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RESEARCH

Subgroup analyses of the phase 3 FOCUS study of melphalan/hepatic delivery system in patients with unresectable metastatic uveal melanoma

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Abstract

Purpose To assess efficacy and safety in subgroups of patients treated with Melphalan/Hepatic Delivery System (melphalan/HDS), a drug/device combination for liver-directed treatment of metastatic UM (mUM) patients. Previously reported FOCUS study results indicated melphalan/HDS treatment provides a clinically meaningful response rate and favorable benefit-risk ratio in patients with unresectable mUM.

Methods Patients with mUM received treatment with melphalan (3.0 mg/kg ideal body weight) every 6–8 weeks for up to 6 cycles. Post hoc analyses of efficacy and safety were conducted for patient subgroups based on demographic and baseline disease characteristics.

Results 102 patients with mUM were enrolled; treatment was attempted in 95 patients; 91 patients received treatment. Subgroup analyses showed consistent tumor response regardless of age, sex, geographic region, presence/absence of extrahepatic lesions, and prior therapy. Patients with lower tumor burden had better objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) than those with higher tumor burden (ORR: 51.1 vs. 22.2%, $p=0.008$; mPFS: 11.3 vs. 5.8 months, $p=0.007$; mOS: 26.7 vs. 15.4 months, $p=0.008$). Patients with 1–25% liver involvement had higher mOS than those with 26–50% liver involvement (22.4 vs. 16.9 months; $p=0.030$); patients with low or normal lactate dehydrogenase (LDH) had higher mOS than those with elevated LDH (23.5 vs. 15.3 months; $p=0.019$). The overall safety profile was similar across subgroups without evidence of cumulative toxicity with successive treatment cycles.

Conclusion Results demonstrate a favorable benefit-risk profile for melphalan/HDS across clinically relevant subgroups. However, early treatment in patients with low tumor burden may offer best results.

Key words Metastatic uveal melanoma · Percutaneous Hepatic Perfusion (PHP) · Melphalan/Hepatic Delivery System · Melphalan/HDS · Liver-directed therapy · Ocular melanoma

Introduction

Uveal melanoma (UM) is the most common intraocular malignancy in adults, accounting for approximately 3 to 5% of all melanoma cases globally (Carvajal et al. 2023). Up to 50% of patients with UM eventually develop metastatic disease (mUM), primarily to the liver (approximately 90% of cases). The prognosis of patients with mUM is poor, with median overall survival (mOS) of approximately 1 year (Carvajal et al. 2023; Rantala et al. 2019; Khoja et al. 2019; Lane et al. 2018).

Treatment options for patients with mUM are limited. Tebentafusp, a bispecific immunotherapeutic agent, is indicated for HLA-A*02:01-positive adult patients with unresectable mUM and represents a treatment option for approximately 45% of the mUM patients who are

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HLA-A*02:01-positive (KIMMTRAK Prescribing Information; Nathan et al. 2021). Since 90% of mUM patients present with liver metastases and liver failure is a common outcome, liver-directed therapies have been widely explored including the minimally invasive procedure percutaneous hepatic perfusion (PHP) (Moy et al. 2001; NCCN guidelines 2025). PHP requires the use of a Hepatic Delivery System (HDS), commercially available in Europe as CHEMOSAT® and in the US as the HEPZATO KIT™ (melphalan/HDS), which was recently approved by the US Food and Drug Administration (FDA) (HEPZATO Kit US Prescribing Information). The drug/device combination of melphalan/HDS enables loco-regional delivery of a high melphalan dose to the liver and minimizes systemic exposure and melphalan-related AEs with the use of active filters to remove excess melphalan after liver perfusion. It is currently the only FDA-approved liver-directed treatment for patients with mUM and is not limited by tumor genotype, thus offering broad utility in this indication.

Approval for melphalan/HDS was based on results from the multicenter, open-label, Phase 3 FOCUS study, which demonstrated a clinically meaningful response rate with a manageable safety profile in patients with unresectable mUM. The ORR per RECIST 1.1 by central review was 36.3% (95% confidence interval [CI] 26.4–47.0) among patients treated with melphalan/HDS, including 7.7% of patients with a complete response (CR) (Zager et al. 2024). Median PFS was 9.0 months, with 65% PFS at 6 months; and median OS was 20.5 months, with 80% OS at 1 year. The safety profile was mainly characterized by hematological toxicity due to systemic exposure to residual melphalan. The most common serious treatment-emergent adverse events were thrombocytopenia (15.8%) and neutropenia (10.5%), mostly treated as an outpatient with observation. No treatment-related deaths were observed (Zager et al. 2024).

The FOCUS study population was heterogenous, providing an opportunity to further understand the effects of melphalan/HDS in specific subgroups of patients. Here, we present post hoc efficacy and safety results from the FOCUS study in patient subgroups based on baseline demographic and disease characteristics, including age, gender, presence of extrahepatic disease, previous treatment, liver tumor burden and LDH levels at baseline. Response to treatment and incidence of toxicities are also examined by treatment cycle.

Methods

Patients

The study population included male or female patients ≥ 18 years of age with histologically verified unresectable mUM with up to 50% liver tumor involvement, at least one measurable liver lesion, and an Eastern Cooperative Oncology Group (ECOG) (Oken et al. 1982) performance status of 0 to 1 at screening. Patients could be previously treated or treatment-naïve and could have limited extrahepatic disease that was amenable to resection or radiation. The PHP procedure requires general anesthesia and active coagulation/anti-coagulation control; eligibility criteria were designed to minimize the risks associated with the procedure (e.g., exclusion of patients with moderate or severe liver cirrhosis, portal hypertension, NYHA II-IV status). The eligibility criteria remained unchanged throughout the study. Detailed inclusion and exclusion criteria are described in the previous publication.

Study design and treatment

The FOCUS study was conducted at 23 centers across the US and Europe. The study was initiated as a 2-arm, controlled, randomized study; eligible patients were randomized 1:1 to receive melphalan/HDS or best alternative care (investigator's choice of TACE, pembrolizumab, ipilimumab, or dacarbazine). Due to slow enrollment with patient reluctance to receive best alternative care treatment, the study design was amended (after discussion with FDA) to a single-arm study, after which all eligible patients received treatment with melphalan/HDS. Once the study design was changed to single-arm, sample size re-estimation was implemented and a meta-analysis of historical data (16 publications including 476 patients with mUM treated with monotherapy or combination systemic immunotherapy) was conducted to establish an ORR benchmark. The study population was comprised of all patients who were randomized to the melphalan/HDS group in the initial 2-arm portion of the study or were enrolled in the subsequent single-arm portion.

Patients received melphalan (3.0 mg/kg ideal body weight; maximum dose: 220 mg for a single treatment) treatment once every 6–8 weeks for a maximum of 6 cycles. Prior to each treatment, liver venous outflow was isolated by a double-balloon catheter placed into the inferior vena cava. Melphalan was administered over 30 min via an infusion catheter placed in the hepatic artery; the infusion was followed by 30 min of washout with extracorporeal filtration to further reduce systemic exposure to melphalan. Treatment procedures were administered by a team of medical or surgical oncology, interventional radiology, anesthesiology, and a perfusionist. Details of the procedure have been previously described.

Endpoints and assessments

Efficacy endpoints included in the subgroup analyses were objective response rate (ORR), as determined by the Independent Review Committee (IRC) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009), progression-free survival (PFS), and overall survival (OS). In addition, the number of responders (complete response [CR] or partial response [PR]) was summarized by cycle. Response assessment was based on tumor response in hepatic and extrahepatic lesions.

Adverse events (AEs) were assessed by investigators and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.0 2009). Serious adverse events (SAEs) and Grade 3/4 events were summarized by subgroup and by cycle at onset.

Patient subgroups were defined based on age (<65 years, ≥65 years), sex (male, female), geographic region (US, Europe), extent of liver involvement as assessed by the investigator (1–25%, 26–50%), presence/absence of extrahepatic tumors per IRC, baseline LDH status (low or normal, elevated), number of prior therapies (0, ≥1), and hepatic tumor burden at baseline (below, above the median) defined as the sum of target hepatic lesion diameters per IRC. No subgroup analyses were performed for race or ethnicity since over 90% of patients enrolled were white and non-Hispanic or Latino.

Study oversight

The Sponsor and all authors contributed to various elements of study design, protocol development, and data analysis. The protocol was approved by the institutional review board or independent ethics committee at each study center, as well as by all relevant competent authorities. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines as outlined by the International Council for Harmonization. An IRC and an independent data safety monitoring board provided determination of efficacy and oversight of safety, respectively. The IRC was comprised of board-certified radiologists with extensive experience in oncology. Imaging was assessed by 2 independent readers; any disagreement about a patient's response to treatment was adjudicated by a third reader. All participants provided written informed consent. All authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Statistical analysis

All analyses were conducted in all patients treated with melphalan/HDS (pooled from the randomized and non-randomized portions of the study). Objective response rate was presented as frequency counts and percentages (percent responders) for each subgroup with corresponding 95% exact binomial confidence intervals. Time-to-event variables (PFS and OS) were presented as medians for each subgroup with corresponding 95% CI. In addition, time-to-event variables were summarized for selected subgroups using Kaplan–Meier methods. For the calculation of time-to-event endpoints, the start date was the patient eligibility date. Descriptive statistics were utilized for analysis of adverse events by subgroup and cycle in the treated population. Analyses were performed using Statistical Analysis System (SAS) v9.4.

Results

Patient disposition and baseline characteristics

A total of 102 patients were enrolled and/or assigned to the melphalan/HDS group (pooled from the randomized and non-randomized portions of the study). Of these, 95 patients had at least one PHP procedure initiated (safety population), and 91 patients received treatment with melphalan/HDS (treated population). At the time of analysis, all patients had discontinued or finished (all 6 PHPs) treatment; 37.4% of patients had completed the maximum of 6 cycles permitted per protocol. At the time of the data cut-off, median duration of follow-up was 36.4 months and 17.6% of the treated patients were still being followed for survival.

Approximately two-thirds (67.0%) of treated patients were less than 65 years of age; the population was balanced with respect to percentage of males and females (48.4% and 51.6%, respectively) and percentage of patients enrolled in Europe and the US (49.5% and 50.5%, respectively) (Table 1). Forty-four percent (44.0%) of treated patients had received at least one prior therapy for mUM, with 23% having received prior treatment with immune checkpoint inhibitors. The extent of liver involvement as assessed by the investigator was 1–25% in 79.1% of patients; median hepatic tumor burden as assessed by the IRC was 52.99 mm. Approximately one-third of patients (29.7%) had extrahepatic lesions; LDH levels were elevated in 37.2% of patients (Table 1).

Efficacy

Of the 33 patients with objective response of CR or PR, 19 (57.6%) responded within the first or second cycle of treatment (Table 2). One-third of responses (33.3%) were observed in Cycles 4–6.

Table 1 Subgroups of patients treated with melphalan/Hepatic Delivery System (Treated population)

Characteristic	Melphalan/HDS (N=91)
Age group—no. (%)	
<65 years	61 (67.0)
≥65 years	30 (33.0)
Gender—no. (%)	
Male	44 (48.4)
Female	47 (51.6)
Geographic region—no. (%)	
Ex-US	45 (49.5)
US	46 (50.5)
Extent of baseline liver involvement—no. (%)[a]	
1–25%	72 (79.1)
26–50%	19 (20.9)
Median hepatic tumor burden—mm[b]	52.99
Presence of extrahepatic lesions—no. (%)[c]	
No	64 (70.3)
Yes[d]	27 (29.7)
Baseline LDH—no./N (%)	
Low or normal	54/86 (62.8)
Elevated	32/86 (37.2)
Number of prior therapies—no. (%)[e]	
0	51 (56.0)
≥1	40 (44.0)

LDH Lactate dehydrogenase; *US* United States

[a]Assessed by the investigator

[b]Hepatic tumor burden is the sum of target hepatic lesion diameters per Independent Review Committee assessment

[c]Based on Independent Review Committee assessment

[d]Includes lung, lymph node, bone (spine, lumbar spine, pelvis, ribs, sacrum, and skull), soft tissue (subcutaneous, trunk, and chest wall), and other visceral (spleen and adrenal gland)

[e]Includes radiation, systemic therapy and/or surgery (excluding non-therapeutic prior surgeries/procedures, e.g., biopsy)

Table 2 Objective response by cycle in patients treated with melphalan/Hepatic Delivery System (Treated population—Assessed by Independent Review Committee)

Treatment cycle of first objective response	Patients with objective response (N=33) n (%)
Cycle 1	3 (9.1)
Cycle 2	16 (48.5)
Cycle 3	3 (9.1)
Cycle 4	8 (24.2)
Cycle 5	1 (3.0)
Cycle 6	2 (6.1)

Analyses of ORR by subgroup did not indicate marked differences in response to treatment based on age, sex, region, extent (%) of liver involvement, presence/absence of extrahepatic lesions, baseline LDH level, or number of prior therapies (Table 3; Fig. S1). Patients for whom baseline hepatic tumor burden was below the median had a markedly higher ORR compared to those with baseline hepatic tumor burden above the median (51.1 vs. 22.2%, $p=0.008$) (Table 3; Fig. S1**)**. Similar effects of baseline hepatic tumor burden were observed for PFS (medians: 11.3 vs. 5.8 months; $p=0.007$) and OS (medians: 26.7 vs. 15.4 months, $p=0.008$) (Table 3; Fig. S1**)**. Patients with 1–25% liver involvement at baseline had longer OS compared to those with 26–50% liver involvement (medians: 22.4 vs. 16.9 months, $p=0.030$), as did patients with low or normal LDH values compared to those with elevated values (medians: 23.5 vs. 15.3 months, $p=0.019$) (Table 3; Fig. S1**)**. Numerical differences in PFS were observed among patients enrolled in Europe compared to those in the US (medians: 14.1 vs. 9.0 months, $p=0.110$), patients with no extrahepatic tumors at baseline compared to those with extrahepatic involvement (medians: 9.3 vs. 6.2 months, $p=0.164$), and patients with low or normal LDH values at baseline compared to those with elevated values (medians: 10.8 vs. 6.2 months, $p=0.153$), but those differences were not statistically significant (Table 3; Fig. S1**)**.

Kaplan–Meier curves of PFS illustrate the similarities between patients with and without extrahepatic lesions, patients with 1–25% liver involvement at baseline and those with 26–50% liver involvement ($p=0.377$), and those who were treatment-naïve compared to those previously treated for metastatic disease ($p=0.860$) (Fig. 1a–c); and the differences between patients with baseline hepatic burden below the median versus above the median (Fig. 1d).

For OS, there is a marked separation of Kaplan–Meier curves for subgroups of patients based on extent (%) of liver involvement at baseline and for subgroups based on hepatic tumor burden at baseline, while OS curves were substantially overlapping for subgroups based on presence/absence of extrahepatic lesions (medians: 20.8 vs. 18.9 months, $p=0.593$) and prior treatment ($p=0.499$) (Fig. 2a–d).

Safety

The incidence of SAEs among patient subgroups was similar to that for the overall safety population (45.3%), with the exception of a higher incidence observed for patients with only hepatic lesions compared to those with hepatic and extrahepatic lesions (53.0 vs. 25.9%), which appeared to be driven by differing rates of serious thrombocytopenia (21.2 vs. 3.7%) and leukopenia (7.3 vs. 0%), and patients with low or normal LDH compared to those with elevated LDH (50.9 vs. 37.1%), which appeared to be driven by differing rates of serious thrombocytopenia (20.0 vs. 11.4%) (Table 4). Across patient subgroups, the percentage of patients with Grade 3 or 4 AEs was similar to that of the overall population (81.1%) (Table 4). Overall, 17.9% of patients in the

Table 3 Clinical outcomes in subgroups of patients treated with melphalan/Hepatic Delivery System (Treated population)

	Age group		Sex		Geographic region		Extent of liver involvement	
	<65 years	≥65 years	Male	Female	Ex-US	US	1 to 25%	26 to 50%
	(n=61)	(n=30)	(n=44)	(n=47)	(n=45)	(n=46)	(n=72)	(n=19)
Objective response rate[a]								
% (n)	39.3 (24)	30.0 (9)	34.1 (15)	38.3 (18)	40.0 (18)	32.6 (15)	37.5 (27)	31.6 (6)
95% CI[b]	27.07–52.69	14.73–49.40	20.49–49.92	24.51–53.62	25.70–55.67	19.53–48.02	26.36–49.70	12.58–56.55
P Value[c]	0.4882		0.8276		0.5173		0.7901	
Best overall response[d,e]								
Complete response	6 (9.8)	1 (3.3)	4 (9.1)	3 (6.4)	4 (8.9)	3 (6.5)	7 (9.7)	0
Partial response	18 (29.5)	8 (26.7)	11 (25.0)	15 (31.9)	14 (31.1)	12 (26.1)	20 (27.8)	6 (31.6)
Stable disease	20 (32.8)	14 (46.7)	15 (34.1)	19 (40.4)	14 (31.1)	20 (43.5)	27 (37.5)	7 (36.8)
Progressive disease	16 (26.2)	7 (23.3)	14 (31.8)	9 (19.1)	13 (28.9)	10 (21.7)	17 (23.6)	6 (31.6)
Not evaluable	1 (1.6)	0	0	1 (2.1)	0	1 (2.2)	1 (1.4)	0
Progression-free survival								
Events, n (%)	43 (70.5)	24 (80.0)	31 (70.5)	36 (76.6)	31 (68.9)	36 (78.3)	55 (76.4)	12 (63.2)
Censored, n (%)	18 (29.5)	6 (20.0)	13 (29.5)	11 (23.4)	14 (31.1)	10 (21.7)	17 (23.6)	7 (36.8)
Median (95% CI), months[f]	9.07 (6.11–13.80)	9.00 (5.68–14.32)	9.03 (4.44–16.43)	9.07 (6.24–12.81)	14.06 (5.68–16.85)	9.00 (5.82–9.30)	9.07 (8.67–11.83)	9.26 (3.29–16.82)
P Value (Log-rank)[f]	0.4941		0.8097		0.1096		0.3767	
Hazard ratio (95% CI)[g]	1.17 (0.69–1.98)		0.96 (0.59–1.55)		0.67 (0.41–1.09)		0.74 (0.40–1.40)	
P Value (Chi-square)[g]	0.5626		0.8541		0.1076		0.3587	
PFS at 6 months, % (95% CI)[f]	67 (53–77)	61 (41–76)	58 (41–71)	72 (56–83)	66 (50–78)	64 (49–77)	67 (54–76)	59 (31–78)
PFS at 12 months, % (95% CI)[f]	40 (27–53)	33 (16–51)	40 (24–55)	36 (22–51)	58 (41–71)	20 (9–34)	38 (26–49)	40 (15–65)
Overall survival								
Events, n (%)	43 (70.5)	24 (80.0)	34 (77.3)	33 (70.2)	30 (66.7)	37 (80.4)	52 (72.2)	15 (78.9)
Censored, n (%)	18 (29.5)	6 (20.0)	10 (22.7)	14 (29.8)	15 (33.3)	9 (19.6)	20 (27.8)	4 (21.1)
Median (95% CI), months[f]	20.83 (16.79–28.25)	20.53 (12.68–26.71)	18.30 (15.08–25.26)	22.41 (17.61–28.16)	24.34 (16.85–28.25)	18.41 (14.03–23.00)	22.41 (16.79–28.16)	16.85 (9.26–25.86)
P Value (Log-rank)[f]	0.5742		0.3511		0.1241		0.0296	
Hazard ratio (95% CI)[g]	1.08 (0.64–1.81)		1.32 (0.81–2.15)		0.68 (0.42–1.12)		0.53 (0.29–0.95)	
P Value (Chi-square)[g]	0.7738		0.2618		0.1269		0.0325	
OS at 12 months, % (95% CI)[f]	83 (71–91)	72 (52–85)	74 (58–85)	85 (71–93)	84 (69–92)	76 (61–86)	83 (72–90)	66 (39–83)
OS at 24 months, % (95% CI)[f]	45 (32–57)	38 (21–55)	38 (24–52)	47 (32–60)	52 (35–66)	35 (21–48)	46 (34–57)	30 (11–52)
	Hepatic Tumor Burden[h]		Presence of extrahepatic lesions		Baseline LDH		Number of prior therapies	
	Below the median	Above the median	Hepatic only	Hepatic and extra-hepatic	Low or normal	Elevated	0	≥1
	(n=45)	(n=45)	(n=64)	(n=27)	(n=54)	(n=32)	(n=51)	(n=40)
Objective response rate[a]								
% (n)	51.1 (23)	22.2 (10)	37.5 (24)	33.3 (9)	40.7 (22)	28.1 (9)	35.3 (18)	37.5 (15)
95% CI[b]	35.77–66.30	11.20–37.09	25.70–50.49	16.52–53.96	27.57–54.97	13.75–46.75	22.43–49.93	22.73–54.20
P Value[c]	0.0082		0.8131		0.2571		0.8302	
Best overall response[d,e]								
Complete response	7 (15.6)	0	6 (9.4)	1 (3.7)	5 (9.3)	1 (3.1)	3 (5.9)	4 (10.0)
Partial response	16 (35.6)	10 (22.2)	18 (28.1)	8 (29.6)	17 (31.5)	8 (25.0)	15 (29.4)	11 (27.5)
Stable disease	15 (33.3)	18 (40.0)	25 (39.1)	9 (33.3)	22 (40.7)	10 (31.3)	23 (45.1)	11 (27.5)
Progressive disease	7 (15.6)	16 (35.6)	14 (21.9)	9 (33.3)	10 (18.5)	12 (37.5)	10 (19.6)	13 (32.5)

Table 3 (continued)

	Hepatic Tumor Burden[h]		Presence of extrahepatic lesions		Baseline LDH		Number of prior therapies	
	Below the median	Above the median	Hepatic only	Hepatic and extra-hepatic	Low or normal	Elevated	0	≥1
	(n = 45)	(n = 45)	(n = 64)	(n = 27)	(n = 54)	(n = 32)	(n = 51)	(n = 40)
Not evaluable	0	1 (2.2)	1 (1.6)	0	0	1 (3.1)	0	1 (2.5)
Progression-free survival								
Events, n (%)	31 (68.9)	36 (80.0)	47 (73.4)	20 (74.1)	39 (72.2)	25 (78.1)	34 (66.7)	33 (82.5)
Censored, n (%)	14 (31.1)	9 (20.0)	17 (26.6)	7 (25.9)	15 (27.8)	7 (21.9)	17 (33.3)	7 (17.5)
Median (95% CI), months[f]	11.33 (9.00–15.90)	5.82 (3.68–9.17)	9.26 (8.97–14.06)	6.24 (3.42–11.33)	10.84 (8.97–13.90)	6.24 (3.42–11.56)	9.00 (6.11–12.81)	9.18 (4.44–14.06)
P Value (Log-rank)[f]	0.0074		0.1642		0.1527		0.8598	
Hazard ratio (95% CI)[g]	0.51 (0.31–0.85)		0.71 (0.42–1.21)		0.69 (0.41–1.15)		0.93 (0.57–1.52)	
P Value (Chi-square)[g]	0.0099		0.2085		0.1559		0.7773	
PFS at 6 months, % (95% CI)[f]	80 (65–89)	48 (33–63)	69 (56–79)	55 (35–72)	73 (59–83)	51 (33–67)	67 (51–78)	63 (46–75)
PFS at 12 months, % (95% CI)[f]	49 (33–64)	24 (12–38)	44 (31–56)	20 (6–40)	43 (29–56)	28 (13–46)	36 (22–51)	39 (24–54)
Overall survival								
Events, n (%)	28 (62.2)	38 (84.4)	47 (73.4)	20 (74.1)	38 (70.4)	27 (84.4)	38 (74.5)	29 (72.5)
Censored, n (%)	17 (37.8)	7 (15.6)	17 (26.6)	7 (25.9)	16 (29.6)	5 (15.6)	13 (25.5)	11 (27.5)
Median (95% CI), months[f]	26.71 (22.28–34.46)	15.44 (12.25–18.63)	20.83 (16.30–26.71)	18.89 (13.77–28.25)	23.46 (18.30–28.16)	15.31 (11.70–20.83)	20.53 (16.72–28.16)	20.83 (14.03–26.71)
P Value (Log-rank)[f]	0.0081		0.5931		0.0190		0.4988	
Hazard ratio (95% CI)[g]	0.39 (0.23–0.65)		0.88 (0.52–1.48)		0.60 (0.36–1.00)		0.88 (0.54–1.44)	
P Value (Chi-square)[g]	0.0004		0.6208		0.0499		0.6071	
OS at 12 months, % (95% CI)[f]	91 (78–97)	68 (51–79)	79 (67–87)	81 (60–92)	87 (74–93)	67 (47–81)	84 (71–92)	74 (57–85)
OS at 24 months, % (95% CI)[f]	60 (44–73)	23 (12–37)	45 (32–57)	37 (19–56)	50 (36–63)	27 (13–43)	42 (28–55)	44 (27–59)

CI Confidence interval; *CR* Complete response; *Ex-US* Outside of United States; *IRC* Independent Review Committee; *LDH* Lactate dehydrogenase; *OS* Overall survival; *PFS* Progression-free survival; *PR* partial response; *RECIST 1.1* Response Evaluation Criteria in Solid Tumors version 1.1; *SD* Stable disease; *US* United States

[a]Patients without at least 1 post-baseline response assessment were designated as non-responders

[b]Exact binomial CI

[c]Fisher's exact test

[d]Best overall response per IRC (RECIST 1.1) from the date of randomization/eligibility until disease progression

[e]For CR or PR, confirmation was required by repeat assessment≥4 weeks after initial documentation. To qualify as SD, the image must have been taken at least 9 weeks after start of therapy

[f]Kaplan–Meier estimate

[g]Hazard ratio is from a Cox regression model with geographical region (US vs. ex-US) and extent of liver involvement (1–25% vs. 26–50%) as covariates

[h]Hepatic tumor burden (median of 52.99 mm) is the sum of target hepatic lesion diameters per IRC assessment. Per IRC, 1 patient had no hepatic lesions that qualified as target lesions per RECIST 1.1

safety population had AEs leading to discontinuation of study treatment; numerical differences in rates of discontinuation due to AEs were observed for patients enrolled in Europe compared to those enrolled in the US (26.1 vs. 10.2%), patients with 26–50% liver involvement compared to those with 1–25% (30.0 vs. 14.7%), patients with hepatic-only compared to hepatic and extrahepatic lesions (21.2 vs. 11.1%), and patients with low or normal LDH compared to those with elevated LDH (21.8 vs. 8.6%) (Table 4). Overall, 13.7% of patients had AEs leading to dose reduction; a similar incidence was observed across subgroups with the exception of a higher incidence observed for males compared to females (23.4 vs. 4.2%) (Table 4).

Among patients receiving multiple cycles of melphalan/HDS treatment (treated population), there was no apparent

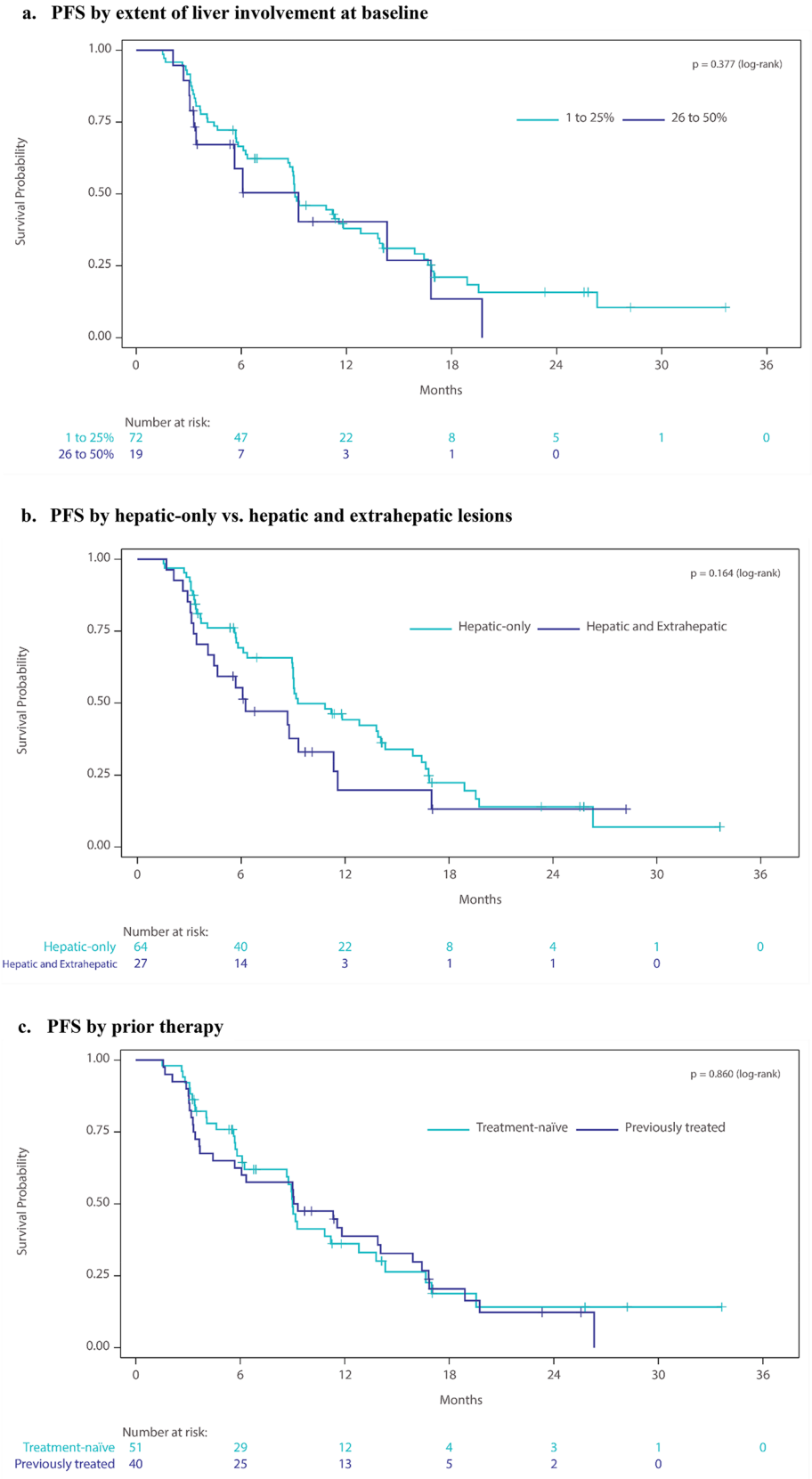
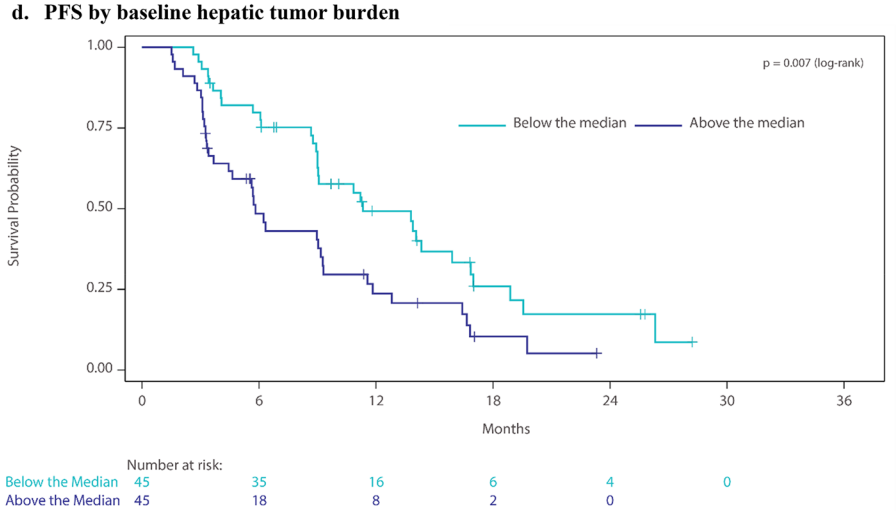


Fig. 1 Kaplan–Meier plots of progression-free survival in subgroups of patients treated with melphalan/Hepatic Delivery System—subgroups based on extent of liver involvement at baseline as assessed by the investigator **a**, hepatic-only vs. hepatic and extrahepatic lesions as assessed by Independent Review Committee **b**, prior therapies **c** and baseline hepatic tumor burden as assessed by Independent Review Committee **d** (Treated population—progression-free survival assessed by Independent Review Committee)

Fig. 1 (continued)



trend toward an increase in SAEs or Grade 3/4 AEs with successive cycles (Table 5).

Discussion

The FOCUS study patient population was heterogenous and included patients with hepatic-only disease and those with hepatic and limited extrahepatic disease; patients with up to 50% of liver tumor involvement (79.1% of patients had 1–25% liver tumor burden), and both previously treated (44%) and treatment-naïve (56%) patients. The diverse study population, along with operational conduct at 23 study centers enabled a robust evaluation of the efficacy and safety of melphalan/HDS in patients with unresectable mUM.

Since PHP with melphalan/HDS is a liver directed therapy, it is important to assess efficacy results in patients with liver metastases only and in patients with both hepatic and extrahepatic disease. ORRs were very similar in patients with both hepatic-only and hepatic and extrahepatic disease, 37.5% and 33.3%, respectively. One possible explanation is "leakage" of melphalan due to anatomical variations in hepatic veins and due to filtration efficiency of up to 86% (Leede et al. 2017), which results in a systemic melphalan dose of typically 20–40 mg and therefore the potential of direct antitumor effects in extrahepatic lesions. Consistent OS results in both groups of patients on the FOCUS study contrasts with mOS results reported with nivolumab plus ipilimumab treatment, which suggest shorter survival in patients with hepatic-only mUM at a median of 9.2 vs. 15.5 months for patients with hepatic and extrahepatic disease (Piulats et al. 2021). In the FOCUS study median PFS was numerically longer in patients with hepatic disease only than in patients with hepatic and extrahepatic disease (9.3 vs. 6.2 months).

These results compare favorably to the overall ORR of 11.5% and mPFS of 1.5 and 3.7 months (hepatic-only versus hepatic and extrahepatic disease, respectively) reported in treatment-naïve mUM patients receiving nivolumab plus ipilimumab (Piulats et al. 2021). In the FOCUS study, median OS was similar in patients with hepatic-only and patients with hepatic and extrahepatic disease: 20.8 and 18.9 months, respectively, and compares favorably to mOS of 12.7 months reported in treatment-naïve mUM patients receiving nivolumab plus ipilimumab (Piulats et al. 2021).

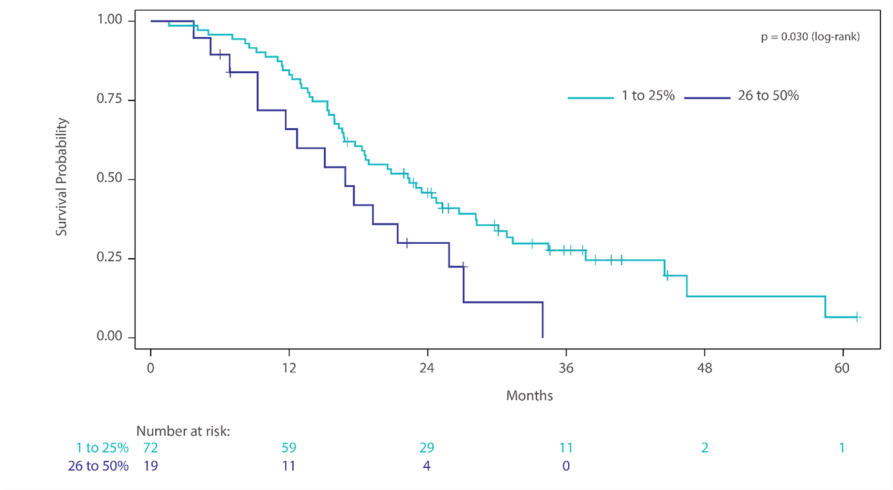
Another important consideration for treatment choices is efficacy in treatment-naïve and previously treated patients. ORR and PFS in the FOCUS study were very similar in treatment-naïve and previously treated patients; ORR of 35.3% and 37.5%, and mPFS of 9.0 and 9.2 months, respectively.

Median OS was also virtually identical in the two groups: 20.5 months and 20.8 months respectively. These results support the use of melphalan/HDS irrespective of line of treatment and allow clinicians more flexibility when designing treatment plans. Most contemporary clinical trials in patients with mUM, including Nathan et al (2021) and Piulats et al (2021) were conducted in treatment-naïve patients; Carvajal et al (2022) reported ORR, mPFS and mOS for 2nd line mUM patients treated with tebentafusp of 5%, 2.8 months and 16.8 months, respectively.

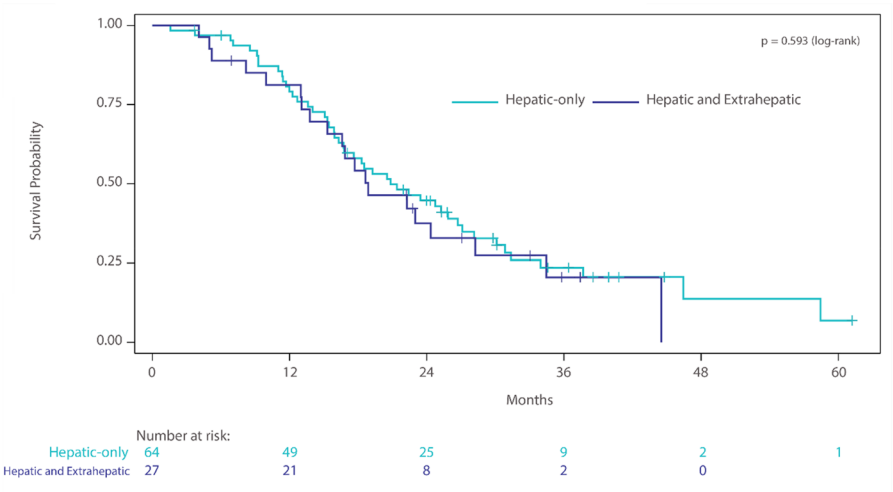
Efficacy results in previously treated mUM patients in the FOCUS study compare favorably to efficacy reported for tebentafusp in previously treated mUM patients.

Size of liver metastases is a prognostic factor in mUM (Khoja et al. 2019) and larger lesion sizes are associated with shorter PFS and OS. Consistent with historical results,

a. OS by extent of liver involvement at baseline



b. OS by hepatic-only vs. hepatic and extrahepatic lesions



c. OS by prior therapy

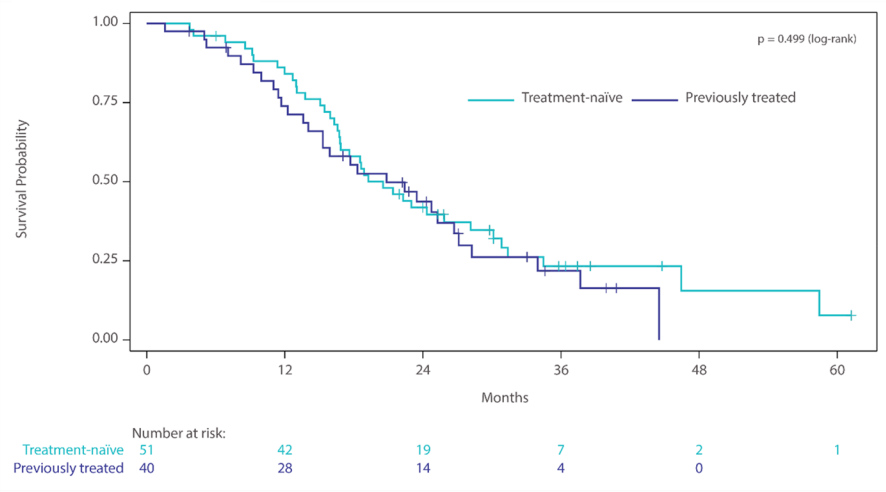


Fig. 2 Kaplan–Meier plots of overall survival in subgroups of patients treated with melphalan/Hepatic Delivery System—subgroups based on extent of liver involvement at baseline as assessed by the investigator **a**, hepatic-only vs. hepatic and extrahepatic lesions as assessed by Independent Review Committee **b**, prior therapies **c** and baseline hepatic tumor burden as assessed by Independent Review Committee **d** (Treated population)

d. OS by baseline hepatic tumor burden

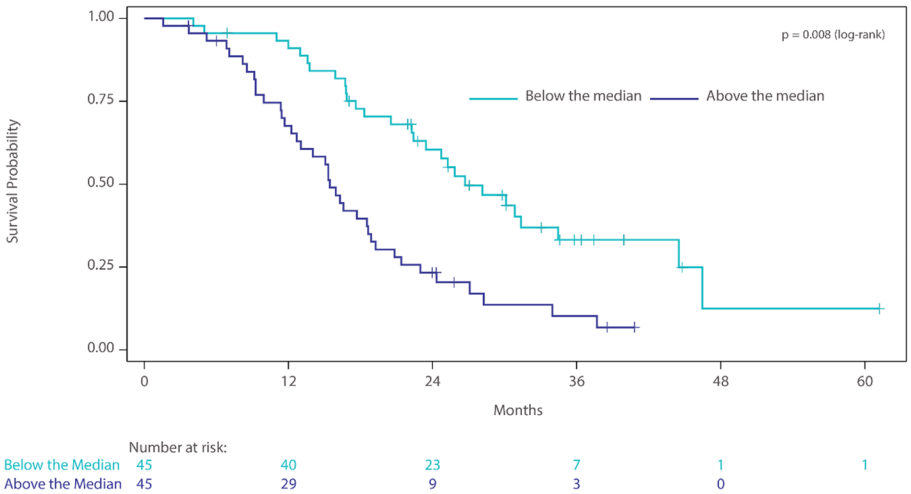


Fig. 2 (continued)

Table 4 Summary of treatment-emergent adverse events in subgroups of patients treated with melphalan/Hepatic Delivery System (Safety population)

Subgroup	N	SAE n (%)	Grade 3/4 AE n (%)	AE Leading to Discontinuation n (%)	AE Leading to Dose Reduction n (%)
Overall	95	43 (45.3)	77 (81.1)	17 (17.9)	13 (13.7)
Age group					
<65 years	65	30 (46.2)	53 (81.5)	11 (16.9)	9 (13.8)
≥65 years	30	13 (43.3)	24 (80.0)	6 (20.0)	4 (13.3)
Gender					
Male	47	22 (46.8)	35 (74.5)	8 (17.0)	11 (23.4)*
Female	48	21 (43.8)	42 (87.5)	9 (18.8)	2 (4.2)*
Geographic region					
Ex-US	46	20 (43.5)	35 (76.1)	12 (26.1)	5 (10.9)
US	49	23 (46.9)	42 (85.7)	5 (10.2)	8 (16.3)
Extent of liver involvement[a]					
1–25%	75	33 (44.0)	60 (80.0)	11 (14.7)	10 (13.3)
26–50%	20	10 (50.0)	17 (85.0)	6 (30.0)	3 (15.0)
Baseline hepatic tumor burden[b]					
Below the median	46	22 (47.8)	39 (84.8)	9 (19.6)	8 (17.4)
Above the median	46	20 (43.5)	36 (78.3)	8 (17.4)	5 (10.9)
Presence of extrahepatic lesions[c]					
No	66	35 (53.0)*	55 (83.3)	14 (21.2)	9 (13.6)
Yes[d]	27	7 (25.9)*	21 (77.8)	3 (11.1)	4 (14.8)
Baseline LDH					
Low or normal	55	28 (50.9)	48 (87.3)	12 (21.8)	8 (14.5)
Elevated	35	13 (37.1)	25 (71.4)	3 (8.6)	5 (14.3)
Number of prior therapies[e]					
0	54	23 (42.6)	41 (75.9)	11 (20.4)	7 (13.0)
≥1	41	20 (48.8)	36 (87.8)	6 (14.6)	6 (14.6)

AE Adverse event; *LDH* Lactate dehydrogenase; *SAE* Serious adverse event; *US* United States

*Difference in rate of AEs between subgroups is significant at $p<0.05$

[a]Assessed by the investigator

[b]Hepatic tumor burden (median of 52.99 mm) is the sum of target hepatic lesion diameters per Independent Review Committee assessment

[c]Based on Independent Review Committee assessment

[d]Includes lung, lymph node, bone (spine, lumbar spine, pelvis, ribs, sacrum, and skull), soft tissue (subcutaneous, trunk, and chest wall), and other visceral (spleen and adrenal gland)

[e]Includes radiation, systemic therapy and/or surgery (excluding non-therapeutic prior surgeries/procedures, e.g., biopsy)

Table 5 Serious and grade 3/4 treatment-emergent adverse events by cycle in patients treated with melphalan/Hepatic Delivery System (Treated population)

Treatment Cycle	Serious TEAE n (%)	Grade 3/4 TEAE n (%)
Cycle 1 (n = 91)	20 (22.0)	49 (53.8)
Cycle 2 (n = 84)	13 (15.5)	48 (57.1)
Cycle 3 (n = 66)	9 (13.6)	35 (53.0)
Cycle 4 (n = 55)	3 (5.5)	25 (45.5)
Cycle 5 (n = 40)	3 (7.5)	20 (50.0)
Cycle 6 (n = 34)	6 (17.6)	16 (47.1)

TEAE Treatment emergent adverse event

efficacy endpoints in the FOCUS study, including ORR, PFS and OS, were numerically lower in patients with higher hepatic tumor burden at baseline (sum of hepatic target lesion diameters above the median) than in patients with lower hepatic tumor burden at baseline (sum of hepatic target lesion diameters below the median). This finding of less favorable outcomes in patients with higher hepatic tumor burden is consistent with results from contemporary studies of immune checkpoint inhibitors (less favorable PFS and OS) (Piulats et al. 2021) and tebentafusp (less favorable OS) (Hassel et al. 2023), which examined differences between patients with largest liver lesion measuring more or less than 3 cm.

Evaluation of tumor response, SAE and NCI CTC Grade 3/4 AEs by treatment cycle was conducted to better understand the benefit/risk evaluation for melphalan/HDS treatment. Approximately 58% of all tumor responses occurred within the first two PHP treatment cycles; while encouraging, this result also means that 42% of responses occur at later treatment cycles. In that context, it is important to understand whether continued treatment with melphalan/HDS would result in cumulative or chronic toxicity. By treatment cycle analysis of SAEs and NCI CTC Grade 3/4 AEs shows no evidence of cumulative or chronic toxicity, thus enabling the treating physician to make informed decisions on the length of treatment.

The safety profile of melphalan/HDS in the current study is mainly characterized by hematological toxicity due to systemic exposure to residual melphalan. Melphalan/HDS patients receive high doses (up to 220 mg per treatment) of melphalan loco-regionally, and the perfusion system filters remove up to 86% of the administered melphalan dose (Leede et al. 2017). As expected with the resultant level of systemic melphalan exposure, a majority of patients experienced severe myelosuppression; the observed safety profile is consistent with previous experience at these exposure levels (Tong et al. 2022; Meijer et al. 2019).

Evaluation of key safety and tolerability parameters, including SAE, NCI CTC Grade 3 or 4 AEs, and AEs leading to discontinuation or dose reduction did not show consistent signals or trends in the subgroups analyzed, suggesting an acceptable benefit/risk profile across several clinically relevant subgroups.

Conclusions

The FOCUS study provides robust evidence of the clinical benefit of melphalan/HDS in a heterogeneous population of patients with unresectable mUM. This therapy offers a potential treatment option for patients with this rare indication, which is associated with a poor prognosis and limited treatment options. Overall, the results demonstrate a favorable benefit-risk profile for melphalan/HDS across multiple clinically relevant subgroups, including patients that are previously treated/treatment-naïve, patients with and without extrahepatic metastases and patients with smaller/larger liver tumor burden.

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Author contribution All authors contributed to the data collection, interpretation of the results, and approved the final version of the manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interests Jonathan Zager–global principal investigator in the FOCUS phase 3 study and serves on Delcath Systems Medical Advisory Board. Education and Training grant through Delcath. Marlana Orloff–Advisory Board: Delcath, Replimune. Consultant: Immunocore. Steering Committee: Ideaya. Speaker: Immunocore. David Eschelman–Received < $5 K consulting fees from Delcath. Evan Glazer–My institution was a site for the clinical trial. I received no direct payment. Delcath paid for the clinical trial to my institution. Erika Richtig–Medical University of Graz received payments for conducting the Phase 3 study. Sebastian Ochsenreither–Advice: Immunocore, Delcath, Janssen. Speakers' bureau: Immunocore. Georgia Beasley–Clinical trial funding paid to institution from Replimune, checkmate pharmaceuticals, Philogen, Delcath. Advisory board BMS 10.2023.

Anja Gesierich–University Hospital Würzburg received payments for conducting the Phase 3 study. Reinhard Dummer–intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, Alligator, T3 Pharma, MaxiVAX SA, Pfizer, Sim-cere and touchIME outside the submitted work. Ana Arance–Consulting or advisory role: Pierre- Fabre, Novartis, Roche, BMS, MSD, Biontech. Speakers' Bureau: Pierre- Fabre, Novartis, Roche, BMS, MSD. Travel, Accommodations, Expenses: BMS, MSD. Stephen Fenwick–Liverpool University Hospitals NHS Trust received support for conducting this Phase 3 study from the trial sponsor. Joseph Sacco–I have been a paid member of advisory boards for Delcath, Replimune and Immunocore. I have received grant funding from Astra Zeneca and BMS (paid to institution). I have had travel and conference attendance paid for by MSD, BMS and Replimune. Johnny John is an employee of Delcath Systems Inc. Matthew Wheater–Institutional (University Hospital Southampton) funding for conducting a commercial trial. Personal funding for participation in advisory board for Delcath. Pier Francesco Ferrucci, Junsung Choi, Aslam Ejaz, Sunil A. Reddy, Michael C. Lowe, Martin Gschnell, and Christian H. Ottensmeier have nothing to disclose.

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