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RESEARCH ARTICLE

Liver-directed treatment is associated with improved survival and increased response to immune checkpoint blockade in metastatic uveal melanoma: results from a retrospective multicenter trial

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Abstract Metastases of uveal melanoma (UM) spread predominantly to the liver. Due to low response rates to systemic therapies, liver-directed therapies (LDT) are commonly used for tumor control. The impact of LDT on the response to systemic treatment is unknown. A total of 182 patients with metastatic UM treated with immune checkpoint blockade (ICB) were included in this analysis. Patients were recruited from prospective skin cancer centers and the German national skin cancer registry (ADOReg) of the German Dermatologic Cooperative Oncology Group (DeCOG). Two cohorts were compared: patients with LDT (cohort A, *n* = 78) versus those without LDT (cohort B, *n* = 104). Data were analyzed for response to treatment, progression-free survival (PFS), and overall survival (OS). The median OS was significantly longer in cohort A than in cohort B (20.1 vs. 13.8 months; *P* = 0.0016) and a trend towards improved PFS was observed for cohort A (3.0 vs. 2.5 months;

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P = 0.054). The objective response rate to any ICB (16.7% vs. 3.8%, P = 0.0073) and combined ICB (14.1% vs. 4.5%, P = 0.017) was more favorable in cohort A. Our data suggest that the combination of LDT with ICB may be associated with a survival benefit and higher treatment response to ICB in patients with metastatic UM.

Keywords uveal melanoma; liver-directed therapy; immune checkpoint blockade; SIRT; anti-PD-1; anti-CTLA-4

Introduction

Uveal melanoma (UM) is the most common aggressive tumor of the eye in adults but it is an orphan tumor condition with a mean age-adjusted incidence of 5.2 per million in the Caucasian population [1]. Depending on genetic alterations of the tumor, at least 40%–50% of patients develop metastases [2,3]. Once metastases develop, the median overall survival (OS) is approximately 1.07 years and the survival rate decreases rapidly from 52% at 1 year to 25% at 2 years, and 13% at 3 years [4,5]. Although the treatment with immune checkpoint blockade (ICB; including anti-PD1 and/or anti-CTLA-4 antibodies) was associated with improved survival in several retrospective studies [6,7], tebentafusp was the first drug to show a significant survival benefit in a prospective randomized controlled trial. Nevertheless, the overall prognosis of UM remains dismal due to low response rates and the availability of tebentafusp restricted to patients with HLA type A02:01, which is present in approximately 40%–60% of Caucasian populations [8].

The metastases of UM spread predominantly to the liver (> 90%) and only hepatic metastases are associated with a poor OS compared to patients with extrahepatic disease [6,9]. In cutaneous melanoma (CM), hepatic metastases are the least responsive metastatic site to combined ICB (anti-PD1 and anti-CTLA-4 antibodies) with a median of 3% tumor regression compared to extrahepatic sites with a median of 77% [10]. Mechanistically, macrophages can induce apoptosis of $CD8^+$ T cells in the liver through fas-ligand binding, which may explain ineffective tumor control and poor response to immunotherapy [11–13]. However, under consideration of the highly immunosuppressive microenvironment of the liver, the high frequency of hepatic metastases, and the low response rates to systemic therapies, liver-directed locoregional therapies (LDT) are commonly applied for hepatic disease of UM. Predominantly retrospective, uncontrolled studies with heterogeneous results are available for a panel of distinct LDT [14]. Due to differences in patient selection and treatment protocols, the cross-comparison of these LDT modalities is barely possible.

The most commonly performed procedures for small and solitary lesions are radiofrequency ablation or microwave ablation. Early surgical resection of solitary metastases is not inferior to radiofrequency ablation but more invasive [15]. Selected patients with UM with limited liver tumor burden and a long interval to metastases occurrence may benefit from laparoscopic management of liver metastases [16]. Larger solitary lesions (> 3–4 cm) are treated in some centers with transarterial chemoembolization (TACE). For TACE, a variety of chemotherapeutic agents and treatment protocols are used and no standard of care or comparative clinical trials are available [14]. If multiple lesions are present within one hepatic lobe, selective internal radiotherapy (SIRT) may be applied [17]. The largest retrospective analysis including 71 patients showed progression-free survival (PFS) of 5.9 and OS of 12.3 months. A prospective phase II study demonstrated PFS and OS of 8.1 and 18.5 months, respectively, in treatment-naïve patients [18]. If multiple or disseminated hepatic metastases are present, more than one cycle of SIRT cycle or chemosaturation (CS) may be applied as LDT. CS is a more recent technique in which affected liver tissue is saturated with high doses of melphalan through an artery catheter. Venous blood is aspirated and cleansed of melphalan by an extracorporeal filtration system. The cleansed blood returns to the systemic circulation minimizing systemic toxicity [19–22]. A phase III study in 93 patients applying CS with a first-generation filter system revealed a PFS of 5.4 and OS of 10.6 months [23]. A phase II trial using the second-generation filter system caused less damage to blood cells than first-generation filters, which is crucial in an era of immunotherapy [24]. However, PFS and OS did not differ compared to the first generation [22]. The results following SIRT or CS demonstrated improved PFS compared to systemic therapies but a clear survival benefit was not evident [6,8,25–27]. In this study, we hypothesized that the concurrent use of LDT improves the response to ICB and is associated with a survival benefit in patients with UM.

Materials and methods

Patient population and study design

We performed a retrospective multicenter explorative analysis. Patients with metastatic UM receiving any type of ICB (anti-PD1 antibodies: nivolumab or pembrolizumab; anti-CTLA-4 antibody: ipilimumab, and

anti-CTLA-4 plus anti-PD-1 antibody: combined ICB) were eligible. A total of 182 patients were included and stratified into two cohorts: Cohort A comprised patients who underwent LDT with ICB (n = 78, cohort A) while cohort B included those without LDT (n = 104, cohort B). Cohort A was further stratified according to the timing between ICB and LDT. LDT before ICB was summarized as A1 (n = 23), LDT concurrent with ICB as A2 (n = 14), and LDT after ICB as A3 (n = 19). In 22 patients, the exact timing between ICB and LDT was not assessable.

Clinical data and the treatment outcomes of interest were extracted from the original patient records from 14 German skin cancer centers (Erlangen n = 62, München n = 17, Tübingen n = 15, Mainz n = 7, Mannheim n = 5, Heidelberg n = 4, Kiel n = 4, Dresden n = 3, Frankfurt n = 3, Köln n = 3, Homburg n = 2, Ludwigshafen n = 2, Würzburg n = 2, Göttingen n = 1), as well as from the prospective multicentric skin cancer registry ADOReg of the German Dermatologic Cooperative Oncology Group (DeCOG) (n = 54). The ADOReg collects data for high-quality real-world evidence studies; all ADOReg patient IDs included in this study were checked for duplicates. The data were collected and merged into a central database before analysis. This study was approved by the scientific board of the ADOReg registry, the institutional review board of the medical faculty of the Munich University Hospital (approval number 413-16 UE), and it was conducted following the principles of the Helsinki Declaration in its current version.

Data collection and treatment outcomes

The recorded clinical data at baseline comprised demographics with sex, age, number of organ systems affected by metastasis, and date of death or last documented patient contact. At the date of ICB initiation, the Eastern Cooperative Oncology Group (ECOG) performance status and serum lactate dehydrogenase (LDH) levels were collected from patient charts and analyzed for their prognostic values. Regarding the treatment, we recorded the number and type of therapies (notably: not all centers had access to the same type of LDT), date of LDT application, ICB start and end dates, date of the first progression to ICB, the best response to ICB (based on the RECIST criteria version 1.1), and adverse event (AE) assessment based on the CTCAE criteria (version 5). We summarized any metastases besides liver, bone, pulmonary, CNS, lymph node, connective tissue, and skin metastases as a category "other metastases" .

OS was calculated as the time from the date of treatment initiation of ICB until melanoma-specific or treatment-related death. PFS was determined as the time from treatment start of ICB until disease progression was confirmed by radiologic imaging or until clinically evident. In case of rapid impairment of clinical condition, radiologic imaging was lacking. Complete (CR) and partial (PR) responses were summarized as objective response rate (ORR) and CR, PR, and stable disease (SD) as disease control rate (DCR). Time-to-event analyses were calculated where death or disease progression were considered as events. If neither occurred or if patients were lost to follow-up, the date of the last documented presentation was used as a censored observation.

Statistical analyses

The survival and progression probabilities were calculated with the Kaplan–Meier method. Log-rank tests were performed to compare the survival and progression probabilities of both cohorts. Furthermore, χ^2 tests and t-tests were conducted (i) to test the comparability of the two cohorts, i.e., concerning possible different baseline characteristics, and (ii) to compare the response to ICB between both cohorts. In all cases, two-tailed P values were calculated and considered significant with values $P < 0.05$. Patients with missing values for a given variable were excluded. No imputation of missing data was performed.

Results

Baseline patient characteristics

A total of 182 patients with metastatic UM undergoing ICB were included and divided into 2 cohorts according to whether they received LDT or not; 52.7% of the patients had an ECOG status of 0 (n = 96), the serum LDH was elevated in 46.7% of cases (n = 85) at baseline. Both parameters showed no significant difference between the cohorts with a trend toward elevated ECOG status in cohort B (61.5% vs. 46.2%, P = 0.056, and 43.6% vs. 49.0%, P = 0.56, respectively). The patients had predominantly metastases to the liver (93.4%), lung (47.8%), bone (26.9%), lymph node (22%), central nervous system (15.4%), skin (13.2%), connective tissue (4.9%), and in 26.4% "other metastases." The ICB regimes were evenly distributed in both cohorts; 121 patients (66.5%) received combined ICB, 54 (29.7%) PD-1 antibody monotherapy, and 7 (3.8%) CTLA-4 antibody monotherapy (P = 0.23). All baseline characteristics are listed in detail in Table 1.

Response rates to ICB

The ORR to any ICB in the entire population was 9.3% (17/182); 1.6% (3/182) achieved a CR, while 7.7% (14/182) had a PR. The ORR was 5.6% (3/54) and 11.6% (14/121) for anti-PD-1 monotherapy and combined ICB, respectively. The ORR for any ICB and combined ICB

Table 1 Baseline characteristics of the study population

Parameter	Categories	Total (n = 182)	Cohort A (n = 78)	Cohort B (n = 104)	P value
Age	Median in years	65.2 (17.7–87.6)	63.8 (31.7–85.0)	66.2 (17.7–87.6)	0.31
Sex	Female	91 (50%)	36 (46.2%)	55 (52.9%)	0.45
	Male	91 (50%)	42 (53.8%)	49 (47.1%)	
ECOG performance status	0	96 (52.7%)	48 (61.5%)	48 (46.2%)	0.056
	1	16 (8.8%)	3 (3.8%)	13 (12.5%)	
	2	4 (2.2%)	0 (0%)	4 (3.8%)	
	3	1 (0.5%)	0 (0%)	1 (1%)	
	Not indicated	65 (35.7%)	27 (34.6%)	38 (36.5%)	
LDH	Not elevated	49 (26.9%)	26 (33.3%)	23 (22.1%)	0.56
	Elevated	85 (46.7%)	34 (43.6%)	51 (49%)	
	Not indicated	48 (26.4%)	18 (23.1%)	30 (28.8%)	
Sites of metastasis	Liver	170 (93.4%)	78 (100%)	92 (88.5%)	0.11
	Pulmonary	87 (47.8%)	32 (41%)	55 (52.9%)	
	Bone	49 (26.9%)	18 (23.1%)	31 (29.8%)	
	CNS	28 (15.4%)	11 (14.1%)	17 (16.3%)	
	Lymph node	40 (22%)	16 (20.5%)	24 (23.1%)	
	Connective tissue	9 (4.9%)	3 (3.8%)	6 (5.8%)	
	Skin	24 (13.2%)	9 (11.5%)	15 (14.4%)	
	Disseminated	10 (5.5%)	5 (6.4%)	5 (4.8%)	
	Other	48 (26.4%)	16 (20.5%)	32 (30.8%)	
Number of metastatic sites (at the time of immunotherapy)	Median (range)	2.5 (1–8)	2.4 (1–8)	2.7 (1–7)	0.43
Time from metastasis to treatment start	Medians in months (range)	11.7 (0–329.7)	14.4 (0–329.7)	8 (0–46.6)	0.297
Treatment lines throughout patient course	Median (range)	2 (1–7)	2 (1–7)	2 (1–6)	0.094
Radiation therapy	Yes	42 (23.1%)	29 (37.2%)	13 (12.5%)	<0.001
	No	96 (52.7%)	33 (42.3%)	63 (60.6%)	
	Unknown	44 (24.2%)	16 (20.5%)	28 (26.9%)	
Liver directed treatment	RFA		8 (10.3%)		
	SIRT		53 (67.9%)		
	TACE		9 (11.5%)		
	Chemosaturation		5 (6.4%)		
	Liver-surgery		1 (1.3%)		
	Other		2 (2.6%)		
ICB therapy	Single anti-PD1	54 (29.7%)	19 (24.4%)	35 (33.7%)	0.23
	Single anti- CTLA-4	7 (3.8%)	4 (5.1%)	3 (2.9%)	
	Combined ICB	121 (66.5%)	55 (70.5%)	66 (63.5%)	

CNS, central nervous system; ICB, immune checkpoint blockade; RFA, radiofrequency ablation; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolization.

was significantly higher in cohort A compared to cohort B (16.7% vs. 3.8%, P = 0.0073; and 14.1% vs. 4.5%, P = 0.017, respectively). Details of the patterns of response to ICB are summarized in Table 2.

The ORR to any ICB was 26.1% (6/23) in patients receiving LDT before ICB (A1), 14.3% (2/14) in patients receiving LDT during ICB (A2), and 5.3% (1/19) in patients receiving LDT after ICB (A3). Further information about the response rates to ICB in the subpopulations of cohort A is listed in Table 3.

Survival data

The entire cohort showed a median OS of 14.9 months (95% CI 12.7–17.8) and a median PFS of 2.7 months (95% CI 2.4–3) (Figs. 1A and S2A). There was a statistical difference in OS (P = 0.0016) and a trend in PFS (P = 0.054) in favor of cohort A (Figs. 1B and S2B).

Table 2 Response rates to ICB

Response to ICB (any)	Total (n = 182)	Cohort A (n = 78)	Cohort B (n = 104)	Test (A vs. B)
CR	3 (1.6%)	2 (2.6%)	1 (1.0%)	
PR	14 (7.7%)	11 (14.1%)	3 (2.9%)	
SD	34 (18.7%)	16 (20.5%)	18 (17.3%)	
PD	99 (54.4%)	36 (46.2%)	63 (60.6%)	
MR	5 (2.7%)	3 (3.8%)	2 (1.9%)	
NA	26 (14.3%)	10 (12.8%)	17 (16.3%)	
ORR	17 (9.3%)	13 (16.7%)	4 (3.8%)	P = 0.0073
DCR	51 (28.0%)	29 (37.2%)	22 (28.2%)	P = 0.027
Response to anti-PD1 monotherapy	**Total (n = 54)**	**Cohort A (n = 19)**	**Cohort B (n = 35)**	**Test (A vs. B)**
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)	
PR	3 (5.6%)	2 (10.5%)	1 (2.9%)	
SD	6 (11.1%)	3 (15.8%)	3 (8.6%)	
PD	35 (64.8%)	10 (52.6%)	25 (71.4%)	
MR	2 (3.7%)	1 (5.3%)	1 (2.9%)	
NA	8 (14.8%)	3 (15.8%)	5 (14.3%)	
ORR	3 (5.6%)	2 (10.5%)	1 (2.9%)	P = 0.57
DCR	9 (16.7%)	5 (26.3%)	4 (11.4%)	P = 0.31
Response to combined ICB	**Total (n = 121)**	**Cohort A (n = 55)**	**Cohort B (n = 66)**	**Test (A vs. B)**
CR	3 (2.5%)	2 (3.6%)	1 (1.5%)	
PR	11 (9.1%)	9 (16.4%)	2 (3.0%)	
SD	27 (22.3%)	13 (23.6%)	14 (21.2%)	
PD	59 (48.8%)	22 (40.0%)	37 (56.1%)	
MR	3 (2.5%)	2 (3.6%)	1 (1.5%)	
NA	18 (14.9%)	7 (12.7%)	11 (16.7%)	
ORR	14 (11.6%)	11 (14.1%)	3 (4.5%)	P = 0.017
DCR	41 (33.9%)	24 (30.8%)	17 (25.8%)	P = 0.061

CR, complete response; DCR, disease control rate; ICB, immune checkpoint blockade; MR, mixed response; NA, not available; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3 Response rates to ICB in the subpopulations of cohort A

Subgroups of cohort A	n	ORR	DCR
A1: LDT before ICB	23	6/23 = 26.1%	11/23 = 47.8%
A2: LDT during ICB	14	2/14 = 14.3%	5/14 = 35.7%
A3: LDT after ICB*	19	1/19 = 5.3%	6/19 = 31.6%
Time of LDT unknown	22	3/22 = 13.6%	6/22 = 27.3%
P value (before vs. during vs. after)		Underpowered	0.54

* The mean time from ICB to LDT was 4.5 months (standard deviation 3.5 months)
ICB, immune checkpoint blockade; LDT, liver-directed therapies; ORR, objective response rate; DCR, disease control rate.

This survival benefit was also evident in swimmer plots for both cohorts (Fig. 2). Patients with clinical benefit to ICB (ORR, DCR) showed significantly improved OS (P < 0.001, Fig. 1C and 1D). Elevated serum LDH and poor ECOG performance status were associated with poor OS (P < 0.001, P = 0.0032, respectively; Fig. S1). Notably, OS after 24 months was higher in cohort A2 compared to A1 and A3 (74.1% vs. 47.3% vs. 48.8%, respectively). The survival data of the subpopulations of cohort A are presented in Table 4 and Fig. S3.

Adverse events

Adverse events (AE) were reported in 81 patients (44.5%). They were estimated as severe in 46 patients (25.3%) with no significant difference between both

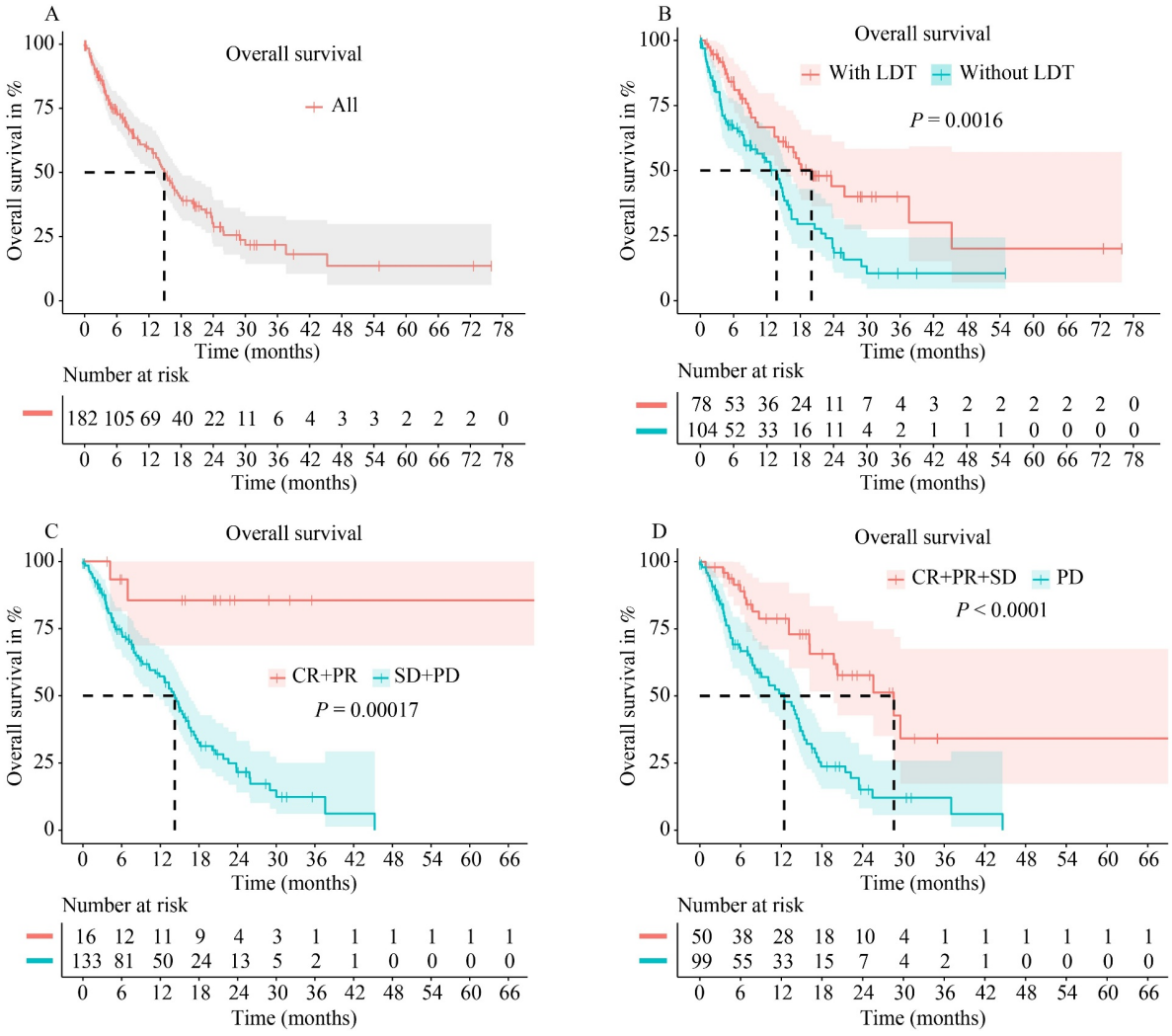

Fig. 1 Kaplan–Meier estimates of the patient population for (A) OS of the entire population with a median OS of 14.9 months (CI 95% 12.7–17.8). (B) OS comparing cohort A (red) vs. B (turquoise) with a median OS of 20.1 months (CI 95% 14.1-NR) vs. 13.8 months (CI 95% 9.2–16.0; $P = 0.0016$). (C) compares CR, PR (red) vs. SD, PD (turquoise) revealing a median OS of NR (NR-NR) vs. 14.3 months (CI 95% 11.3–16.4; $P < 0.001$). (D) compares CR, PR, SD (red) vs. PD (turquoise) with a median OS of 29 months (20.1-NR) vs. 12.6 months (CI 95% 8.6–15.4; $P < 0.001$).

cohorts ($P = 0.081$ and $P = 0.34$, respectively) although there was a trend toward more AE in cohort A. AE in cohort A2 were higher compared to A1 and A3 (71.1% vs. 47.7% vs. 47.4%, respectively, $P = 0.3021$; Table 5).

Discussion

In this retrospective analysis, we present a large cohort of patients with metastatic UM undergoing treatment with ICB ($n = 184$). The median OS of the entire population was 14.9 months (95% CI 12.7–17.8), with a significantly improved OS in patients (1) receiving LDT, (2) achieving a radiologic response to ICB, (3) without elevated LDH, and a normal ECOG performance status. Although there was no statistical difference, LDH and ECOG showed a less favorable trend in cohort B, possibly confounding the prognosis in this cohort. Cohort A showed a significantly improved ORR for any ICB (16.7% vs. 3.8%) and combined ICB (14.1% vs. 4.5%). Taken together, these results suggest that LDT may be associated with higher response rates and improved survival compared to ICB alone. Previous analyses revealed that patients with liver metastases only had poorer OS compared to those with multiple affected organ systems [6,7].

In the subgroup analyses of cohort A, we observed a tendency toward better ORR in A1 and A2 compared to A3. Furthermore, OS after 12 months was higher in subgroup A2 compared to A1 and A3 (74.1% vs. 47.3% vs. 48.8%, respectively). Similarly, the rate of AE was the highest in this subgroup (71.1% vs. 47.7% vs. 47.4%, respectively). These data suggest that LDT may show the most favorable effects when it is performed concurrently

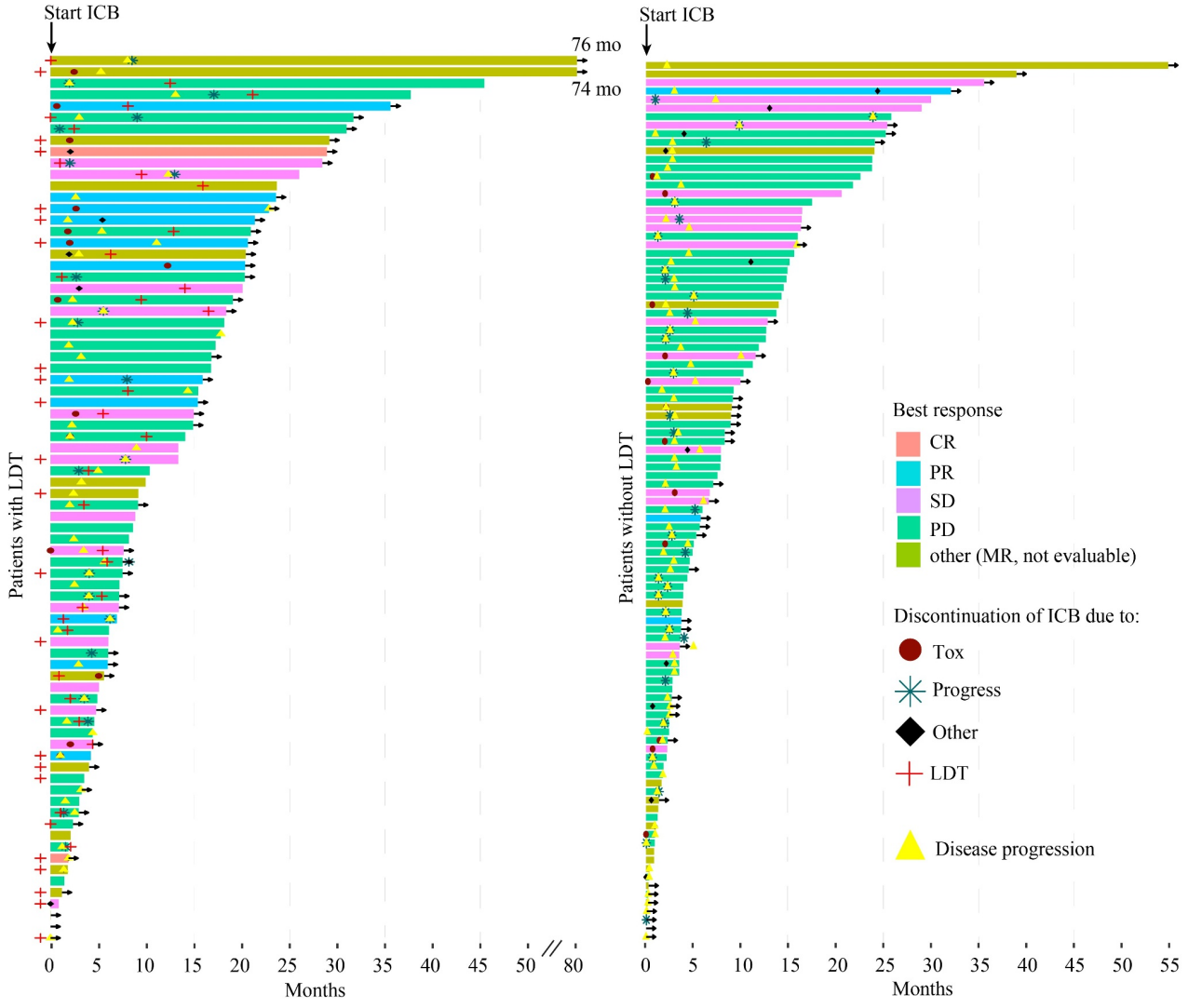

Fig. 2 Swimmer plots for cohorts A (lower) and B (top) demonstrating the OS for each patient. The color shows the best response to ICB, the symbols depict the reason for treatment discontinuation and the yellow triangle shows the time of tumor progression. If a patient was censored, an arrow is drawn. The red cross marks the time of LDT.

Table 4 Survival times for the subpopulations of cohort A

Subgroups of cohort A	N (OS)	Median OS in months (95% CI)	OS after 6 months (95% CI)	OS after 12 months (95% CI)	OS after 24 months (95% CI)
LDT without SIRT	25	13.4 (8.8-NR)	84.7% (70.1%–100%)	56.4% (37.6%–84.6%)	38.1% (20.8%–69.8%)
Only SIRT	53	23.7 (17.8-NR)	84.0% (74.3%–94.8%)	71.7% (59.6%–86.3%)	46.9% (31.8%–69.1%)
A1	23	18.2 (13.4-NR)	80.3% (64.6%–99.7%)	68.3% (50.0%–93.3%)	48.3% (29.2%–80.0%)
A2	14	26.0 (26.0-NR)	83.3% (64.7%–100%)	74.1% (52.6%–100%)	74.1% (52.6%–100%)
A3	19	23.7 (15.4-NR)	100%	86.3% (70.1%–100%)	48.8% (26.1%–91.3%)
Subgroups of cohort A	**N (PFS)**	**Median PFS in months (95% CI)**	**PFS after 3 months (95% CI)**	**PFS after 6 months (95% CI)**	
LDT without SIRT	13	2.6 (2.4–5.3)	38.5% (19.3%–76.5%)	7.7% (1.2%–50.6%)	
Only SIRT	36	3.5 (2.3–5.5)	52.8% (38.8%–71.9%)	25.0% (14.2%–44.0%)	
A1	14	2.4 (1.9–11.1)	42.9% (23.4%–78.5%)	28.6% (12.5%–65.4%)	
A2	9	3.5 (2.5-NR)	55.6% (31.0%–99.7%)	22.2% (6.6%–75.4%)	
A3	13	3.5 (2.0-NR)	53.8% (32.6%–89.1%)	15.4% (4.3%–55.0%)	

ICB, immune checkpoint blockade; LDT, liver-directed therapies; OS, overall survival; PFS, progression free survival; SIRT, selective internal radiotherapy.

Table 5 Occurrence of adverse events

	Total	Cohort A	Cohort B	Test (Cohorts A vs. B)
Any ICB: Nr. of patients with AE	81/182 (44.5%)	41/78 (52.6%)	40/104 (38.5%)	$P = 0.081$
Any ICB: Nr. of patients with severe AE	46/182 (25.3%)	23/78 (29.5%)	23/104 (22.1%)	$P = 0.34$
Comb. ICB: Nr. of patients with AE	66/121 (54.4%)	33/55 (60%)	33/66 (50%)	$P = 0.36$
Comb. ICB: Nr. of patients with severe AE	42/121 (34.6%)	22/55 (40%)	20/66 (30.2%)	$P = 0.36$
	Cohort A1 LDT before ICB	Cohort A2 LDT during ICB	Cohort A3 LDT after ICB	Cohort A Time of LDT unknown
Number of patients with AE	11/23 (47.7%)	10/14 (71.1%)	9/19 (47.4%)	11/22 (50%)
Number of patients with severe AE	7/23 (30.3%)	4/14 (28.6%)	7/19 (36.7%)	5/22 (22.6%)

AE, adverse event; ICB, immune checkpoint blockade; LDT, liver-directed therapies.

with ICB, however at the cost of increased risk for toxicity. Due to the small sample size of these subgroups, statistical analyses may be underpowered and the results need to be interpreted with caution. Importantly, the exact time point of LDT was not exactly known in a major subset of patients, limiting the conclusion on the best timing of LDT and ICB.

The ORR to combined ICB in cohort A with 14.1% was significantly higher than in the control cohort B in this study, but it is in line with data from two prospective single-arm studies, in which patients with metastatic UM received combined ICB without LDT (11.5% and 18%) [26,28]. In another small retrospective single-center analysis, the ORR following combined ICB in combination with SIRT was 22.2% [29]. Notably, the same study compared combined ICB and SIRT to SIRT only and found a significant survival benefit in the cohort treated in combination with ICB. The median OS from the first treatment was 46.6 (95% CI 22.0-not reached) vs. 11.8 (95% CI 8.5-not reached) months ($P = 0.039$) [29], which is slightly better than in our population. The other way around, a further retrospective single-center study showed a significant survival benefit for the combination of LDT with ICB compared to other systemic therapies (mainly ICB) with a median OS of 22.5 months ($n = 19$) vs. 11.4 months ($n = 23$) when calculating the survival times from date of liver metastasis to death ($P = 0.036$) [30]. Response rates were not reported in this study. Our comparably large multi-center retrospective trial goes beyond these previous analyses and provides strong evidence for a survival benefit when LDT and ICB are applied. Similar results were observed in a population with metastatic CM ($n = 127$) where local peripheral treatments such as radiotherapy or electrochemotherapy in addition to anti-CTLA-4 demonstrated a survival benefit and improved DCR compared to anti-CTLA-4 monotherapy without additional safety signals [31]. However, the mechanisms by which LDT induces improved immune responses remain unclear. Over the decades the combination of ICB and other immunotherapies with radiotherapy showed in several pre-clinical studies the ability to induce anti-tumor T cells and improve responses to ICB [32,33]. Theoretically, LDT results in tumor cell death and releases non-targeted antigens. These antigens might prime subsequent immune responses boosted by ICB [34].

The OS after 24 months was 74.1% in the A2 subgroup (LDT during ICB) compared to 48.3% in A1 and 48.8% in A3. These results were better than in the prospective single-arm trials of combined ICB with a 12 months OS of 56% and 51.9% [26,28] and comparable to the survival times with tebentafusp achieving a 12 months OS of 73% in a recent randomized trial [8]. Within cohort A, the subgroup with SIRT showed the most favorable OS after 12 and 24 months compared to other LDT modalities in combination with ICB (71.7% vs. 56.4% and 46.9% vs. 38.1%, respectively. However, due to the small number of patients and uncertainties on the timing of LDT in these subgroups, interpretation should be performed with utmost caution.

AE occurred in 44.5% of patients with a trend ($P = 0.081$) toward a higher occurrence rate in cohort A (52.6% vs. 38.5%). Notably, AE in cohort A2 was higher compared to A1 and A3 (71.1% vs. 47.7% vs. 47.4%, respectively). These results indicate a slightly increased risk of AE when LDT is performed while patients receive ICB. Aedo-Lopez *et al.* observed AE in 66.7% when patients were treated with SIRT and combined ICB, which were graded as severe in 44.4% [29]. These rates are in line with the data from our population where AE and severe AE were reported at 60% and 40%, respectively. Furthermore, the occurrence of severe AE is comparable to previously published studies where immune-related grade 3/4 toxicities occurred in about 30%–60% of patients treated with combined ICB [7,25,26,28,35].

The major limitation of this study is its retrospective design and the high number of missing values, especially on ECOG and LDH. Although the pertinent prognostic factors were evenly in balance in both cohorts at baseline, bias and possible confounding cannot be completely excluded. Due to the different timing of the various therapies, the population of this study is heterogeneous and prospective studies are warranted to confirm that the

additional use of LDT increases the efficacy of systemic treatments. Finally, cohort A received significantly more radiation therapy. This confers a risk of bias as radiation therapy of extrahepatic metastases was linked to improved OS in a previous study [6].

Conclusions

Our data demonstrated that the combination of LDT, in particular SIRT, with ICB was associated with a survival benefit in patients with metastatic UM and resulted in increased response to ICB. Concurrent use of LDT with ICB showed the most favorable effects and should be investigated in future trials.

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Compliance with ethics guidelines

This study was approved by the institutional review board of the medical faculty of the Munich University Hospital (approval number 413-16 UE) and was conducted following the principles of the *Helsinki Declaration* in its current version. The Patient consent was waived due to retrospective design involving anonymized data from several centers.

Conflict of Interests M.E.: Personal fees, travel costs and speaker's honoraria from MSD, AstraZeneca, Janssen-Cilag, Cepheid, Roche, Astellas, Diaceutics; research funding from AstraZeneca, Janssen-Cilag, STRATIFYER, Cepheid, Roche, Gilead; advisory roles for Diaceutics, MSD, AstraZeneca, Janssen-Cilag, GenomicHealth; outside the submitted work. A.G.: Speaker's honoraria from Allmiral, Bristol-Myers Squibb, MSD Sharp & Dohme and Roche; intermittent advisory board relationships with Amgen, Bristol-Myers Squibb, Novartis, MSD Sharp & Dohme, Pierre Fabre Pharmaceuticals, Pfizer, Roche and Sanofi Genzyme; travel and congress fee support from Bristol-Myers Squibb, MSD Sharp & Dohme, Novartis, Pierre Fabre Pharmaceuticals and Roche. Clinical studies with Amgen, Array, Bristol-Myers Squibb, Delcath Systems Inc, GSK, Novartis, Merck, MSD Sharp & Dohme, Pfizer and Roche. R.G.: Research support: Pfizer, Johnson & Johnson, Novartis, SUN, Amgen, Sanofi, Merck-Serono, Kyowa-Kirin, Almirall-Hermal. Honoraria for lectures: Roche Pharma, Bristol-MyersSquibb, Novartis, MSD, Almirall-Hermal, Amgen, Merck-Serono, Bayer, SUN, Pierre-Fabre, Sanofi. Honoraria for advice: Roche Pharma, Bristol-MyersSquibb, Novartis, MSD, Almirall-Hermal, Amgen, Pierre-Fabre, Merck-Serono, 4SC, SUN, Merck-Serono, Sanofi, Immunocore; outside the submitted work. C.L. received Advisory board, Speekers fee, travel reimbusment from MSD, BMS, Sanofi, Pierre Fabre, Roche, Novartis, Biontech, Almirall Hermal, Sun Pharma, Kyowa Kirin, Merck, Immunocore. F.M.: Travel support or/and speaker's fees or/and advisor's honoraria by Novartis, Roche, BMS, MSD, Pierre Fabre, Sanofi and Immunocore and research funding from Novartis and Roche; outside the submitted work. K.-M.T.: Honoraria from BMS, MSD, Roche, Novartis, Pierre Fabre, Sun Pharma, LEO, Almirall, Galderma, Candela; Consultant or Advisory Role for BMS, MSD, Roche, Novartis, Pierre Fabre, Sun Pharma, LEO, Almirall; Travel support from BMS, MSD, Roche, Novartis, Pierre Fabre, LEO; outside the submitted work. C.P.: Received honoraria (speaker honoraria or honoraria as a consultant) and travel support from: Novartis, BMS, MSD, Merck Serono, MSD, Celgene, AbbVie, Sunpharma, Pierre Fabre, UCB, Nutricia Milupa, Janssen and LEO outside the submitted work. S.U.: Research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, and Novartis, and travel support from Bristol Myers Squibb, Merck Sharp & Dohme, and Pierre Fabre; outside the submitted work. J.U.: Advisory board or has received honoraria and travel support from Amgen, Bristol Myers Squibb, GSK, Immunocore, LeoPharma, Merck Sharp and Dohme, Novartis, Pierre Fabre, Roche, Sanofi outside the submitted work. A.W.: Speaker's honoraria from Novartis; outside the submitted work. All others authors declare no conflicts of interest.

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