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Original research

Effects of an immunosuppressive therapy on the efficacy of immune checkpoint inhibition in metastatic melanoma – An analysis of the prospective skin cancer registry ADOREG

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ABSTRACT

Background: The impact of immunosuppressive therapy (IST) on immune-checkpoint inhibition (ICI) is unclear.
Methods: Patients with unresectable advanced melanoma (MM) treated with ICI in the years 2011–2020 were identified from the prospective multicenter German skin cancer registry ADOREG. Patients with IST within 60 days before, or within 30 days after start of ICI were compared to patients without IST. End points were disease control rate (DCR), overall survival (OS) and progression-free survival (PFS) determined by Kaplan-Meier method. Prognostic factors were evaluated in a Cox regression model.
Results: Of 814 patients treated with ICI, 73 (9%) received concomitant IST, mainly steroids. Patients with brain metastases (BM) received IST more frequently (n = 34/130 patients; 26%), than patients without BM (39/684 patients; 6%). In patients without BM, IST initiated before, but not IST initiated after start of ICI was significantly associated with worse PFS (univariate hazard ratio (HR) 2.59, 95% confidence interval (95%-CI) 1.07–6.28, p = 0.035; multivariate HR 3.48, 95%-CI 1.26–9.6, p = 0.016). There was no association between IST and OS or DCR. In patients with BM, IST initiated before, but not after start of ICI was significantly associated with worse OS

Abbreviations: AE, adverse events; Braf mut, Braf-mutation; BM, brain metastases; CI, Confidence interval; CR, Complete Response; CTCAE, Common Terminology Criteria of Adverse Events; DCR, Disease Control Rate; DECOG, German Dermatologic Cooperative Oncology Group; ECOG, Eastern Cooperative Oncology Group performance status; HR, Hazard Ratio; ICI, immune checkpoint inhibition; Ipi, Ipilimumab; ir, immune related; IST, immunosuppressive therapy; LDH, Lactate Dehydrogenase; MM, malignant melanoma; NSCLC, non small cell lung cancer; ORR, overall response rate; OS, Overall survival; PD, Progressive Disease; PD-1, Programmed death protein 1; PD-L1, Programmed death protein ligand 1; PFS, Progression-free survival; PR, Partial Response; SD, Stable Disease.

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(univariate HR 2.06, 95%-CI 1.07–3.95, p = 0.031; multivariate HR 5.91, 95%-CI 1.74–20.14, p = 0.004). There was no association between IST and PFS or DCR.
Conclusion: Patients receiving IST 60 days before start of ICI showed a tendency to an impaired therapy outcome. IST initiated within 30 days after start of ICI, mainly due to early side effects, did not affect the efficacy of ICI therapy.

1. Introduction

Immune-checkpoint inhibition (ICI) is standard of treatment of advanced melanoma (MM), since controlled studies showed an OS benefit first for CTLA4-inhibitor ipilimumab compared to vaccine, and for PD1-inhibitors pembrolizumab and nivolumab versus ipilimumab [1,2] and chemotherapy with dacarbazine [3]. Moreover, the combination therapy nivolumab plus ipilimumab was superior to ipilimumab [2,4] and also to nivolumab alone at least in certain subgroups of patients such as patients with brain metastases [5] and patients with PD-L1 negative tumors [2]. This led to approval of PD1 inhibitors pembrolizumab and nivolumab and the CTLA4-inhibitor ipilimumab for treatment of unresectable metastatic melanoma and later also for the adjuvant situation in stage II to stage IV. The combination of nivolumab plus ipilimumab has also been approved for treatment of unresectable melanoma on the basis of the Checkmate 67 study.

Since the mechanism of ICI is based on T-cell activation, inflammatory side effects frequently occur as immune-related adverse events (irAE). They have been reported in 66% in patients treated with PD1-inhibitors [6], and affect mainly the skin (36%), the gastrointestinal system (16%), endocrine organs (5–8%), the liver (1–6%) or lung (2–5%) [7]. In PD1 monotherapy, these irAE are only of grade > =3 in 8–14% of patients [6,8], whereas the combination therapy nivolumab plus ipilimumab causes irAE in 88% of patients and grade > =3 irAE in approximately 40% of patients [8].

Therefore, clinical trials regularly excluded patients with autoimmune or chronic inflammatory disease, in particular those requiring immunosuppression (IST). It is currently unclear if concomitant IST administered before or shortly after initiation of ICI impairs efficacy of ICI treatment. A number of case series reported experience in patients with autoimmune disease undergoing ICI for advanced melanoma [9–13]. These reports focus mainly on the experience with regard to a flare and management of the concomitant autoimmune disease and other irAE.

To gather more information of the effect of IST on the efficacy of ICI in MM, we performed an analysis in the prospective real-world skin cancer registry ADOREG. Here, patients who underwent first line ICI treatment for metastatic melanoma were selected and data on IST 60 days before up to 30 days after start of ICI were collected.

2. Material and methods

2.1. Patients and data acquisition

Patients (age ≥ 18 years) with unresectable advanced MM treated with ICI were identified from the prospective multicenter skin cancer registry ADOREG of the German Dermatologic Cooperative Oncology Group (DeCOG). Patients presenting at DeCOG academic cancer centers between July 2011 and May 2020. Patients were selected for this study according to the following criteria: first line therapy with ICI and complete baseline as well as follow-up data on ICI treatment. Additional data on details of IST therapy within 60 days before up to 30 days after start of ICI were collected from participating centers (Augsburg, Dortmund, Dresden, Erfurt, Essen, Hannover, Homburg, Mannheim, Regensburg). The ADOREG registry was approved by the medical ethics committee of the University Duisburg-Essen (14–5921-BO). All participating patients gave their informed consent.

2.2. Statistics

Descriptive statistics were used to present epidemiological data and melanoma- specific information. Differences between patient characteristics were tested by Kruskal-Wallis-Test and Post hoc analyses by Bonferroni. Variation in IST therapy were detected by fishers exact and chi-square- test as well as Man-Whitney-U-Test. End points were disease control rate (DCR), overall survival (OS) and progression-free survival (PFS) determined by Kaplan-Meier method with Log-Rank-Test. Median OS and PFS were measured in months and reported with 95% confidence intervals (95% CI) and p-values. The median OS and PFS were defined by the time from the first ICI dose to the clinical event. Prognostic factors were evaluated in univariate and multivariate Cox proportional-hazard regression models stratified according to brain metastases (BM). Relevant prognostic factors included gender, age at first ICI, Eastern Cooperative Oncology Group performance status (ECOG), presence of liver metastases, regime of ICI (PD1 mono therapy vs. Ipilimumab mono or PD1 combined with Ipilimumab), severity of side effects and IST. Results were described by hazard ratios with 95% CI and p values. P-values < 0005 were considered significant. The statistical analyses were performed by IBM SPSS Statistics 27.

3. Results

3.1. Study population

2265 Patients were detected. In 1221 patients, ICI was given as first line therapy and sufficient information on ICI treatment and follow up were available. Finally, 814 patients could be evaluated with complete data on ICI and IST (Fig. 1). Patients with concomitant IST 60 days before (n = 26) up to 30 days after start of ICI (n = 47) were compared to patients without IST (n = 741). Since patients with brain metastases (BM) often received corticosteroids for symptomatic disease (Table 1), we separately analyzed patients with and without BM (Fig. 1). The median follow up was 12 months (mean 17 months, range 0–81 months) for the total population.

3.2. Clinical characterization

In 73 (9%) of patients, concomitant IST was identified (Table 1). Since most of patients with BM the IST was administered for symptomatic BM or as part of radiation or surgical treatment for BM, they were analyzed separately (Table 1). In patients without BM (n = 684), 7 patients received IST in the 60-day interval before start of ICI. 6 patients received corticosteroids (prednisolone n = 5; dexamethasone n = 1; median prednisone equivalent dose 20 mg) in connection with comorbidities or metastases-associated pain, one patient in addition 25 mg methotrexate for rheumatoid arthritis. One patient received 5 mg/kg infliximab for colitis. 32 patients received corticosteroids in the 30-day interval after initiation of ICI, almost all for the management of irAE; one patient for metastases-associated pain (methylprednisolone n = 20; prednisolone n = 10; dexamethasone n = 2; median prednisone equivalent dose 91; 75; 25 mg). (Table 1; A). In patients with BM, all of the 34 patients in the IST cohort received corticosteroids. 5 patients for neurosurgery, 8 post-irradiation and 17 for symptomatic BM. One patient with BM received IST before ICI for rheumatoid arthritis. 2 patients with BM took IST after ICI in association with ir colitis and one patient in case of ir hepatitis. All patients with BM in the IST before ICI group

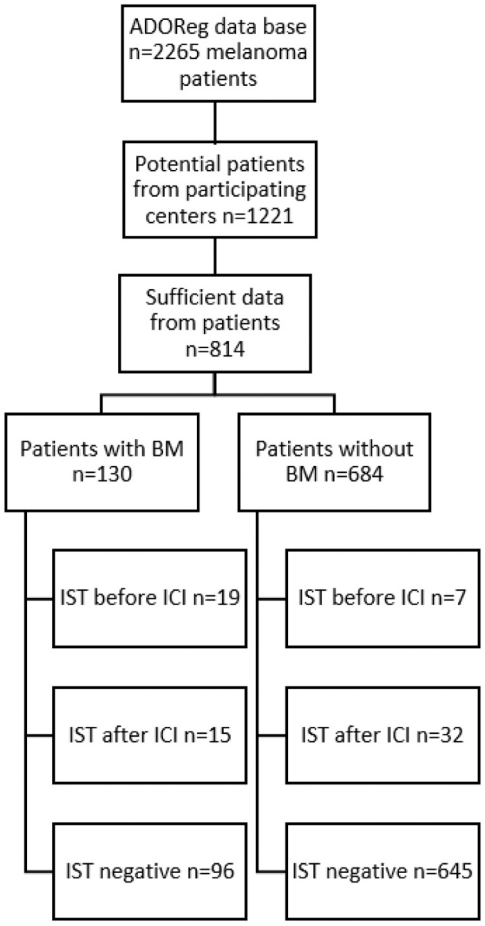

Fig. 1. Flow chart describing the study cohort.

received dexamethasone (median prednisone equivalent dose 25 mg) (Table 1; B). In IST after ICI group 12 patients took dexamethasone, 2 patients methylprednisolone and one patient 3 mg of an unknown steroid (median prednisone equivalent dose 25; 313 mg). The follow up time was 13 months in median in patients without BM (mean 18 months, range 0–81 months). For patients with BM, median follow up was 7 months (mean 13 months, range 0–57 months).

3.3. Patients without BM

Patients without BM who received IST after initiation of ICI were significantly younger, were significantly more often treated with PD1 +Ipilimumab combination and showed a trend towards more irAE (Table 2). In patients who received IST before initiation of ICI, more liver metastases and more previous adjuvant treatment were noted. The majority of patients, who got an adjuvant treatment, received a therapy with interferon (Table 2).

With regard to efficacy, the PFS was significantly shorter in the cohort with IST before initiation of ICI, as compared to the cohorts without IST or IST after initiation of ICI; there was no significant difference with regard to OS nor DCR (Table 2, Figs. 2 and 3). In univariate and multivariate analyses, the presence of liver metastases and an ECOG > 0 were consistently associated with an impaired PFS and OS, whereas the occurrence of (high-grade) irAE was associated with an improved PFS and OS (Figs. 2 and 3).

3.4. Patients with BM

Patients with BM, who required IST either before or after initiation of ICI were more often female (Table 3). With regard to efficacy of ICI, IST

Table 1
Reasons for IST shown for patients with BM and without BM receiving IST within 60 days before or within 30 days after start of ICI. Median dose (range) for steroids indicated as prednisone equivalent dose in mg.

A: Patients without BM **Reason for IST**	**All patients (n = 39)**	**IST before ICI start (n = 7)**	**IST after ICI start (n = 32)**
ir Colitis/Diarrhea	15 (38.5%)	1 (14.3%)	14 (43.7%)
ir Hepatitis	9 (23.1%)	0	9 (28.2%)
ir Pneumonitis	3 (7.7%)	0	3 (9.4%)
Allergic Asthma	1 (2.6%)	1 (14.3%)	0
Exanthema/Pruritus	2 (5.2%)	0	2 (6.2%)
ir Myocarditis	1 (2.6%)	0	1 (3.1%)
ir Thyroiditis	1 (2.6%)	0	1 (3.1%)
Rheumatoid Arthritis	4 (10.3%)	3 (42.8%)	1 (3.1%)
Metastases-associated pain	2 (5.2%)	1 (14.3%)	1 (3.1%)
Concomitant medication (Abiraterone in prostate cancer)	1 (2.6%)	1 (14.3%)	0
Type of IST	**Dose**	**Dose**	**Dose**
methylprednisolone	20 91 (38-313)	0	20 91 (38-313)
prednisolone	15 50 (5-200)	5 20 (5-20)	10 75 (6-200)
dexamethasone	3 25 (25-25)	1 unknown	2 25 (25-25)
infliximab	1 5 mg/kg	1 5 mg/kg	0
methotrexate	1 25 mg	1 25 mg	0
B: Patients with BM **Reason for IST**	**All patients (n = 34)**	**IST before ICI start (n = 19)**	**IST after ICI start (n = 15)**
Symptomatic brain metastasis	17 (49.9%)	11 (57.9%)	6 (40.0%)
Radiation therapy	8 (23.5%)	4 (21.0%)	4 (26.7%)
Surgical therapy	5 (14.7%)	3 (15.8%)	2 (13.4%)
Rheumatoid Arthritis	1 (2.9%)	1 (5.3%)	0
ir Colitis/Diarrhea	2 (5.8%)	0	2 (13.4%)
ir Hepatitis	1 (2.9%)	0	1 (6.7%)
Type of IST	**Dose**	**Dose**	**Dose**
dexamethasone	31 25 (13-150)	19 25 (13-150)	12 25 (25-25)
methylprednisolone	2 313 (313-313)	0	2 313 (313-313)
unknown steroid	1 3 mg	0	1 3 mg

before initiation of ICI was associated with significantly impaired OS (Fig. 5) but not DCR (Table 3) or PFS (Fig. 4), whereas the occurrence of high-grade irAE was associated with an improved PFS (Fig. 4) and OS (Fig. 5).

4. Discussion

In this study, we addressed the question if IST at initiation of ICI has an effect on efficacy of ICI in MM. Therefore, we analyzed patients with MM undergoing first line ICI from the ADOREG registry and sufficient data. Patients who received IST, received mainly steroids. At initial analysis of our ADOREG cohort, our first observation was that in patients without BM only a small number received IST before start of ICI and IST early during ICI was usually triggered by irAE. The second observation was that in patients with BM, IST was more often administered and usually given for symptomatic BM before start of ICI, and after start of ICI cerebral interventions or irAE were more common as reason for IST.

In patients without BM, our analysis confirms well known negative prognostic factors, i.e., increased ECOG status and presence of liver metastases were associated with worse PFS and OS by univariate and multivariate analysis. IST initiated before ICI but not IST initiated after start of ICI was significantly correlated with worse PFS but not with OS or DCR. High grade irAE were associated with an improved PFS and OS and are usually treated with IST, in particular steroids. The positive effect of irAE and associated anti-inflammatory therapy was also reported in other studies [14–16]. However, often a lead-time-bias can not

Table 2
Demographics of patients without brain metastases. P-value in relation to group comparison (Kruskal-Wallis-Test) between IST before ICI, IST after ICI and without IST (* Missing values unreported in database; Braf mut: Braf-mutation, LDH: Lactate Dehydrogenase, ECOG: Eastern Cooperative Oncology Group performance status, DCR: Disease Control Rate, CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, irAE: Treatment related Adverse Event).

Parameter		All patients (n = 684)	IST before ICI start (n = 7)	IST after ICI start (n = 32)	No IST (n = 645)	p-value
Age (years)	Median	67	66	59	67	0024
	Mean	65	59	59	65	
	Range	18-96	23-80	28-83	18-96	
Sex	Female	257 (38%)	3 (43%)	13 (41%)	241 (37%)	0895
	Male	427 (62%)	4 (57%)	19 (59%)	404 (63%)	
ECOG *	0	238 (72%)	6 (100%)	10 (63%)	222 (72%)	0261
	> 0	91 (13%)	0	6 (37%)	85 (28%)	
Melanoma Stage	III	91 (13%)	0	2 (6%)	89 (14%)	0274
	IV	593 (87%)	7 (100%)	30 (94%)	556 (86%)	
BRAF mut *	Yes	144 (26%)	1 (17%)	10 (37%)	133 (25%)	0352
	No	413 (74%)	5 (83%)	17 (63%)	391 (75%)	
Liver metastasis	Yes	167 (24%)	4 (57%)	11 (34%)	152 (24%)	0049
	No	517 (76%)	3 (43%)	21 (66%)	493 (76%)	
LDH *	Increased	93 (54%)	1 (50%)	12 (75%)	80 (52%)	0202
	Not increased	80 (46%)	1 (50%)	4 (25%)	75 (48%)	
Previous adjuvant treatment	Yes	44 (6%)	2 (29%)	0	42 (7%)	0019
	No	640 (94%)	5 (71%)	32 (100%)	603 (93%)	
Treatment	PD1	456 (67%)	4 (47%)	9 (28%)	443 (69%)	< 0,0001
	PD1 +Ipilimumab	228 (33%)	3 (43%)	23 (72%)	202 (31%)	
irAE (at least one)	Yes	161 (24%)	2 (29%)	13 (41%)	146 (23%)	0061
	No	523 (76%)	5 (71%)	19 (59%)	499 (77%)	
irAE grade *	1	39 (23%)	1 (33%)	0	38 (26%)	0297
	2	51 (30%)	0	6 (38%)	45 (30%)	
	3	67 (40%)	1 (33%)	8 (50%)	58 (39%)	
	4	11 (7%)	1 (33%)	2 (12%)	8 (5%)	
2nd or later line treatment of melanoma	Yes	321 (47%)	3 (43%)	18 (56%)	300 (47%)	0547
	No	363 (53%)	4 (57%)	14 (44%)	345 (53%)	
DCR *	CR/PR/SD	193 (37%)	2 (40%)	8 (44%)	183 (37%)	0795
	PD	328 (63%)	3 (60%)	10 (56%)	315 (63%)	
PFS in month (95%CI)	Mean	19 (17-21)	3 (1-6)	28 (15-41)	19 (17-21)	0046
	Median	6 (4-8)	2 (0-4)	16 (2-3)	6 (4-8)	
OS in month (95%CI)	Mean	43 (40-47)	24 (16-32)	33 (23-43)	43 (40-47)	0784
	Median	35 (29-41)	22 (6-38)	39 (2-76)	35 (28-42)	

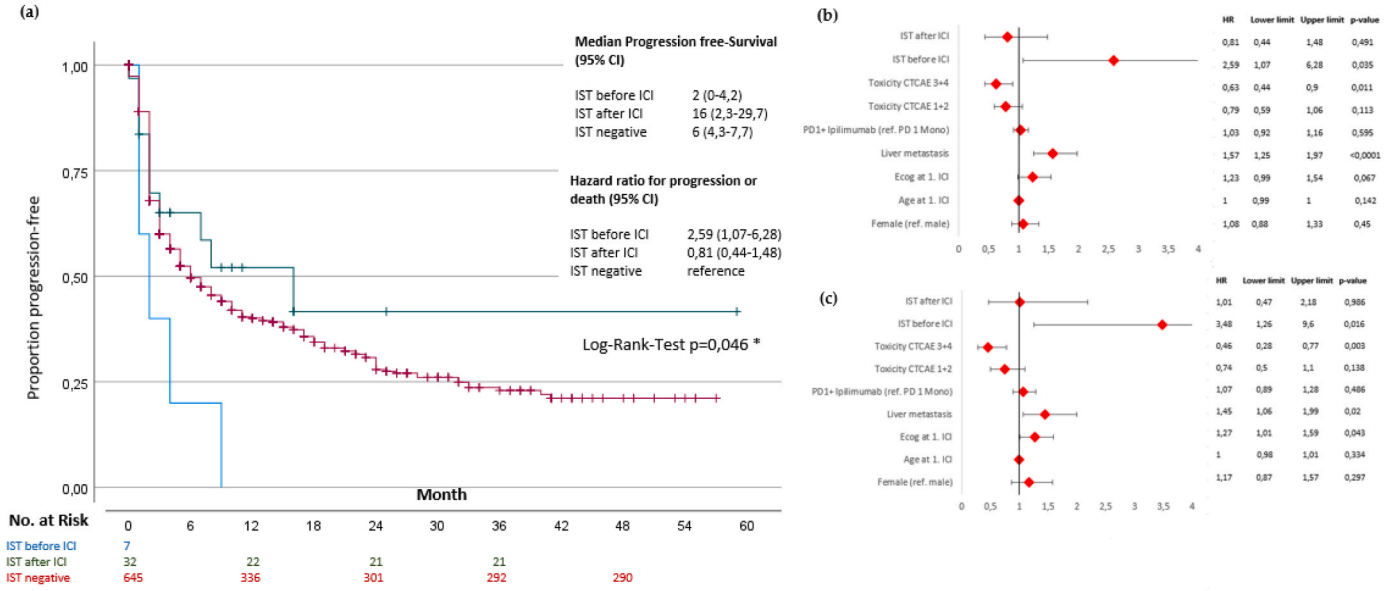

Fig. 2. Kaplan-Meier curves for PFS in patients without BM **(a)**. Hazard Ratios of prognostic factors for PFS in patients without BM in univariate (**b**) and multivariate (**c**) Cox-regression-analyses.

be excluded, i.e., patients staying longer on treatment due to response have a higher probability of irAE. A recent study in a mixed group of patients with melanoma and non-small cell lung cancer (NSCLC) confirmed that irAE are associated with improved survival using a time-varying Cox regression model, but analyses with a landmark method showed no difference in OS or PFS between patients who experienced irAE during the first 12 weeks of treatment and those who did not [17]. Moreover, in an adjuvant study melanoma patients with irAE had a superior recurrence free survival, in particular in patients without the application of steroids for the management of the irAE [18].

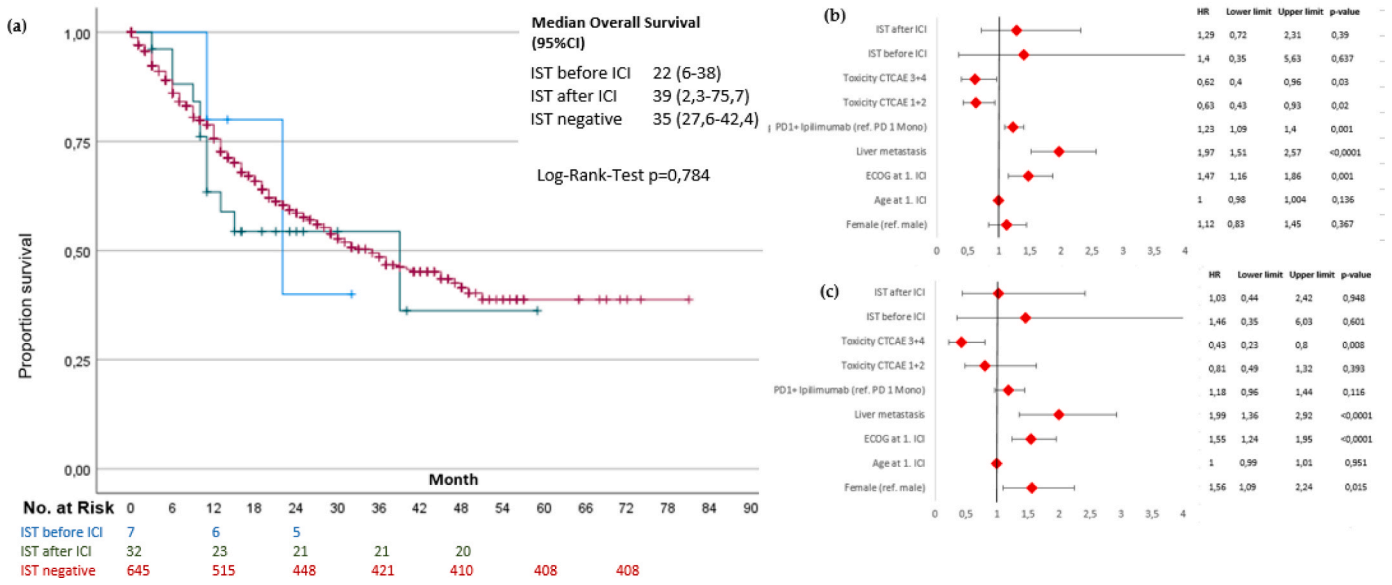

Fig. 3. Kaplan-Meier curves for OS in patients without BM **(a)**. Hazard Ratios of prognostic factors for OS in patients without BM in univariate (**b**) and multivariate (**c**) Cox-regression-analyses.

Table 3
Demographics of patients with brain metastases. P-value in relation to group comparison (Kruskal-Wallis-Test) between IST before ICI, IST after ICI and without IST (* Missing values unreported in database; Braf mut: Braf-mutation, LDH: Lactate Dehydrogenase, ECOG: Eastern Cooperative Oncology Group performance status, DCR: Disease Control Rate, CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, irAE: Treatment related Adverse Event).

Parameter		All patients (n = 130)	IST before ICI start (n = 19)	IST after ICI start (n = 15)	No IST (n = 96)	p-value
Age (years)	Median	65	63	61	66	0518
	Mean	64	63	61	65	
	Range	28-87	47-80	39-79	28-87	
Sex	Female	53 (41%)	12 (63%)	8 (53%)	33 (34%)	0038
	Male	77 (59%)	7 (37%)	7 (47%)	63 (66%)	
ECOG *	0	55 (61%)	5 (83%)	7 (64%)	43 (59%)	0,49
	> 0	35 (39%)	1 (17%)	4 (36%)	30 (41%)	
Melanoma Stage	III	0	0	0	0	
	IV	130 (100%)	19 (100%)	15 (100%)	96 (100%)	
BRAF mut *	Yes	43 (40%)	6 (38%)	6 (46%)	31 (40%)	0884
	No	64 (60%)	10 (62%)	7 (54%)	47 (60%)	
Liver metastasis	Yes	71 (55%)	3 (16%)	3 (20%)	35 (37%)	0123
	No	59 (45%)	16 (84%)	12 (80%)	61 (63%)	
LDH *	Increased	30 (63%)	4 (44%)	3 (60%)	23 (68%)	0438
	Not increased	18 (37%)	5 (56%)	2 (40%)	11 (32%)	
Previous adjuvant treatment	Yes	8 (6%)	1 (5%)	1 (7%)	6 (6%)	0983
	No	122 (94%)	18 (95%)	14 (93%)	90 (94%)	
Treatment	PD1	77 (59%)	13 (68%)	6 (40%)	58 (60%)	0221
	PD1 +Ipilimumab	53 (41%)	6 (32%)	9 (60%)	38 (40%)	
irAE (at least one)	Yes	37 (28%)	7 (37%)	6 (40%)	24 (25%)	0333
	No	93 (72%)	12 (63%)	9 (60%)	72 (75%)	
irAE grade *	1	9 (25%)	4 (58%)	0	5 (22%)	0821
	2	8 (22%)	1 (14%)	1 (17%)	6 (26%)	
	3	15 (42%)	1 (14%)	4 (66%)	10 (43%)	
	4	4 (11%)	1 (14%)	1 (17%)	2 (9%)	
2nd or later line Treatment of melanoma	Yes	55 (42%)	5 (26%)	7 (47%)	43 (45%)	0312
	No	75 (58%)	14 (74%)	8 (53%)	53 (55%)	
DCR *	CR/PR/SD	31 (31%)	3 (21%)	4 (33%)	24 (32%)	0720
	PD	70 (69%)	11 (79%)	8 (67%)	51 (68%)	
PFS in month (95%CI)	Mean	16 (11-20)	12 (5-20)	16 (6-26)	16 (11-21)	0879
	Median	6 (1-11)	5 (0-15)	3 (1-5)	6 (2-10)	
OS in month (95%CI)	Mean	27 (22-32)	11 (6-16)	19 (10-28)	30 (24-35)	0067
	Median	19 (8-30)	8 (0-19)	16 (0-35)	36 (13-59)	

Thus, the currently available literature supports our association of irAE and improved prognosis. However, the relevance of intensity and type of IST for irAE and the relevance of different organs involved by irAE are less clear [19]. Some studies did not show a negative impact of IST for irAE on PFS and OS in melanoma [20] or a mixed group of patients receiving systemic steroids for cutaneous irAE [21]. A deleterious effect of high dose steroids (>30 mg prednisone equivalent per day) on the efficiency of ICI was suggested by one study [22] but not found in another study [23]. In case of second-line IST (after failure of steroids) for irAE, a recent study showed a negative impact on PFS and OS in

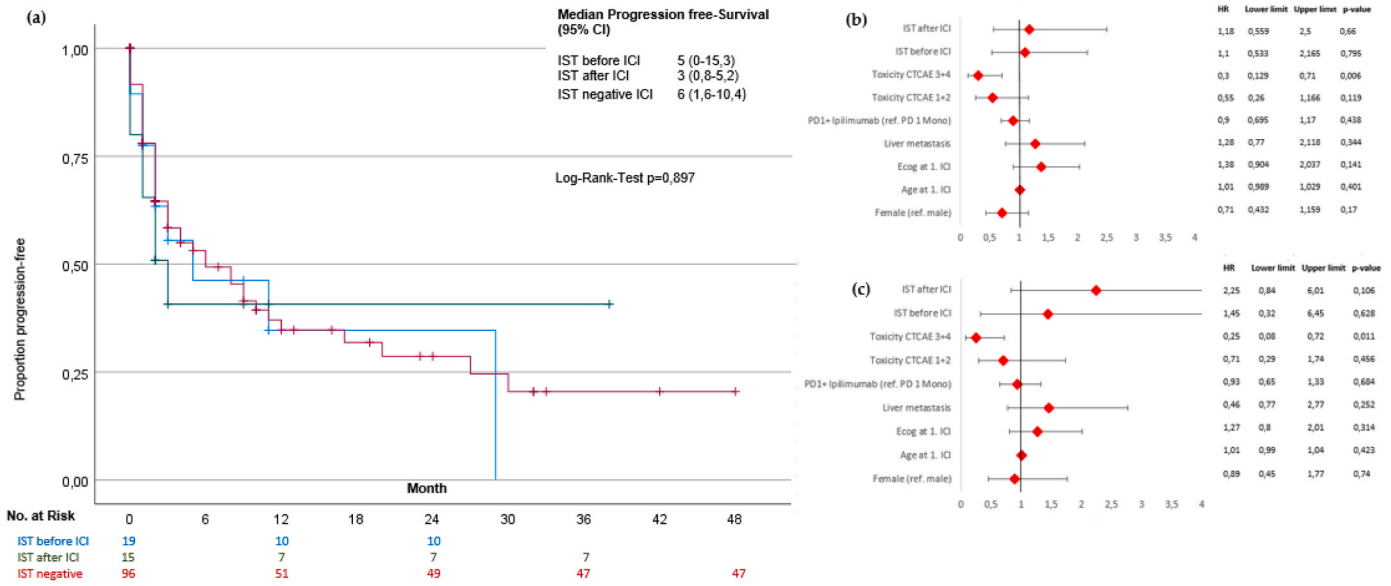

Fig. 4. Kaplan-Meier curves for PFS in patients with BM **(a)**. Hazard Ratios of prognostic factors for PFS in patients with BM in univariate (**b**) and multivariate (**c**) Cox-regression-analyses.

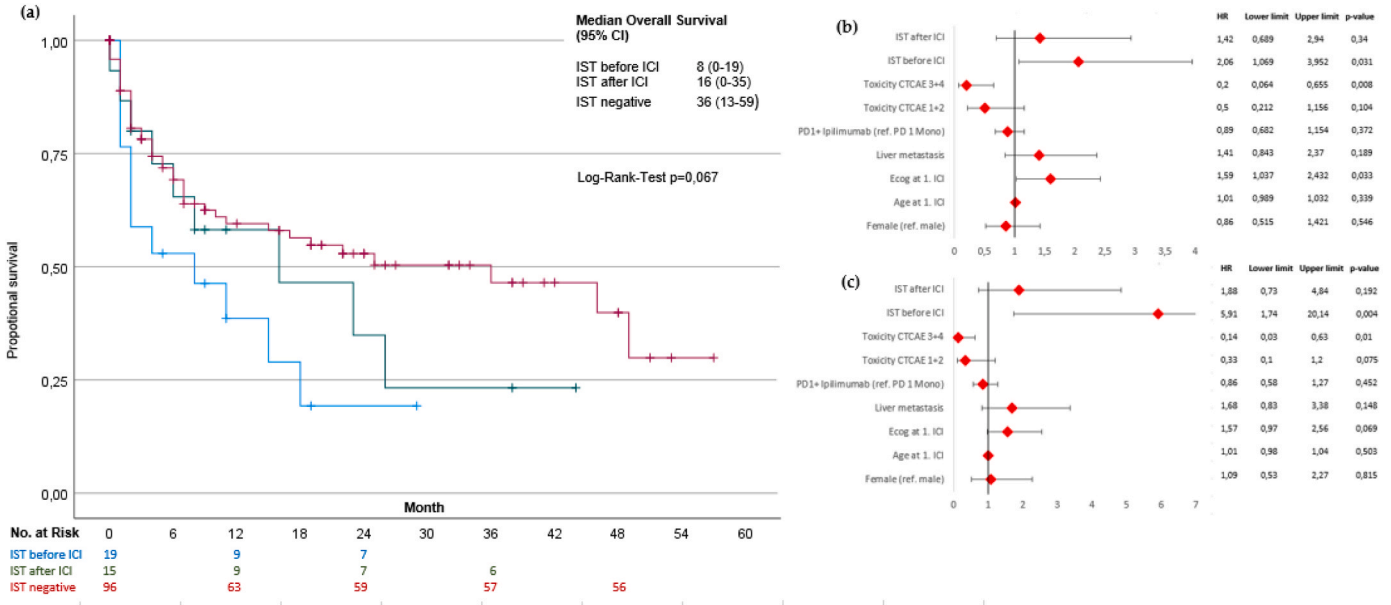

Fig. 5. Kaplan-Meier curves for OS in patients with BM **(a)**. Hazard Ratios of prognostic factors for OS in patients with BM in univariate (**b**) and multivariate (**c**) Cox-regression-analyses.

melanoma [24]. A recent meta-analysis suggested a correlation of non-thyroid endocrine and cutaneous irAE with improved efficiency of ICI, but not in case of other sites of irAE [25], whereas a second meta-analysis associated irAEs in skin, endocrine organs or gastrointestinal tract with significant survival benefits [26] and a third meta-analysis found a negative impact of grade 3–4 gastrointestinal irAE on ICI efficiency in melanoma patients [27].

The relevance of IST before initiation of ICI treatment on ICI efficiency is not clear. Most of the studies investigated the use of steroids since this is – as in our study – the most frequently used type of IST. Data on melanoma is scarce. One study on real world data from the Flatiron Health electronic health record–derived deidentified database defined baseline corticosteroid use as administration of systemic steroid within 14 days before or within 30 days after the ICI start date. In 742 patients with advanced melanoma, 182 (25%) had baseline corticosteroid use, and there was a trend towards shorter OS in patients with baseline corticosteroid use as compared to patients without corticosteroids (16.4 versus 21.5 months; $p = 0.095$) [28]. A population-based study using the SEER-Medicare-linked database analyzed 1671 melanoma patients receiving ICI, 907 patients also received steroids in the 12 months preceding start of ICI [29]. Last steroid exposure $< = 1$ month and 1–3 months prior to ICI increased the OS (hazard ratio (HR): 2.26, 95% confidence interval (CI): 1.65–3.08; and HR: 1.51, 95% CI: 1.01–2.27, respectively). Studies in NSCLC suggest a reduced efficiency of ICI in patients receiving steroids at initiation of ICI in multivariate models taking other prognostic factors into account [30–32]. Moreover, a recent study suggested a lower efficiency of ICI in a mixed population of patients with advanced cancer with higher endogenous glucocorticoid levels as compared to lower levels at initiation of ICI [33]. These data support our observation that patients with MM receiving IST - and

particularly steroids - before ICI initiation have a shorter PFS.

Patients with BM were analyzed separately since BM represent a poor prognostic factor and IST - in particular steroids- are often given for symptomatic disease or peri-interventional for surgery or radiotherapy of BM [5,34]. This is also the case in our patients for IST given before ICI, 60% received steroids for symptomatic BM, 40% peri-interventionally. In patients with IST after start of ICI, 40% received IST for symptomatic BM, 40% peri-interventionally and 20% for irAE. IST administered before ICI but not IST given after start of ICI was significantly correlated with worse OS (univariate analysis HR 2.06, 95%-CI 1.07–3.95, $p = 0.031$; multivariate analysis HR 5.91, 95%-CI 1.74–20.14, $p = 0.004$). The most probable reason, though, is selection bias of symptomatic BM patients. Another reason could yet be a detrimental effect of steroids on ICI efficacy, and if so, other options to cope with brain edema should be developed [35]. In multivariate analysis, a higher ECOG performance status was also associated with reduced OS. The occurrence of grade 3 or 4 irAE was associated with improved PFS and OS, which need to be interpreted similar to the situation discussed above for patients without BM.

We show that IST before start of ICI can result in a decreased effectivity of ICI, whereas IST initiated after start of ICI (mainly due to early irAE) is not associated with decreased effectivity of ICI.

Our study has the limitation of a real-world study, with missing values and underreporting in particular of low-grade irAE. Moreover, the patient number of the IST cohorts are overall small. In addition, a bias of indication cannot be excluded, which leads to the worse OS of the IST before ICI group. Further the presence of 2nd and later treatment of melanoma is not satisfied in multivariate analysis. An impact of this on OS cannot be ruled out. It is possible that in larger patient cohorts there could be an effect detected. Inobservance of a dose correlation with corticosteroids is another limitation of this analysis. Only a small group of patients (6%) got an adjuvant previous treatment, mainly interferon. We did not evaluate the influence of it to efficacy of immune checkpoint inhibition in this analysis. On the other side, our study has the strengths of prospectively collected data on treatment, treatment efficiency and irAE, high quality data with regard to IST which were retrospectively assessed by participating centers, a homogeneous group of patients with regard to disease (unresectable MM) and treatment (first line ICI).

5. Conclusions

Patients receiving IST 60 days before start of ICI may have a decreased effectivity of ICI. IST initiated within 30 days after start of ICI (mainly due to early irAE triggered by ICI) is not associated with decreased effectivity of ICI.

Institutional Review Board Statement

The ADOREG registry was approved by the ethics committee of University Duisburg-Essen (14–5921-BO) and provides real-world data from skin cancer patients of clinical centers of the DeCOG. The analysis was conducted according the guidelines of Declaration of Helsinki. Patient consent was obtained for inclusion in registry, and institutional review board approval for the ADOREG database includes the use of data for research purposes.

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CRediT authorship contribution statement

Corinna Kochanek, Ralf Gutzmer: Writing – review & editing, Conceptualization. **Corinna Kochanek**: Methodology, Software, Validation, Formal analysis, Illustration of tables and figures. **Ralf Gutzmer**: Project administration, Supervision. All authors: Data acquisition. All authors have read and agreed to the published version of manuscript.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon request.

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