PERCUTANEOUS HEPATIC PERFUSION WITH MELPHALAN IN PATIENTS WITH UNRESECTABLE OCULAR MELANOMA METASTASES CONFINED TO THE LIVER: A PROSPECTIVE PHASE II STUDY

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ABSTRACT

Background. Ocular melanoma is the most common primary intraocular malignancy and has a very poor prognosis once liver metastases occur. The aim of this study was to prospectively assess the efficacy and safety of percutaneous hepatic perfusion with melphalan (M-PHP) using the new second-generation (GEN 2) hemofiltration system in patients with ocular melanoma metastases confined to the liver.

Methods. Prospective, single-center, single-arm, phase II study including patients with unresectable ocular melanoma metastases confined to the liver. Treatment consisted of two M-PHP procedures at 6–8 weeks interval. Procedures were performed using the CHEMOSAT (GEN 2) system with 3 mg/kg melphalan. Primary endpoints were overall response rate (ORR) and best overall response (BOR). Secondary endpoints included overall survival (OS), progression-free survival (PFS), hepatic PFS (hPFS), and safety.

Results. Sixty-four M-PHP procedures were performed in 35 patients between February 2014 and June 2017. The ORR was 72%. BOR was as follows: complete response in 3%, partial response in 69%, stable disease in 13%, and progressive disease in 16%. There was no treatment-related mortality. Fourteen serious adverse events occurred. At a median follow-up of 19.1 months (range 5.6–69.5), median OS was 19.1 months and was significantly longer in responders than in nonresponders (27.5 vs. 11.9 months, p < 0.001). The 1- and 2-year OS was 77% and 43%, respectively. PFS and hPFS were 7.6 and 11.2 months, respectively.

Conclusions. M-PHP using the GEN 2 filter can achieve a high ORR and prolonged survival in patients with liver-only ocular melanoma metastases.

Ocular melanoma is the most common primary intraocular malignancy in adults. It most frequently arises from melanocytes in the uveal tract, which is subdivided in an anterior part containing the iris (~ 5%) and a posterior part containing the choroid and ciliary corpus (~ 80%). The rest of ocular melanomas develop in the conjunctiva (~ 5%) or elsewhere in the orbit (~ 10%). The incidence of uveal melanoma in Europe varies with latitude, being

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higher in Northern (≥ 8 per million) than Southern Europe (< 2 per million), due to a positive association with Caucasian ethnicity, fair skin, and light eye colour. Most patients are diagnosed after age 50 years, with a peak range of 65–75 years. Despite successful treatment of the primary tumor, up to 50% of patients will eventually develop metastatic disease with predominant liver involvement.

Metastatic ocular melanoma carries a poor prognosis, because there are no effective systemic treatments. Reported median overall survival (OS) following systemic treatment, including immunotherapy and kinase inhibitors, ranges from 4.4 to 12.7 months with a 1-year OS rate ranging from 29 to 53%. Meta-analyses have demonstrated that patients treated with liver-directed therapies had a significantly longer progression-free survival (PFS) and OS compared with patients receiving systemic therapy. Liver-directed therapies used to treat ocular melanoma liver metastases include chemoembolization, immunoembolization, radioembolization, isolated hepatic perfusion (IHP), and percutaneous hepatic perfusion with melphalan (M-PHP) (Table 1).

**TABLE 1** Summary of progression-free survival and overall survival following chemoembolization, immunoembolization, radioembolization, isolated hepatic perfusion, and percutaneous hepatic perfusion

| First author (year) | Study design | No. of pts | Transarterial catheter-directed therapy and drug | Median PFS (mo) | Median OS (mo) |
|---------------------|--------------|------------|-----------------------------------------------|----------------|----------------|
| Agarwala (2004)8    | Phase I/II, dose-esc. | 19 | Chemoembolization (cisplatin) | N/A | 8.5 |
| Patel (2005)9       | Phase II     | 30 | Chemoembolization (BCNU) | N/A | 5.2 |
| Vogl (2007)10       | PS, pilot    | 12 | Chemoembolization (mitomycin C) | N/A | 21 |
| Schuster (2010)11   | RS           | 25 | Chemoembolization (fotemustine/cisplatin) | 3 | 6 |
| Gupta (2010)12      | RS           | 125 | Chemoembolization (mostly cisplatin)4 | 3.8 | 6.7 |
| Huppert (2010)13    | PS, pilot    | 14 | Chemoembolization (cisplatin/carboplatin) | 8.5 | 11.5 |
| Edelhauser (2012)14 | RS           | 21 | Chemoembolization (fotemustine) | 7.3 | 28.7 |
| Valpione (2015)15   | RS           | 58 | Chemoembolization (irinotecan) | N/A | 16.5 |
| Shibayama (2017)16  | RS           | 29 | Chemoembolization (cisplatin) | 6 | 23 |
| Yamamoto (2009)17   | RS           | 53 | Immuoembolization vs. chemoembolization (BCNU) | 12.4 vs. 4.8 | 20.4 vs. 9.8 |
| Valsecchi (2015)18  | Phase II     | 52 | Immuoembolization vs. bland embolization | 3.9 vs. 5.9 | 21.5 vs. 17.2 |
| Gonsalves (2011)19  | RS           | 32 | Radioembolization (Y-90) | 4.7 | 10 |
| Klingenstein (2013)20 | RS         | 13 | Radioembolization (Y-90) | N/A | 7 |
| Eldredge-Hindy (2016)21 | RS        | 71 | Radioembolization (Y-90) | 5.9 | 12.3 |
| Tulokas (2018)22    | RS           | 16 | Radioembolization (Y-90) | 5.6 | 13.5 |
| Gonsalves (2019)23  | PS           | 24 | Radioembolization (Y-90) | 8.1 | 18.5 |
| Alexander (2000)24  | Phase I/II   | 22 | Isolated hepatic perfusion (melphalan) ± TNF | 9c | 11d |
| Alexander (2003)25  | Phase II     | 29 | Isolated hepatic perfusion (melphalan) | 8 | 12.1 |
| Noter (2004)26      | Phase II     | 8 | Isolated hepatic perfusion (melphalan) | 6.7 | 9.9 |
| van Eten (2009)27   | Phase I/II   | 8 | Isolated hypoxic hepatic perfusion (melphalan) | 6 | 11 |
| Vogl (2017)28       | RS           | 18 | Percutaneous hepatic perfusion (melphalan) | 12.4 | 9.6 |
| Karydis (2018)29    | RS           | 51 | Percutaneous hepatic perfusion (melphalan) | 8.1 | 15.3 |
| Artzner (2019)30    | RS           | 16 | Percutaneous hepatic perfusion (melphalan) | 11.1 | 27.4 |

**BCNU** 1,3-bis (2-chloroethyl)-1-nitrosourea, mo months, N/A not available, OS overall survival, PFS progression-free survival, PS prospective, pts patients, RS retrospective, TNF tumor necrosis factor, Y-90 yttrium-90

4Cisplatin (n = 122), cisplatin + paclitaxel (n = 2), cisplatin + doxorubicin + MMC (n = 1)

6Isolated hepatic perfusion (n = 11), isolated hepatic perfusion with TNF (n = 11)

614 months for patients without TNF vs 6 months for patients with TNF (p = 0.04)

6No difference between both groups (p = 0.17)
PFS was demonstrated in patients treated with M-PHP compared with best alternative care, but the median OS after M-PHP was only 10.6 months. Approximately 40% of patients in this study had extrahepatic metastases, and M-PHP may have had a limited effect on their OS. Additionally, 11% of patients in the study had metastases from cutaneous melanoma.

Concerns regarding the safety of M-PHP have been raised as high rates of hematologic toxicity were reported in prior studies. To address the issue of hematologic toxicity, a new hemofiltration system with a second-generation detoxification cartridge (GEN 2 filter) was developed. This filter has a higher melphalan extraction rate than the first-generation filters and was shown to reduce hematologic toxicity. So far, only retrospective studies have reported on M-PHP using the GEN 2 filter in ocular melanoma patients.

The purpose of this study was to prospectively investigate the efficacy and safety of M-PHP using the GEN 2 filter in well-selected patients with unresectable metastases from ocular melanoma confined to the liver.

METHODS

This prospective, single-arm, single-center, phase II study was conducted in accordance with the Declaration of Helsinki, approved by the local ethics committee and registered on www.trialregister.nl (NTR4112). All participants provided written informed consent.

Patients

Eligible patients were those with histologically proven, unresectable ocular melanoma metastases confined to the liver. All patients were discussed at a multidisciplinary meeting before inclusion. Exclusion criteria are listed in Table 2.

Study Protocol

Pretreatment angiography was routinely performed approximately 1 week before the first M-PHP to evaluate hepatic arterial vasculature. If deemed necessary, hepaticoenteric shunts (e.g., right gastric and gastroduodenal artery) were embolized to prevent inadvertent leakage of melphalan.

Treatment consisted of two M-PHP procedures with hepatic artery infusion of melphalan 3 mg/kg (maximum dose 220 mg) at 6–8 weeks interval. Patients demonstrating progressive disease (PD) or unacceptable adverse events after the first M-PHP received only one procedure. If grade 3/4 hematologic toxicity occurred after the first procedure, melphalan dose was reduced by 20–25%. Patients routinely received a subcutaneous injection of granulocyte-colony stimulating factor (pegfilgrastim 6 mg) within 72 h after each M-PHP.

Contrast-enhanced CT of chest and abdomen was performed at baseline, 4–8 weeks after each M-PHP, every 3 months in the first year and every 6 months thereafter until PD occurred. MRI of the liver was performed if lesions were not or poorly visible on CT.

| TABLE 2 Exclusion criteria | Laboratory test results | Other |
|---------------------------|-------------------------|-------|
| APTT > 1.5 × ULN          | Age < 18 or > 75 yr     |
| PT > 1.5 × ULN            | Extrahepatic disease (on CECT or FDG-PET/CT) |
| Leukocytes < 3.0 × 10⁹/L  | WHO performance status ≥ 2 |
| Thrombocytes < 100 × 10⁹/L| Severe comorbidity precluding general anesthesia |
| Creatinine clearance < 40 ml/min | Diabetes with nephropathy |
| AST > 2.5 × ULN           | Active infections       |
| ALT > 2.5 × ULN           | < 40% healthy liver tissue |
| Serum bilirubin > 1.5 × ULN| Other liver disease     |
| ALP > 2.5 × ULN           | Vascular anatomy impeding M-PHP |
| LDH > 2 × ULN             | Intracranial lesions with propensity to bleed (on CT/MRI) |
|                           | Pregnancy               |

ALP alkaline phosphatase, ALT alanine aminotransferase, APTT activated partial thromboplastin time, AST aspartate aminotransferase, CECT contrast-enhanced CT of chest and abdomen, FDG-PET/CT positron emission tomography with integrated noncontrast enhanced CT and 18F-2-fluoro-2-deoxy-D-glucose as radiotracer, LDH lactate dehydrogenase, M-PHP percutaneous hepatic perfusion with melphalan, PT prothrombin time, ULN upper limit of normal

*included in the protocol during the course of the study
Quality of life (QoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30 v3.0). Questionnaires were filled out at baseline, 6 weeks after the first and second M-PHP, and 6 months after the first M-PHP.

All adverse events were monitored continuously throughout the entire study and reported according to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).

Procedure

All M-PHP procedures were performed using the CHEMOSAT (GEN 2) system (Delcath Systems Inc, New York). General anesthesia was performed with continuous monitoring of the central venous and arterial pressure. Access to the right internal jugular vein (IJV, 10-F sheath), right common femoral vein (CFV, 18-F sheath), and left common femoral artery (5-F sheath) was created. Heparin was administered at an initial dose of 300 U/kg and an activated clotting time of $\geq 450$ s was maintained throughout the procedure. A 2.4-F or 2.7-F microcatheter was placed into the hepatic artery at the intended location of infusion. A 16-F double-balloon catheter (Isofuse Isolation Aspiration Catheter, Delcath Systems Inc, New York, NY) was placed in the inferior vena cava (IVC) via the right CFV. The cranial and caudal balloons were inflated at the atriocaval junction and infrahepatic IVC, respectively, to prohibit leakage of melphalan into the systemic circulation. The entire dose of melphalan was infused into the proper hepatic artery or split and infused in the right and left hepatic artery. Melphalan-rich blood was aspirated through catheter fenestrations in a segment between the two balloons, pumped through an extracorporeal hemofiltration system and returned to the patient via the sheath in the right IJV. Once all melphalan was administered, filtration was continued for 30 min to allow complete clearance of melphalan from the liver. The anticoagulant effects of heparin were reversed by protamine sulphate 3 mg/kg, the arterial sheath was removed and hemostasis was achieved using a closure device.

Endpoints

All imaging was reviewed by independent radiologists using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Primary endpoints were overall response rate (ORR) and best overall response (BOR) according to RECIST 1.1. Secondary endpoints were best hepatic response according to RECIST 1.1, OS, PFS, hepatic progression-free survival (hPFS), safety, and QoL.

OS was defined as time of first M-PHP until death or censoring. PFS and hPFS were defined as time of first M-PHP until PD, death, or censoring.

Statistical Analysis

Kaplan–Meier estimations were used to assess OS, PFS, and hPFS. OS data were censored at the date of last follow-up if patients were still alive. The log-rank test was used to compare curves.

Cox regression analyses were performed to determine possible independent predictors for OS. The Wilcoxon signed-rank test was used to compare scores from questionnaires filled in at baseline and after treatment. $P < 0.05$ was considered statistically significant. Analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics

A total of 35 patients (16 men; median age 59 years, range 41–71) were prospectively enrolled between February 2014 and June 2017. Baseline demographic and clinical characteristics of all patients are listed in Table 3. A total of 64 M-PHP procedures were performed. Twenty-nine of 35 (83%) patients underwent two M-PHP procedures as per protocol. Six of 35 (17%) patients received only one M-PHP due to PD ($n = 1$) or an adverse event ($n = 5$) after the first M-PHP procedure. An example treatment of a study participant is shown in Fig. 1.

Response Analysis

Thirty-two of 35 patients were included in the response analysis (Fig. 2a). In two patients, a therapeutic melphalan dose could not be administered due to peri-procedural complications and therefore no treatment effect could be evaluated. In one patient, target lesions were absent (all lesions with maximal diameter $\leq 1$ cm). The ORR was 72% with complete response (CR) in 3% ($n = 1$) and partial response (PR) in 69% ($n = 22$). A confirmed hepatic response occurred in 26 (81%) patients (3% CR and 78% PR). Five patients had PD as BOR due to extrahepatic metastases; the sum of target lesions in the liver remained stable ($n = 3$) or decreased with $\geq 30$% ($n = 2$). The magnitude of BOR and best hepatic response is shown in Fig. 2b, c.
Survival Analysis

There was no loss to follow-up. After a median follow-up of 19.1 months, 6 of 35 (17%) patients were still alive. The 1- and 2-year OS was 77% and 43%, respectively. Median OS was 19.1 months for all included patients ($n = 35$; Fig. 3a). Median OS was significantly longer in patients with CR/PR as BOR than in patients with SD/PD as BOR ($p < 0.001$; Fig. 3b). Median OS for patients with CR/PR, SD, and PD as BOR was 27.5 months (95% confidence interval [CI]: 23.7–31.3), 14.2 months (95% CI: 11.4–17.0), and 9.1 months (95% CI: 5.5–12.8), respectively. Median OS also was significantly longer ($p = 0.001$) in patients with CR/PR as best hepatic response than in patients with SD as best hepatic response: 26.3 months

**TABLE 3** Baseline characteristics for all 35 patients with liver metastases from ocular melanoma

| Parameter | N   | Percentage |
|-----------|-----|------------|
| Gender    |     |            |
| Men       | 16  | 46         |
| Women     | 19  | 54         |
| Age, yr [median (range)] | 59 (41–71) | ... |
| BMI, kg/m² [median (range)] | 25 (20–32) | ... |
| Tumor location |     |            |
| Choroid   | 19  | 54         |
| Choroid with ciliary corpus involvement | 12 | 34 |
| Ciliary corpus | 4 | 11 |
| Type of metastases |     |            |
| Synchronous | 4 | 11 |
| Metachronous | 31 | 89 |
| Mutations in liver metastases |     |            |
| GNAQ      | 21  | 60         |
| GNA11     | 12  | 34         |
| No GNAQ/GNA11 | 2 | 6 |
| Time between diagnosis primary tumor and liver metastases, months [median (range)] | 28 (0–71) | ... |
| Prior therapy for liver metastases |     |            |
| Systemic therapy¹ | 8 | 23 |
| Regional therapy² | 4 | 11 |
| Regional and systemic therapy | 2 | 6 |
| None      | 21  | 60         |
| Radiological aspect metastases |     |            |
| Hypovascular | 3 | 9 |
| Hypervascular | 26 | 74 |
| Mixed     | 6   | 17         |
| Total number of metastases ≥ 10 | 20 | 57 |
| Diameter of largest metastasis ≥ 3 cm | 14 | 40 |
| LDH level, IU/L [median (range)] | 196 (78–657) | ... |
| Elevated LDH level³ | 8 | 23 |
| Elevated AFP level⁴ | 7 | 20 |

*AFP* alkaline phosphatase, *BMI* body mass index, *GNAQ* guanine nucleotide-binding protein G(q) subunit alpha, *GNA11* guanine nucleotide-binding protein G(Y) subunit alpha-11, *LDH* lactate dehydrogenase, *SD* standard deviation, *ULN* upper limit of normal

¹Treatment in randomized phase II SUMIT-trial (selumetinib with dacarbazine vs. placebo) or phase I AEB071-study (protein kinase C inhibitor), ipilimumab, or dendritic cell therapy

²Radiofrequency ablation and/or metastasectomy

³Normal limits 0–247 for men and women

⁴Normal limits 0–115 U/L for men and 0–98 U/L for women
Univariate analysis revealed that the presence of a liver metastasis with diameter \( \geq 3 \) cm (95% CI: 15.8–36.8) versus 11.9 months (95% CI: 7.3–16.5) (Fig. 3c).

Median PFS was 7.6 months (95% CI: 4.9–10.3) with a 1-year PFS of 26.5%. PFS for patients with a hepatic response was significantly (95% CI: 11.1–48.7) versus 14.2 months (95% CI: 10.1–18.3).

Twenty of 34 (59%) patients who eventually showed PD during the course of this study received one or more subsequent treatments (Table 4). Twenty-six of 35 (74%) patients developed extrahepatic metastases during follow-up.
No deaths occurred. A total of 14 severe adverse events were recorded, including 5 cases of prolonged hospital stay (4–5 days instead of 3 days) and 8 readmissions with a median hospital stay of 6 days (range 1–15). The majority of patients developed grade 3/4 hematologic events with leukopenia (75.6%) and lymphocytopenia (84.8%) being most common. Fourteen grade 3 nonhematologic events occurred, including one case of peri-procedural transient cardiac ischemia, which was managed conservatively and resolved without sequelae. The only patient with a grade 4 nonhematologic event developed a sepsis with bacterial pharyngitis and retropharyngeal abscess formation. This was successfully treated with the intravenous administration of antibiotics and immunoglobulins, followed by percutaneous abscess aspiration. A more detailed description of safety and toxicity has been reported previously as medical authorities and patient organisations requested for the safety profile of M-PHP using the GEN 2 filter to become publicly available at the earliest possible stage. At that time, the follow-up period was too short to publish data on efficacy.

Quality of Life

At baseline, 18 of 35 (51%) patients completed the EORTC QLQ-C30 v3.0 form. Return rates of the questionnaire at 6 weeks after the first M-PHP procedure, 6 weeks after the second M-PHP procedure, and 6 months after the first M-PHP procedure were 74% (26/35), 59% (17/29), and 49% (17/35), respectively. Questionnaire scores after treatment did not significantly differ from scores prior to treatment, except for physical functioning which was significantly impaired 6 weeks after the second M-PHP (p = 0.011). The level of physical functioning was restored to normal 3 months later (Table 5).

DISCUSSION

This study was designed to prospectively investigate the efficacy of M-PHP with the GEN 2 filter in patients with unresectable ocular melanoma metastases confined to the liver. The ORR of 72% and survival rate (median OS 19.1 months; 1- and 2-year OS of 77% and 43%, respectively) appeared to be much longer compared to published data on other treatment modalities and provide convincing evidence for the efficacy of M-PHP.

The prognosis of patients with metastatic ocular melanoma is very poor, and there is a lack of effective systemic therapies. A meta-analysis that included 29 prospective trials that reported patients with metastatic ocular melanoma who were treated with immunotherapy, kinase inhibitors, chemotherapy, or liver-directed therapy, reported a median OS of 10.2 months, 1-year OS of 43%, and median PFS of 3.3 months. Another recent meta-analysis, which included 78 peer-reviewed articles, reported similar outcomes in patients with metastatic ocular melanoma receiving either surgical, interventional radiology, or systemic treatment. Median OS across all treatment modalities was 1.07 years and 1-year OS was 52%. In both meta-analyses, patients treated with liver-directed therapies had a significantly longer OS but given the paucity of RCTs the evidence is not compelling. Many studies included in the meta-analyses were retrospective cohort studies with a small sample size and differences in OS between various therapies therefore may be attributable to lead-time, selection, and publication bias.
M-PHP is the only liver-directed therapy for which efficacy was shown in an RCT by Hughes et al. This trial included 93 patients with unresectable liver metastases from either ocular (n = 83) or cutaneous (n = 10) melanoma. Patients were randomized to M-PHP (n = 44) or best alternative care (BAC) (n = 49). Approximately 82% of patients in the BAC group received active treatment such as systemic chemotherapy, chemoembolization,

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**FIG. 3** Survival outcomes. (a) Kaplan–Meier estimate of OS for all included patients (n = 35). (b-c) Kaplan–Meier estimates of OS in all evaluable patients stratified by best overall response and best hepatic response. CI confidence interval; CR complete response; M-PHP percutaneous hepatic perfusion with melphalan; OS overall survival; PD progressive disease; PR partial response; SD stable disease.

| Total | Events | Censored | Median OS (95% CI) |
|-------|--------|----------|-------------------|
| 35    | 83% (29) | 17% (6) | 19.1 (9.8-28.4) |

| Time from first M-PHP (months) | Total | Events | Censored | Median OS (95% CI) |
|--------------------------------|-------|--------|----------|-------------------|
| CR/PR                          | 22    | 73% (16) | 27% (6) | 27.5 (23.7-31.3) |
| SD/PD                          | 10    | 100% (10) | 0% (0) | 11.9 (9.6-14.2) |
radioembolization, and surgery. A significant improvement in hepatic and overall PFS was demonstrated in patients treated with M-PHP: 7.0 versus 1.7 months ($p < 0.0001$) and 5.4 versus 1.6 months ($p < 0.0001$), respectively. The gain in PFS did not result in OS benefit though. The failure to demonstrate OS benefit was most likely caused by the substantial number of patients (40%) with extrahepatic metastases, thereby limiting the optimal effect of a liver-directed therapy. Additionally, almost 60% of patients crossed over to the M-PHP group, receiving M-PHP once disease progression occurred.

The median OS of 19.1 months in the current study compares favorably to the median OS reported in the aforementioned systematic reviews and RCT. It is also longer than the median OS of 15.3 months reported in the largest retrospective study on M-PHP in patients (n = 51) with metastatic ocular melanoma. This study included patients with extrahepatic metastases if these were non-progressive following previous treatments or amenable to ablative treatment modalities. Clearly, our favorable survival outcomes can (partly) be attributed to the exclusion of patients with extrahepatic disease. Additionally, we excluded patients with elevated LDH levels ($> 2 \times ULN$) at baseline, and it has been demonstrated that an elevated LDH is associated with a poor OS in patients with metastatic ocular melanoma.6,39,40 Median baseline LDH level was 196 IU/L in our study versus a mean baseline LDH of 524 IU/L in the RCT by Hughes et al.31

The hepatic response rate in our study (81%) is much higher than in the study by Hughes et al. (36%) and Karydis et al. (49%).29,31 The median number of M-PHP procedures that patients received under study protocol was comparable between all these three studies.

The majority of patients received some form of subsequent treatment (i.e., liver-directed therapy and/or systemic therapy) after showing PD. Although this might have influenced survival, all of these therapies were also available and used at the time of the retrospective studies by Karydis et al. (median OS 15.3 months).29 This does not

| Pt study no. | Progression sites* | Subsequent treatments |
|--------------|---------------------|-----------------------|
| 1            | Liver               | 2x M-PHP, RFA liver   |
| 3            | Liver, bone         | RFA liver + ipilimumab^ |
| 4            | Liver, bone, lung   | 2x M-PHP, RTx bone, pembrolizumab, PKC-inhibitor^b, dacarbazine |
| 5            | Bone, liver         | Ipilimumab            |
| 6            | Lung                | Ipilimumab            |
| 8            | (Sub)cutis, parotid gland, rectosigmoid | Resection cutaneous nodes |
| 9            | Liver, subcutis, lung | RFA liver, resection subcutaneous node |
| 10           | Liver, muscles, subcutis, retroperitoneum, lymph nodes | RFA liver, RT lymph nodes |
| 11           | Bone, liver, subcutis | RFA bone and liver |
| 14           | Liver               | Pembrolizumab, PKC inhibitor^b |
| 16           | Liver, lung, kidney | PKC-inhibitor^b |
| 18           | Bone, liver         | PKC-inhibitor^b |
| 20           | Liver, peritoneum, retroperitoneum, lung | 1x M-PHP, PKC-inhibitor^b |
| 22           | Liver, subcutis, peritoneum | Radioembolization, PKC-inhibitor^b, panitumumab^c |
| 26           | Liver, brain        | Resection liver metastases |
| 27           | Liver               | 2x M-PHP              |
| 29           | Liver, bone         | 2x M-PHP, RFA liver   |
| 30           | Liver               | 3x M-PHP              |
| 34           | Liver               | PKC-inhibitor^b |
| 35           | Liver               | RFA liver              |

M-PHP percutaneous hepatic perfusion with melphalan, no. number, PKC-inhibitor protein kinase C-inhibitor, Pt patient, RFA radiofrequency ablation, RTx radiation therapy

^aProgression sites given in bold represent the initial progression sites

^bSECIRA-UM study (EudraCT Number: 2011-004200-38)

^cPhase I study with a protein kinase C-inhibitor

^dPhase II study with various targeted anti-cancer drugs

TABLE 4 All patients that received subsequent treatment(s) after showing progressive disease (n = 20)
We found that the median OS in patients with a relatively long hPFS (≥ median hPFS) was significantly longer than in patients with a shorter hPFS (< median hPFS). This, together with the finding that the median OS was significantly longer in responders than nonresponders, suggests that controlling liver disease with M-PHP in patients with liver-only disease improves OS. Ideally, this should be confirmed in a phase III RCT with OS as primary endpoint and no permission for crossover. This, however, has already been proven to be difficult as the FOCUS trial (M-PHP versus best available care, NCT02678572) was recently modified into a single-arm study due to a slow inclusion rate.

We found the presence of a liver metastasis with diameter ≥ 3 cm and elevated LDH level to be poor prognostic factors for OS, as was already reported by Khoja et al. We were unable to confirm their findings that an age ≥ 65 years, male sex, and elevated ALP are also poor prognostic factors for OS.

Concerns have been raised about the safety of M-PHP as prior studies reported high rates of hematologic toxicity. In previous publications, it was demonstrated that the GEN 2 filter has an improved filter extraction rate and improved safety profile. We now also provide evidence that M-PHP is well-tolerated with maintenance of QoL. The QoL was only mildly affected with a temporary impaired physical functioning at 6 weeks after the second M-PHP. The majority of patients (74%) developed extrahepatic metastatic disease during follow-up. These may have been new metastases that developed after M-PHP or metastases that were radiologically occult at baseline. This indicates that many patients with ocular melanoma will suffer from systemic spread for which liver-directed therapy is only a temporally treatment solution. We recently started a phase I/II study investigating combination therapy of M-PHP with ipilimumab/nivolumab in order to better control both hepatic and extrahepatic disease (CHOPIN trial, NCT04283890). Results of trials investigating the efficacy of check-point inhibitors alone have been disappointing in patients with ocular melanoma metastases. Ocular

| TABLE 5 | Quality of life. Scores for each scale evaluated in the EORTC QLQ-C30 v3.0 questionnaire |
|----------|--------------------------------------------------------------------------------------|
|          | Prior to treatment | 6 wk after 1st M-PHP | 6 wk after 2nd M-PHP | 6 mo after 1st M-PHP |
|          | Median (range) | Median (range) | Median (range) | Median (range) |
| Functional scales (0–100) |                           |                       |                       |                       |
| Physical functioning  | 97 (20–100) | 93 (33–100) | 87 (33–100) | 93 (0–100) |
| Role functioning  | 92 (33–100) | 67 (17–100) | 83 (33–100) | 100 (0–100) |
| Emotional functioning  | 88 (33–100) | 92 (42–100) | 83 (58–100) | 83 (50–100) |
| Cognitive functioning | 100 (67–100) | 100 (50–100) | 100 (67–100) | 100 (0–100) |
| Social functioning | 100 (50–100) | 83 (33–100) | 100 (33–100) | 100 (50–100) |
| Symptom scales (0–100) |                           |                       |                       |                       |
| Fatigue  | 6 (0–78) | 22 (0–100) | 22 (0–78) | 11 (0–100) |
| Nausea and vomiting | 0 (0–83) | 0 (0–83) | 0 (0–33) | 0 (0–33) |
| Pain  | 0 (0–67) | 0 (0–67) | 0 (0–50) | 0 (0–100) |
| Dyspnoea  | 0 (0–67) | 0 (0–67) | 0 (0–67) | 0 (0–33) |
| Insomnia | 0 (0–67) | 0 (0–67) | 0 (0–100) | 0 (0–100) |
| Appetite loss | 0 (0–67) | 0 (0–67) | 0 (0–67) | 0 (0–67) |
| Constipation | 0 (0–33) | 0 (0–33) | 0 (0–0) | 0 (0–67) |
| Diarrhoea | 0 (0–33) | 0 (0–67) | 0 (0–33) | 0 (0–0) |
| Financial difficulties | 0 (0–33) | 0 (0–67) | 0 (0–67) | 0 (0–0) |
| Global health status/QoL (0–100) |                           |                       |                       |                       |
| Global health status/QoL  | 83 (33–100) | 83 (33–100) | 83 (42–100) | 83 (25–100) |

EORTC QLQ-C30 v3.0 European organization for research and treatment of cancer quality of life questionnaire version 3.0, mo months, M-PHP percutaneous hepatic perfusion with melphalan, QoL quality of life, wk week

aStatistically different compared to baseline score, p = 0.011. All other scores were not statistically different compared to scores prior to treatment.
melanoma cancer cells carry a low tumor mutational burden, which is thought to decrease the likelihood of neoantigen presentation necessary to evoke antitumoral response by T-cells. Tumor lysis and necrosis induced by M-PHP could potentially provoke antigen release that may stimulate cancer-specific immune response and increase the efficacy of check-point inhibitors.

Our study had several limitations. First, this was a single-arm study with a relatively small sample size. Second, we studied a selected group of patients by applying multiple specific exclusion criteria such as the presence of extrahepatic disease, elevated LDH level, and patient age. The relatively high median OS could therefore partly be attributed to selection.

CONCLUSIONS

Although this prospective study was not designed for direct comparison, the results indicate that M-PHP using the GEN 2 filter is more effective in treating liver metastases from uveal melanoma than systemic therapies. We found a high ORR and median OS of 19.1 months in patients with liver-only ocular melanoma metastases. As responders demonstrated an improved survival compared with nonresponders, controlling liver disease with M-PHP seems to prolong the life expectancy of these patients. Future research should aim to reproduce these results in a multicenter trial with larger study populations and to develop standardized criteria for patient selection.

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