, H., Sinnberg, T., Forschner, A., Flatz, L., & Amaral, T. (2023, May). Features and Long-Term Outcomes of Stage IV Melanoma Patients Achieving Complete Response Under Anti-PD-1-Based Immunotherapy. *Am J Clin Dermatol, 24*(3), 453-467. https://doi.org/10.1007/s40257-023-00775-7

Chen, D. S., & Mellman, I. (2013, Jul 25). Oncology meets immunology: the cancer-immunity cycle. *Immunity, 39*(1), 1-10. https://doi.org/10.1016/j.immuni.2013.07.012

Colantonio, S., Bracken, M. B., & Beecker, J. (2014, 2014-05). The association of indoor tanning and melanoma in adults: systematic review and meta-analysis. *Journal of the American Academy of Dermatology, 70*(5), 847-857.e841-818. https://doi.org/10.1016/j.jaad.2013.11.050

Common Terminology Criteria for Adverse Events (CTCAE). (2017, 2017).

Conway, J. W., Rawson, R. V., Lo, S., Ahmed, T., Vergara, I. A., Gide, T. N., Attrill, G. H., Carlino, M. S., Saw, R. P. M., Thompson, J. F., Spillane, A. J., Shannon, K. F., Shivalingam, B., Menzies, A. M., Wilmott, J. S., Long, G. V., Scolyer, R. A., & Pires da Silva, I. (2022, Sep). Unveiling the tumor immune microenvironment of organ-specific melanoma metastatic sites. *J Immunother Cancer, 10*(9). https://doi.org/10.1136/jitc-2022-004884

Cortellini, A., Buti, S., Santini, D., Perrone, F., Giusti, R., Tiseo, M., Bersanelli, M., Michiara, M., Grassadonia, A., Brocco, D., Tinari, N., De Tursi, M., Zoratto, F., Veltri, E., Marconcini, R., Malorgio, F., Garufi, C., Russano, M., Anesi, C., Zeppola, T., Filetti, M., Marchetti, P., Botticelli, A., Antonini Cappellini, G. C., De Galitiis, F., Vitale, M. G., Sabbatini, R., Bracarda, S., Berardi, R., Rinaldi, S., Tudini, M., Silva, R. R., Pireddu, A., Atzori, F., Chiari, R., Ricciuti, B., Iacono, D., Migliorino, M. R., Rossi, A., Porzio, G., Cannita, K., Ciciarelli, V., Fargnoli, M. C., Ascierto, P. A., & Ficorella, C. (2019, 2019-6). Clinical Outcomes of Patients with Advanced Cancer and Pre-Existing Autoimmune Diseases Treated with Anti-Programmed Death-1 Immunotherapy: A Real-World Transverse Study. *The Oncologist, 24*(6), e327-e337. https://doi.org/10.1634/theoncologist.2018-0618

Curiel, T. J., Coukos, G., Zou, L., Alvarez, X., Cheng, P., Mottram, P., Evdemon-Hogan, M., Conejo-Garcia, J. R., Zhang, L., Burow, M., Zhu, Y., Wei, S., Kryczek, I., Daniel, B., Gordon, A., Myers, L., Lackner, A., Disis, M. L., Knutson, K. L., Chen, L., & Zou, W. (2004, Sep). Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med, 10*(9), 942-949. https://doi.org/10.1038/nm1093

Danlos, F.-X., Voisin, A.-L., Dyevre, V., Michot, J.-M., Routier, E., Taillade, L., Champiat, S., Aspeslagh, S., Haroche, J., Albiges, L., Massard, C., Girard, N., Dalle, S., Besse, B., Laghouati, S., Soria, J.-C., Mateus, C., Robert, C., Lanoy, E., Marabelle, A., & Lambotte, O. (2018, 2018-03). Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. *European Journal of Cancer (Oxford, England: 1990), 91*, 21-29. https://doi.org/10.1016/j.ejca.2017.12.008

Davies, M. A., Liu, P., McIntyre, S., Kim, K. B., Papadopoulos, N., Hwu, W. J., Hwu, P., & Bedikian, A. (2011, Apr 15). Prognostic factors for survival in melanoma patients with brain metastases. *Cancer, 117*(8), 1687-1696. https://doi.org/10.1002/cncr.25634

Diem, S., Kasenda, B., Spain, L., Martin-Liberal, J., Marconcini, R., Gore, M., & Larkin, J. (2016a, 2016-02-02). Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma.

British Journal of Cancer, 114(3), 256-261. https://doi.org/10.1038/bjc.2015.467

Diem, S., Kasenda, B., Spain, L., Martin-Liberal, J., Marconcini, R., Gore, M., & Larkin, J. (2016b, Feb 2). Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. *Br J Cancer, 114*(3), 256-261. https://doi.org/10.1038/bjc.2015.467

Donato, R. (2001, Jul). S100: a multigenic family of calcium-modulated proteins of the EF-hand type with intracellular and extracellular functional roles. *Int J Biochem Cell Biol, 33*(7), 637-668. https://doi.org/10.1016/s1357-2725(01)00046-2

Dunn, G. P., Bruce, A. T., Ikeda, H., Old, L. J., & Schreiber, R. D. (2002, Nov). Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol, 3*(11), 991-998. https://doi.org/10.1038/ni1102-991

Eggermont, A. M. M., Blank, C. U., Mandala, M., Long, G. V., Atkinson, V., Dalle, S., Haydon, A., Lichinitser, M., Khattak, A., Carlino, M. S., Sandhu, S., Larkin, J., Puig, S., Ascierto, P. A., Rutkowski, P., Schadendorf, D., Koornstra, R., Hernandez-Aya, L., Maio, M., van den Eertwegh, A. J. M., Grob, J.-J., Gutzmer, R., Jamal, R., Lorigan, P., Ibrahim, N., Marreaud, S., van Akkooi, A. C. J., Suciu, S., & Robert, C. (2018, 2018-05-10). Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *New England Journal of Medicine, 378*(19), 1789-1801. https://doi.org/10.1056/NEJMoa1802357

Eggermont, A. M. M., Blank, C. U., Mandala, M., Long, G. V., Atkinson, V. G., Dalle, S., Haydon, A. M., Meshcheryakov, A., Khattak, A., Carlino, M. S., Sandhu, S., Larkin, J., Puig, S., Ascierto, P. A., Rutkowski, P., Schadendorf, D., Koornstra, R., Hernandez-Aya, L., Di Giacomo, A. M., van den Eertwegh, A. J. M., Grob, J.-J., Gutzmer, R., Jamal, R., Lorigan, P. C., van Akkooi, A. C. J., Krepler, C., Ibrahim, N., Marreaud, S., Kicinski, M., Suciu, S., & Robert, C. (2020, 2020-11-20). Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 38*(33), 3925-3936. https://doi.org/10.1200/JCO.20.02110

Eigentler, T. K., Figl, A., Krex, D., Mohr, P., Mauch, C., Rass, K., Bostroem, A., Heese, O., Koelbl, O., Garbe, C., Schadendorf, D., Dermatologic Cooperative Oncology, G., & the National Interdisciplinary Working Group on, M. (2011, Apr 15). Number of metastases, serum lactate dehydrogenase level, and type of treatment are prognostic factors in patients with brain metastases of malignant melanoma. *Cancer, 117*(8), 1697-1703. https://doi.org/10.1002/cncr.25631

Eigentler, T. K., Hassel, J. C., Berking, C., Aberle, J., Bachmann, O., Grunwald, V., Kahler, K. C., Loquai, C., Reinmuth, N., Steins, M., Zimmer, L., Sendl, A., & Gutzmer, R. (2016, Apr). Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev, 45*, 7-18. https://doi.org/10.1016/j.ctrv.2016.02.003

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., Rubinstein, L., Shankar, L., Dodd, L., Kaplan, R., Lacombe, D., & Verweij, J. (2009, 2009-01-01). New response evaluation criteria in solid tumours: Revised RECIST guideline

(version 1.1). *European Journal of Cancer, 45*(2), 228-247. https://doi.org/10.1016/j.ejca.2008.10.026

Fachinformation KEYTRUDA®. (2022, 2022). 50.

Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J. W. W., Comber, H., Forman, D., & Bray, F. (2013, 2013-04). Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *European Journal of Cancer (Oxford, England: 1990), 49*(6), 1374-1403. https://doi.org/10.1016/j.ejca.2012.12.027

Friedrich, S., & Kraywinkel, K. (2018, 2018-06-01). Faktenblatt: Epidemiologie des malignen Melanoms in Deutschland. *Der Onkologe, 24*(6), 447-452. https://doi.org/10.1007/s00761-018-0384-1

Fritz, J. M., & Lenardo, M. J. (2019, 2019-6-03). Development of immune checkpoint therapy for cancer. *The Journal of Experimental Medicine, 216*(6), 1244-1254. https://doi.org/10.1084/jem.20182395

Garcia-Diaz, A., Shin, D. S., Moreno, B. H., Saco, J., Escuin-Ordinas, H., Rodriguez, G. A., Zaretsky, J. M., Sun, L., Hugo, W., Wang, X., Parisi, G., Saus, C. P., Torrejon, D. Y., Graeber, T. G., Comin-Anduix, B., Hu-Lieskovan, S., Damoiseaux, R., Lo, R. S., & Ribas, A. (2017, 2017-5-09). Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. *Cell reports, 19*(6), 1189-1201. https://doi.org/10.1016/j.celrep.2017.04.031

Gershenwald, J. E., Scolyer, R. A., Hess, K. R., Sondak, V. K., Long, G. V., Ross, M. I., Lazar, A. J., Faries, M. B., Kirkwood, J. M., McArthur, G. A., Haydu, L. E., Eggermont, A. M. M., Flaherty, K. T., Balch, C. M., & Thompson, J. F. (2017, 2017-11). Melanoma Staging: Evidence-Based Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. *CA: a cancer journal for clinicians, 67*(6), 472-492. https://doi.org/10.3322/caac.21409

Gutzmer, R., Koop, A., Meier, F., Hassel, J. C., Terheyden, P., Zimmer, L., Heinzerling, L., Ugurel, S., Pföhler, C., & Gesierich, A. (2017, 2017). Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. *European Journal of Cancer, 75*, 24–32. https://www.ejcancer.com/article/S0959-8049(17)30057-6/fulltext

Haanen, J., Ernstoff, M., Wang, Y., Menzies, A., Puzanov, I., Grivas, P., Larkin, J., Peters, S., Thompson, J., & Obeid, M. (2020, Jun). Rechallenge patients with immune checkpoint inhibitors following severe immune-related adverse events: review of the literature and suggested prophylactic strategy. *J Immunother Cancer, 8*(1). https://doi.org/10.1136/jitc-2020-000604

Haanen, J., Obeid, M., Spain, L., Carbonnel, F., Wang, Y., Robert, C., Lyon, A. R., Wick, W., Kostine, M., Peters, S., Jordan, K., Larkin, J., & clinicalguidelines@esmo.org, E. G. C. E. a. (2022, Dec). Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol, 33*(12), 1217-1238. https://doi.org/10.1016/j.annonc.2022.10.001

Hamid, O., Robert, C., Daud, A., Hodi, F. S., Hwu, W.-J., Kefford, R., Wolchok, J. D., Hersey, P., Joseph, R. W., Weber, J. S., Dronca, R., Gangadhar, T. C., Patnaik, A., Zarour, H., Joshua, A. M., Gergich, K., Elassaiss-Schaap, J., Algazi, A., Mateus, C., Boasberg, P., Tumeh, P. C., Chmielowski, B., Ebbinghaus, S. W.,

Li, X. N., Kang, S. P., & Ribas, A. (2013, 2013-07-11). Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma. *New England Journal of Medicine, 369*(2), 134-144. https://doi.org/10.1056/NEJMoa1305133

Haslam, A., & Prasad, V. (2019, 2019-05-03). Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs. *JAMA network open, 2*(5), e192535. https://doi.org/10.1001/jamanetworkopen.2019.2535

Hergovich, A., Stegert, M. R., Schmitz, D., & Hemmings, B. A. (2006, Apr). NDR kinases regulate essential cell processes from yeast to humans. *Nat Rev Mol Cell Biol, 7*(4), 253-264. https://doi.org/10.1038/nrm1891

Hoa, S., Laaouad, L., Roberts, J., Ennis, D., Ye, C., Al Jumaily, K., Pope, J., Nevskaya, T., Saltman, A., & Himmel, M. (2021, 2021). Preexisting autoimmune disease and immune-related adverse events associated with anti-PD-1 cancer immunotherapy: a national case series from the Canadian Research Group of Rheumatology in Immuno-Oncology. *Cancer Immunology, Immunotherapy, 70*(8), 2197–2207. https://link.springer.com/article/10.1007/s00262-021-02851-5

Hodi, F. S., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Rutkowski, P., Cowey, C. L., Lao, C. D., Schadendorf, D., Wagstaff, J., Dummer, R., Ferrucci, P. F., Smylie, M., Hill, A., Hogg, D., Marquez-Rodas, I., Jiang, J., Rizzo, J., Larkin, J., & Wolchok, J. D. (2018, Nov). Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol, 19*(11), 1480-1492. https://doi.org/10.1016/S1470-2045(18)30700-9

Hofmann, L., Forschner, A., Loquai, C., Goldinger, S. M., Zimmer, L., Ugurel, S., Schmidgen, M. I., Gutzmer, R., Utikal, J. S., Goppner, D., Hassel, J. C., Meier, F., Tietze, J. K., Thomas, I., Weishaupt, C., Leverkus, M., Wahl, R., Dietrich, U., Garbe, C., Kirchberger, M. C., Eigentler, T., Berking, C., Gesierich, A., Krackhardt, A. M., Schadendorf, D., Schuler, G., Dummer, R., & Heinzerling, L. M. (2016, Jun). Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer, 60*, 190-209. https://doi.org/10.1016/j.ejca.2016.02.025

Ishida, Y., Agata, Y., Shibahara, K., & Honjo, T. (1992, 1992-11). Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *The EMBO Journal, 11*(11), 3887-3895. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC556898/pdf/emboj00096-0084.pdf

Jiang, A., Bloom, O., Ono, S., Cui, W., Unternaehrer, J., Jiang, S., Whitney, J. A., Connolly, J., Banchereau, J., & Mellman, I. (2007, Oct). Disruption of E-cadherin-mediated adhesion induces a functionally distinct pathway of dendritic cell maturation. *Immunity, 27*(4), 610-624. https://doi.org/10.1016/j.immuni.2007.08.015

Jiang, A. J., Rambhatla, P. V., & Eide, M. J. (2015, 2015-04). Socioeconomic and lifestyle factors and melanoma: a systematic review. *The British Journal of Dermatology, 172*(4), 885-915. https://doi.org/10.1111/bjd.13500

Johnpulle, R. A. N., Conry, R. M., Sosman, J. A., Puzanov, I., & Johnson, D. B. (2016, 2016-10-18). Responses to immune checkpoint inhibitors in nonagenarians.

Oncoimmunology, 5(11), e1234572. https://doi.org/10.1080/2162402X.2016.1234572

Johnson, D. B., Sullivan, R. J., Ott, P. A., Carlino, M. S., Khushalani, N. I., Ye, F., Guminski, A., Puzanov, I., Lawrence, D. P., Buchbinder, E. I., & others. (2016, 2016). Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA oncology, 2*(2), 234–240. https://doi.org/10.1001/jamaoncol.2015.4368

Keir, M. E., Butte, M. J., Freeman, G. J., & Sharpe, A. H. (2008, 2008). PD-1 and its ligands in tolerance and immunity. *Annual Review of Immunology, 26*, 677-704. https://doi.org/10.1146/annurev.immunol.26.021607.090331

Khan, S. A., Pruitt, S. L., Xuan, L., & Gerber, D. E. (2016, 2016-11-01). Prevalence of Autoimmune Disease Among Patients With Lung Cancer: Implications for Immunotherapy Treatment Options. *JAMA oncology, 2*(11), 1507-1508. https://doi.org/10.1001/jamaoncol.2016.2238

Kooi, S., Zhang, H. Z., Patenia, R., Edwards, C. L., Platsoucas, C. D., & Freedman, R. S. (1996, Dec 15). HLA class I expression on human ovarian carcinoma cells correlates with T-cell infiltration in vivo and T-cell expansion in vitro in low concentrations of recombinant interleukin-2. *Cell Immunol, 174*(2), 116-128. https://doi.org/10.1006/cimm.1996.0301

Kraywinkel, K., Barnes, B., Dahm, S., Haberland, J., Nennecke, A., & Stabenow, R. (2014, 2014-01). [Nationwide statements from regional data: methods of the Center for Cancer Registry Data]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz, 57*(1), 13-21. https://doi.org/10.1007/s00103-013-1878-z

Larkin, J., Hodi, F. S., & Wolchok, J. D. (2015, Sep 24). Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *New England Journal of Medicine, 373*(13), 1270-1271. https://doi.org/10.1056/NEJMc1509660

Lee, J. H., Choi, J. W., & Kim, Y. S. (2011, Apr). Frequencies of BRAF and NRAS mutations are different in histological types and sites of origin of cutaneous melanoma: a meta-analysis. *Br J Dermatol, 164*(4), 776-784. https://doi.org/10.1111/j.1365-2133.2010.10185.x

Leonardi, G. C., Gainor, J. F., Altan, M., Kravets, S., Dahlberg, S. E., Gedmintas, L., Azimi, R., Rizvi, H., Riess, J. W., & Hellmann, M. D. (2018, 2018). Safety of programmed Death–1 pathway inhibitors among patients with Non–Small-Cell lung cancer and preexisting autoimmune disorders. *Journal of Clinical Oncology, 36*(19), 1905. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6553840/pdf/JCO.2017.77.0305.pdf

Matthews, N. H., Li, W.-Q., Qureshi, A. A., Weinstock, M. A., & Cho, E. (2017). Epidemiology of Melanoma. In W. H. Ward & J. M. Farma (Eds.), *Cutaneous Melanoma: Etiology and Therapy*. Codon Publications.

Mellman, I., & Steinman, R. M. (2001, Aug 10). Dendritic cells: specialized and regulated antigen processing machines. *Cell, 106*(3), 255-258. https://doi.org/10.1016/s0092-8674(01)00449-4

Menzies, A. M., Johnson, D. B., Ramanujam, S., Atkinson, V. G., Wong, A. N. M., Park, J. J., McQuade, J. L., Shoushtari, A. N., Tsai, K. K., Eroglu, Z., Klein, O., Hassel, J. C., Sosman, J. A., Guminski, A., Sullivan, R. J., Ribas, A., Carlino,

M. S., Davies, M. A., Sandhu, S. K., & Long, G. V. (2017, 2017-02-01). Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Annals of Oncology, 28*(2), 368-376. https://doi.org/10.1093/annonc/mdw443

Michielin, O., van Akkooi, A. C. J., Ascierto, P. A., Dummer, R., Keilholz, U., & clinicalguidelines@esmo.org, E. G. C. E. a. (2019, Dec 1). Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. *Ann Oncol, 30*(12), 1884-1901. https://doi.org/10.1093/annonc/mdz411

Okazaki, T., & Honjo, T. (2007, 2007-07-01). PD-1 and PD-1 ligands: from discovery to clinical application. *International Immunology, 19*(7), 813-824. https://doi.org/10.1093/intimm/dxm057

Okazaki, T., Iwai, Y., & Honjo, T. (2002, 2002-12). New regulatory co-receptors: inducible co-stimulator and PD-1. *Current Opinion in Immunology, 14*(6), 779-782. https://doi.org/10.1016/s0952-7915(02)00398-9

Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer, 12*(4), 252-264. https://doi.org/10.1038/nrc3239

Pedersen, S., Moller, S., Donia, M., Persson, G. F., Svane, I. M., & Ellebaek, E. (2022, Jun 1). Real-world data on melanoma brain metastases and survival outcome. *Melanoma Res, 32*(3), 173-182. https://doi.org/10.1097/CMR.0000000000000816

Philip, M., Fairchild, L., Sun, L., Horste, E. L., Camara, S., Shakiba, M., Scott, A. C., Viale, A., Lauer, P., Merghoub, T., Hellmann, M. D., Wolchok, J. D., Leslie, C. S., & Schietinger, A. (2017, 2017-05-25). Chromatin states define tumour-specific T cell dysfunction and reprogramming. *Nature, 545*(7655), 452-456. https://doi.org/10.1038/nature22367

Pires da Silva, I., Lo, S., Quek, C., Gonzalez, M., Carlino, M. S., Long, G. V., & Menzies, A. M. (2020, Jan 1). Site-specific response patterns, pseudoprogression, and acquired resistance in patients with melanoma treated with ipilimumab combined with anti-PD-1 therapy. *Cancer, 126*(1), 86-97. https://doi.org/10.1002/cncr.32522

Placais, L., Dalle, S., Dereure, O., Trabelsi, S., Dalac, S., Legoupil, D., Montaudie, H., Arnault, J. P., De Quatrebarbes, J., Saiag, P., Brunet-Possenti, F., Lesimple, T., Maubec, E., Aubin, F., Granel-Brocard, F., Grob, J. J., Stoebner, P. E., Allayous, C., Oriano, B., Dutriaux, C., Mortier, L., & Lebbe, C. (2022, Oct). Risk of irAEs in patients with autoimmune diseases treated by immune checkpoint inhibitors for stage III or IV melanoma: results from a matched case-control study. *Ann Rheum Dis, 81*(10), 1445-1452. https://doi.org/10.1136/ard-2022-222186

Postow, M. A., Chesney, J., Pavlick, A. C., Robert, C., Grossmann, K., McDermott, D., Linette, G. P., Meyer, N., Giguere, J. K., Agarwala, S. S., Shaheen, M., Ernstoff, M. S., Minor, D., Salama, A. K., Taylor, M., Ott, P. A., Rollin, L. M., Horak, C., Gagnier, P., Wolchok, J. D., & Hodi, F. S. (2015, May 21). Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *New England Journal of Medicine, 372*(21), 2006-2017. https://doi.org/10.1056/NEJMoa1414428

Rastrelli, M., Tropea, S., Rossi, C. R., & Alaibac, M. (2014, 2014). Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. *In Vivo*

(Athens, Greece), 28(6), 1005-1011. https://iv.iiarjournals.org/content/invivo/28/6/1005.full.pdf

Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A., Gottfried, M., Peled, N., Tafreshi, A., Cuffe, S., O'Brien, M., Rao, S., Hotta, K., Leiby, M. A., Lubiniecki, G. M., Shentu, Y., Rangwala, R., Brahmer, J. R., & Investigators, K.-. (2016, 2016-11-10). Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *New England Journal of Medicine, 375*(19), 1823-1833. https://doi.org/10.1056/NEJMoa1606774

Ribas, A. (2012, 2012-06-28). Tumor Immunotherapy Directed at PD-1. *New England Journal of Medicine, 366*(26), 2517-2519. https://doi.org/10.1056/NEJMe1205943

Ribas, A. (2015, 2015-09). Adaptive Immune Resistance: How Cancer Protects from Immune Attack. *Cancer Discovery, 5*(9), 915-919. https://doi.org/10.1158/2159-8290.CD-15-0563

Ribas, A., Puzanov, I., Dummer, R., Schadendorf, D., Hamid, O., Robert, C., Hodi, F. S., Schachter, J., Pavlick, A. C., Lewis, K. D., Cranmer, L. D., Blank, C. U., O'Day, S. J., Ascierto, P. A., Salama, A. K. S., Margolin, K. A., Loquai, C., Eigentler, T. K., Gangadhar, T. C., Carlino, M. S., Agarwala, S. S., Moschos, S. J., Sosman, J. A., Goldinger, S. M., Shapira-Frommer, R., Gonzalez, R., Kirkwood, J. M., Wolchok, J. D., Eggermont, A., Li, X. N., Zhou, W., Zernhelt, A. M., Lis, J., Ebbinghaus, S., Kang, S. P., & Daud, A. (2015, 2015-08). Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *The Lancet. Oncology, 16*(8), 908-918. https://doi.org/10.1016/S1470-2045(15)00083-2

Ribas, A., & Wolchok, J. D. (2018, 2018-03-23). Cancer immunotherapy using checkpoint blockade. *Science, 359*(6382), 1350-1355. https://doi.org/10.1126/science.aar4060

Ribero, S., Zugna, D., Osella-Abate, S., Glass, D., Nathan, P., Spector, T., & Bataille, V. (2016, 2016-02). Prediction of high naevus count in a healthy U.K. population to estimate melanoma risk. *The British Journal of Dermatology, 174*(2), 312-318. https://doi.org/10.1111/bjd.14216

Robert, C., Schachter, J., Long, G. V., Arance, A., Grob, J. J., Mortier, L., Daud, A., Carlino, M. S., McNeil, C., Lotem, M., Larkin, J., Lorigan, P., Neyns, B., Blank, C. U., Hamid, O., Mateus, C., Shapira-Frommer, R., Kosh, M., Zhou, H., Ibrahim, N., Ebbinghaus, S., & Ribas, A. (2015, 2015-06-25). Pembrolizumab versus Ipilimumab in Advanced Melanoma. *New England Journal of Medicine, 372*(26), 2521-2532. https://doi.org/10.1056/NEJMoa1503093

S3 – Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms. (2020, 10/2020). *JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 18*(10), ddg.14307_g. https://doi.org/10.1111/ddg.14307_g

Schachter, J., Ribas, A., Long, G. V., Arance, A., Grob, J.-J., Mortier, L., Daud, A., Carlino, M. S., McNeil, C., Lotem, M., Larkin, J., Lorigan, P., Neyns, B., Blank, C., Petrella, T. M., Hamid, O., Zhou, H., Ebbinghaus, S., Ibrahim, N., & Robert, C. (2017, 2017-10-21). Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label

phase 3 study (KEYNOTE-006). *Lancet (London, England), 390*(10105), 1853-1862. https://doi.org/10.1016/S0140-6736(17)31601-X

Schadendorf, D., Long, G. V., Stroiakovski, D., Karaszewska, B., Hauschild, A., Levchenko, E., Chiarion-Sileni, V., Schachter, J., Garbe, C., Dutriaux, C., Gogas, H., Mandala, M., Haanen, J., Lebbe, C., Mackiewicz, A., Rutkowski, P., Grob, J. J., Nathan, P., Ribas, A., Davies, M. A., Zhang, Y., Kaper, M., Mookerjee, B., Legos, J. J., Flaherty, K. T., & Robert, C. (2017, Sep). Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. *Eur J Cancer, 82*, 45-55. https://doi.org/10.1016/j.ejca.2017.05.033

Schoenewolf, N. L., Belloni, B., Simcock, M., Tonolla, S., Vogt, P., Scherrer, E., Holzmann, D., & Dummer, R. (2014, Mar-Apr). Clinical implications of distinct metastasizing preferences of different melanoma subtypes. *Eur J Dermatol, 24*(2), 236-241. https://doi.org/10.1684/ejd.2014.2292

Schwartz, L. H., Seymour, L., Litière, S., Ford, R., Gwyther, S., Mandrekar, S., Shankar, L., Bogaerts, J., Chen, A., Dancey, J., Hayes, W., Hodi, F. S., Hoekstra, O. S., Huang, E. P., Lin, N., Liu, Y., Therasse, P., Wolchok, J. D., & Vries, E. d. (2016, 2016-07-01). RECIST 1.1 – Standardisation and disease-specific adaptations: Perspectives from the RECIST Working Group. *European Journal of Cancer, 62*, 138-145. https://doi.org/10.1016/j.ejca.2016.03.082

Sen, D. R., Kaminski, J., Barnitz, R. A., Kurachi, M., Gerdemann, U., Yates, K. B., Tsao, H.-W., Godec, J., LaFleur, M. W., Brown, F. D., Tonnerre, P., Chung, R. T., Tully, D. C., Allen, T. M., Frahm, N., Lauer, G. M., Wherry, E. J., Yosef, N., & Haining, W. N. (2016, 2016-12-02). The epigenetic landscape of T cell exhaustion. *Science (New York, N.Y.), 354*(6316), 1165-1169. https://doi.org/10.1126/science.aae0491

Staudt, M., Lasithiotakis, K., Leiter, U., Meier, F., Eigentler, T., Bamberg, M., Tatagiba, M., Brossart, P., & Garbe, C. (2010, Apr 13). Determinants of survival in patients with brain metastases from cutaneous melanoma. *Br J Cancer, 102*(8), 1213-1218. https://doi.org/10.1038/sj.bjc.6605622

Tio, M., Wang, X., Carlino, M. S., Shivalingam, B., Fogarty, G. B., Guminski, A. D., Lo, S., Hong, A. M., Menzies, A. M., & Long, G. V. (2018, Jul). Survival and prognostic factors for patients with melanoma brain metastases in the era of modern systemic therapy. *Pigment Cell Melanoma Res, 31*(4), 509-515. https://doi.org/10.1111/pcmr.12682

Tison, A., Quéré, G., Misery, L., Funck-Brentano, E., Danlos, F.-X., Routier, E., Robert, C., Loriot, Y., Lambotte, O., Bonniaud, B., Scalbert, C., Maanaoui, S., Lesimple, T., Martinez, S., Marcq, M., Chouaid, C., Dubos, C., Brunet-Possenti, F., Stavris, C., Chiche, L., Beneton, N., Mansard, S., Guisier, F., Doubre, H., Skowron, F., Aubin, F., Zehou, O., Roge, C., Lambert, M., Pham-Ledard, A., Beylot-Barry, M., Veillon, R., Kramkimel, N., Giacchero, D., De Quatrebarbes, J., Michel, C., Auliac, J.-B., Gonzales, G., Decroisette, C., Le Garff, G., Carpiuc, I., Vallerand, H., Nowak, E., Cornec, D., Kostine, M., & Groupe de Cancérologie Cutanée, G. F. d. P.-C., and Club Rhumatismes et Inflammations. (2019, 2019-12). Safety and Efficacy of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease: A Nationwide,

Multicenter Cohort Study. *Arthritis & Rheumatology (Hoboken, N.J.), 71*(12), 2100-2111. https://doi.org/10.1002/art.41068

Tobón, G. J., Pers, J.-O., Cañas, C. A., Rojas-Villarraga, A., Youinou, P., & Anaya, J.-M. (2012, 2012-02). Are autoimmune diseases predictable? *Autoimmunity Reviews, 11*(4), 259-266. https://doi.org/10.1016/j.autrev.2011.10.004

Topalian, S. L., Hodi, F. S., Brahmer, J. R., Gettinger, S. N., Smith, D. C., McDermott, D. F., Powderly, J. D., Carvajal, R. D., Sosman, J. A., Atkins, M. B., Leming, P. D., Spigel, D. R., Antonia, S. J., Horn, L., Drake, C. G., Pardoll, D. M., Chen, L., Sharfman, W. H., Anders, R. A., Taube, J. M., McMiller, T. L., Xu, H., Korman, A. J., Jure-Kunkel, M., Agrawal, S., McDonald, D., Kollia, G. D., Gupta, A., Wigginton, J. M., & Sznol, M. (2012, 2012/06/28). Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. *New England Journal of Medicine, 366*(26), 2443-2454. https://doi.org/10.1056/NEJMoa1200690

Topalian, S. L., Sznol, M., McDermott, D. F., Kluger, H. M., Carvajal, R. D., Sharfman, W. H., Brahmer, J. R., Lawrence, D. P., Atkins, M. B., Powderly, J. D., Leming, P. D., Lipson, E. J., Puzanov, I., Smith, D. C., Taube, J. M., Wigginton, J. M., Kollia, G. D., Gupta, A., Pardoll, D. M., Sosman, J. A., & Hodi, F. S. (2014, 2014-04-01). Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 32*(10), 1020-1030. https://doi.org/10.1200/JCO.2013.53.0105

Trombetta, E. S., & Mellman, I. (2005). Cell biology of antigen processing in vitro and in vivo. *Annu Rev Immunol, 23*, 975-1028. https://doi.org/10.1146/annurev.immunol.22.012703.104538

Tully, K. H., Cone, E. B., Cole, A. P., Sun, M., Chen, X., Marchese, M., Roghmann, F., Kilbridge, K. L., & Trinh, Q.-D. (2021, 2021). Risk of immune-related adverse events in melanoma patients with preexisting autoimmune disease treated with immune checkpoint inhibitors: a population-based study using SEER-Medicare data. *American Journal of Clinical Oncology, 44*(8), 413–418. https://doi.org/10.1097/COC.0000000000000840

Tumeh, P. C., Hellmann, M. D., Hamid, O., Tsai, K. K., Loo, K. L., Gubens, M. A., Rosenblum, M., Harview, C. L., Taube, J. M., Handley, N., Khurana, N., Nosrati, A., Krummel, M. F., Tucker, A., Sosa, E. V., Sanchez, P. J., Banayan, N., Osorio, J. C., Nguyen-Kim, D. L., Chang, J., Shintaku, I. P., Boasberg, P. D., Taylor, E. J., Munster, P. N., Algazi, A. P., Chmielowski, B., Dummer, R., Grogan, T. R., Elashoff, D., Hwang, J., Goldinger, S. M., Garon, E. B., Pierce, R. H., & Daud, A. (2017, May). Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC. *Cancer Immunol Res, 5*(5), 417-424. https://doi.org/10.1158/2326-6066.CIR-16-0325

Vosoughi, E., Lee, J. M., Miller, J. R., Nosrati, M., Minor, D. R., Abendroth, R., Lee, J. W., Andrews, B. T., Leng, L. Z., Wu, M., Leong, S. P., Kashani-Sabet, M., & Kim, K. B. (2018, Apr 27). Survival and clinical outcomes of patients with melanoma brain metastasis in the era of checkpoint inhibitors and targeted therapies. *BMC Cancer, 18*(1), 490. https://doi.org/10.1186/s12885-018-4374-x

Waldman, A. D., Fritz, J. M., & Lenardo, M. J. (2020, 11/2020). A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nature Reviews Immunology, 20*(11), 651-668. https://doi.org/10.1038/s41577-020-0306-5

Wang, P., Vanky, F., Vegh, Z., Persson, U., Hising, C., & Klein, E. (1992, Jul). Assembly of MHC class I molecules in ex vivo carcinoma cells induced by IFN-gamma or by a binding peptide. *Cell Immunol, 142*(2), 296-302. https://doi.org/10.1016/0008-8749(92)90291-v

Weber, J., Mandala, M., Del Vecchio, M., Gogas, H. J., Arance, A. M., Cowey, C. L., Dalle, S., Schenker, M., Chiarion-Sileni, V., Marquez-Rodas, I., Grob, J.-J., Butler, M. O., Middleton, M. R., Maio, M., Atkinson, V., Queirolo, P., Gonzalez, R., Kudchadkar, R. R., Smylie, M., Meyer, N., Mortier, L., Atkins, M. B., Long, G. V., Bhatia, S., Lebbé, C., Rutkowski, P., Yokota, K., Yamazaki, N., Kim, T. M., de Pril, V., Sabater, J., Qureshi, A., Larkin, J., Ascierto, P. A., & Collaborators, C. (2017, 2017-11-09). Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *New England Journal of Medicine, 377*(19), 1824-1835. https://doi.org/10.1056/NEJMoa1709030

Weber, J. S., Hodi, F. S., Wolchok, J. D., Topalian, S. L., Schadendorf, D., Larkin, J., Sznol, M., Long, G. V., Li, H., Waxman, I. M., Jiang, J., & Robert, C. (2017, 2017-03). Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 35*(7), 785-792. https://doi.org/10.1200/JCO.2015.66.1389

Weide, B., Elsasser, M., Buttner, P., Pflugfelder, A., Leiter, U., Eigentler, T. K., Bauer, J., Witte, M., Meier, F., & Garbe, C. (2012, Jul 24). Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis. *Br J Cancer, 107*(3), 422-428. https://doi.org/10.1038/bjc.2012.306

Wolchok, J. D., Chiarion-Sileni, V., Gonzalez, R., Rutkowski, P., Grob, J. J., Cowey, C. L., Lao, C. D., Wagstaff, J., Schadendorf, D., Ferrucci, P. F., Smylie, M., Dummer, R., Hill, A., Hogg, D., Haanen, J., Carlino, M. S., Bechter, O., Maio, M., Marquez-Rodas, I., Guidoboni, M., McArthur, G., Lebbe, C., Ascierto, P. A., Long, G. V., Cebon, J., Sosman, J., Postow, M. A., Callahan, M. K., Walker, D., Rollin, L., Bhore, R., Hodi, F. S., & Larkin, J. (2017, Oct 5). Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *New England Journal of Medicine, 377*(14), 1345-1356. https://doi.org/10.1056/NEJMoa1709684

Wolchok, J. D., Kluger, H., Callahan, M. K., Postow, M. A., Rizvi, N. A., Lesokhin, A. M., Segal, N. H., Ariyan, C. E., Gordon, R.-A., Reed, K., Burke, M. M., Caldwell, A., Kronenberg, S. A., Agunwamba, B. U., Zhang, X., Lowy, I., Inzunza, H. D., Feely, W., Horak, C. E., Hong, Q., Korman, A. J., Wigginton, J. M., Gupta, A., & Sznol, M. (2013, 2013-07-11). Nivolumab plus ipilimumab in advanced melanoma. *New England Journal of Medicine, 369*(2), 122-133. https://doi.org/10.1056/NEJMoa1302369

Xie, W., Huang, H., Xiao, S., Fan, Y., Deng, X., & Zhang, Z. (2020, 2020-12). Immune checkpoint inhibitors therapies in patients with cancer and preexisting autoimmune diseases: A meta-analysis of observational studies. *Autoimmunity Reviews, 19*(12), 102687. https://doi.org/10.1016/j.autrev.2020.102687

Zhao, B., Zhao, H., & Zhao, J. (2020, 2020). Efficacy of PD-1/PD-L1 blockade monotherapy in clinical trials. *Therapeutic Advances in Medical Oncology, 12*, 1758835920937612. https://doi.org/10.1177/1758835920937612

Zimmer, L., Goldinger, S. M., Hofmann, L., Loquai, C., Ugurel, S., Thomas, I., Schmidgen, M. I., Gutzmer, R., Utikal, J. S., Goppner, D., Hassel, J. C., Meier, F., Tietze, J. K., Forschner, A., Weishaupt, C., Leverkus, M., Wahl, R., Dietrich, U., Garbe, C., Kirchberger, M. C., Eigentler, T., Berking, C., Gesierich, A., Krackhardt, A. M., Schadendorf, D., Schuler, G., Dummer, R., & Heinzerling, L. M. (2016, Jun). Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer, 60*, 210-225. https://doi.org/10.1016/j.ejca.2016.02.024

7. Erklärungen zum Eigenanteil

Die Arbeit wurde an der Universitäts-Hautklinik der Eberhard Karls Universität Tübingen, Sektion Dermatologische Onkologie, unter Betreuung von Herrn Prof. Dr. med. Lukas Flatz durchgeführt.

Die Konzeption der vorliegenden Dissertation erfolgte in Zusammenarbeit mit Herrn Prof. Dr. med. Lukas Flatz, ärztliche Leitung Sektion Dermatologische Onkologie, und Frau Ph.D. Dr. med. Teresa Amaral, Fachärztin für Onkologie und Mitarbeiterin in der Sektion Dermatologische Onkologie Tübingen. Herr Prof. Flatz hat das Manuskript kritisch kommentiert und mir Hinweise für die Korrektur gegeben.

Die retrospektive Datenerhebung wurde von mir, Jens Sören Sattler, B. Sc., durchgeführt. Die statistische Auswertung erfolgte eigenständig durch mich unter Anleitung von Frau Dr. med. Amaral.

Ich versichere, das Manuskript selbstständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Mir ist bewusst, dass eine falsche Erklärung rechtliche Folgen haben wird.

_____	_____
Ort und Datum	Unterschrift

8. Acknowledgement

All mein Dank gehört den Personen, die mich mit ihrem fachlichen Rat, organisatorischem Engagement und guter Unterstützung bei der Anfertigung und Realisierung meiner Doktorarbeit begleitet haben.

Mein besonderer Dank gilt meinem Doktorvater Prof. Dr. med. Lukas Flatz für die Überlassung des Themas.

Ebenso möchte ich mich bei Dr. Teresa Amaral für die hervorragende Betreuung und zahlreichen konstruktiven Anregungen bedanken, die mich bei der Umsetzung stets vorangebracht und bestärkt haben.

Für die Zweitbegutachtung dieser Doktorarbeit danke ich herzlich Prof. Dr. Dr. med. Dominik Fischer.

Der größte Dank geht an meine Kinder, Romi und Jakob — alles, was ich mache, mache ich für Euch.