



Universiteit
Leiden
The Netherlands

Combining melphalan percutaneous hepatic perfusion with ipilimumab plus nivolumab in advanced uveal melanoma: first safety and efficacy data from the phase Ib part of the Chopin trial

Tong, T.M.L.; Burgmans, M.C.; Speetjens, F.M.; Erkel, A.R. van; Meer, R.W. van der; Rijswijk, C.S.P. van; ... ; Kapiteijn, E.

Citation

Tong, T. M. L., Burgmans, M. C., Speetjens, F. M., Erkel, A. R. van, Meer, R. W. van der, Rijswijk, C. S. P. van, ... Kapiteijn, E. (2023). Combining melphalan percutaneous hepatic perfusion with ipilimumab plus nivolumab in advanced uveal melanoma: first safety and efficacy data from the phase Ib part of the Chopin trial. *Cardiovascular And Interventional Radiology*, 46(3), 350-359. doi:10.1007/s00270-022-03338-1

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3731435>

Note: To cite this publication please use the final published version (if applicable).

Combining Melphalan Percutaneous Hepatic Perfusion with Ipilimumab Plus Nivolumab in Advanced Uveal Melanoma: First Safety and Efficacy Data from the Phase Ib Part of the Chopin Trial

T. M. L. Tong^{1,2}  · M. C. Burgmans² · F. M. Speetjens¹ · A. R. van Erkel² · R. W. van der Meer² · C. S. P. van Rijswijk² · M. A. Jonker-Bos¹ · C. F. M. Roozen¹ · M. Sporrel-Blokland¹ · J. Lutjeboer² · E. L. van Persijn van Meerten² · C. H. Martini⁴ · R. W. M. Zoethout⁴ · F. G. J. Tijnl⁵ · C. U. Blank^{1,3} · E. Kapiteijn¹

Received: 8 June 2022 / Accepted: 6 December 2022 / Published online: 9 January 2023
© Springer Science+Business Media, LLC, part of Springer Nature and the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) 2022

Abstract

Purpose To define a safe treatment dose of ipilimumab (IPI) and nivolumab (NIVO) when applied in combination with percutaneous hepatic perfusion with melphalan (M-PHP) in metastatic uveal melanoma (mUM) patients (NCT04283890), primary objective was defining a safe

treatment dose of IPI/NIVO plus M-PHP. Toxicity was assessed according to Common Terminology Criteria for Adverse Events version 4.03 (CTCAEv4.03). Secondary objective was response rate, PFS and OS.

Materials and Methods Patients between 18–75 years with confirmed measurable hepatic mUM according to RECIST

✉ E. Kapiteijn
h.w.kapiteijn@lumc.nl

T. M. L. Tong
t.m.l.tong@lumc.nl

M. C. Burgmans
m.c.burgmans@lumc.nl

F. M. Speetjens
f.m.speetjens@lumc.nl

A. R. van Erkel
a.r.van_erkel@lumc.nl

R. W. van der Meer
r.w.van_der_meer@lumc.nl

C. S. P. van Rijswijk
c.s.p.van_rijswijk@lumc.nl

M. A. Jonker-Bos
m.a.jonker-bos@lumc.nl

C. F. M. Roozen
c.f.m.roozen@lumc.nl

M. Sporrel-Blokland
m.sporrel-blokland@lumc.nl

J. Lutjeboer
j.lutjeboer@lumc.nl

E. L. van Persijn van Meerten
e.l.van_persijn-van_meerten@lumc.nl

C. H. Martini
c.h.martini@lumc.nl

R. W. M. Zoethout
r.w.m.zoethout@lumc.nl

F. G. J. Tijnl
f.g.j.tyl@lumc.nl

C. U. Blank
c.blank@nki.nl

- 1 Department of Medical Oncology, Leiden University Medical Center, Postal Zone C7-P, Albinusdreef 2, 2333ZA, Leiden, The Netherlands
- 2 Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
- 3 Department of Medical Oncology, The Netherlands Cancer Institute - Antoni Van Leeuwenhoek Hospital, Amsterdam, The Netherlands
- 4 Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands
- 5 Department of Extra Corporal Circulation, Leiden University Medical Center, Leiden, The Netherlands

1.1 and WHO performance score 0–1 were included. Intravenous IPI was applied at 1 mg/kg while NIVO dose was increased from 1 mg/kg in cohort 1 to 3 mg/kg in cohort 2. Transarterial melphalan dose for M-PHP was 3 mg/kg (maximum of 220 mg) in both cohorts. Treatment duration was 12 weeks, consisting of four 3-weekly courses IPI/NIVO and two 6-weekly M-PHPs.

Results Seven patients were included with a median age of 63.6 years (range 50–74). Both dose levels were well tolerated without dose-limiting toxicities or deaths. Grade III/IV adverse events (AE) were observed in 2/3 patients in cohort 1 and in 3/4 patients in cohort 2, including Systemic Inflammatory Response Syndrome (SIRS), febrile neutropenia and cholecystitis. Grade I/II immune-related AEs occurred in all patients, including myositis, hypothyroidism, hepatitis and dermatitis. There were no dose-limiting toxicities. The safe IPI/NIVO dose was defined as IPI 1 mg/kg and NIVO 3 mg/kg. There was 1 complete response, 5 partial responses and 1 stable disease (3 ongoing responses with a median FU of 29.1 months).

Conclusion Combining M-PHP with IPI/NIVO was safe in this small cohort of patients with mUM at a dose of IPI 1 mg/kg and NIVO 3 mg/kg.

Keywords Advanced uveal melanoma · Liver metastases · Percutaneous hepatic perfusion · Melphalan · Immunotherapy

Introduction

Uveal Melanoma (UM), the most common intraocular tumor in adults, is associated with a poor prognosis once metastasized. Currently, there are limited systemic treatment options [1]. Whereas immune checkpoint inhibitors (ICI) have led to a breakthrough in the treatment of cutaneous melanoma (CM), the efficacy of ICI monotherapy in UM seems limited, with 0–11.7% reported response rates [2–5]. Dual-agent immunotherapy shows more promising response rates of 11.6%–18% [6–9]. More recently, tebentafusp has been shown to improve 1-year overall survival (OS) in HLA-A*02:01-positive, previously untreated metastatic UM patients [10].

UM metastases primarily spread to the liver and in more than 90% of patients the liver is the only site of detectable metastases at time of diagnosis [11]. Recent systematic reviews have indicated that local, liver-directed therapies may prolong survival in patients with metastatic UM [12, 13]. Percutaneous hepatic perfusion with melphalan (M-PHP) is a liver-directed therapy that

allows delivery of a high dose of melphalan hepatically, but with limited systemic toxicity. M-PHP has been demonstrated to be safe and effective in metastatic UM patients [14–17]. Despite control of hepatic metastases after treatment with M-PHP, approximately 75% of patients eventually progress with extrahepatic disease [18]. Therefore, there is a need for treatment (combinations) that allows tumor control in both hepatic and extrahepatic metastases [8, 19]. In the previous study (SECIRA-UM) testing radio frequency ablation (RFA) + ipilimumab, extrahepatic control was observed from the ICI treatment, while most patients often progressed hepatically [20]. These observations were the basis of combining ICI with M-PHP in the CHOPIN trial.

CHOPIN is a phase Ib/randomized phase II trial evaluating the combination of M-PHP with ipilimumab (IPI) plus nivolumab (NIVO). Here, we report the results of the phase Ib part, which had the primary objective to establish a safe dose of IPI/NIVO in combination with M-PHP.

Materials and Methods

Trial Design and Treatment

Here, we report the phase Ib part of the CHOPIN trial: a combined phase Ib/randomized phase II trial (NCT04283890). The study is currently ongoing in phase II and is conducted according to the principles of the Declaration of Helsinki (Declaration of Helsinki, 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act. Approval was granted by the Central Committee on Research Involving Human Subjects, the Competent Authority and the Medical Research Ethics Committee of Leiden, The Hague and Delft.

The study was conducted in a 3 + 3 dose-escalation design, consisting of 2 cohorts of 3 patients with a pre-defined IPI and NIVO dose. In cohort 1, four courses of intravenous IPI and NIVO were given at 1 mg/kg each, at a 3-week interval. Total treatment duration was 12 weeks. Cohort 2 was opened 12 weeks after cohort 1 was completed without any safety concerns. In the second cohort, IPI and NIVO doses were 1 mg/kg and 3 mg/kg, respectively. One patient in cohort 2 could not complete treatment according to the study schedule as deemed safe by treating physicians due to development of an extensive allergic reaction on CT-contrast. For this reason, 1 additional patient was included in this cohort. All patients are reported here. Following completion of both cohorts, the safe IPI/NIVO dose was defined (Fig. 1).

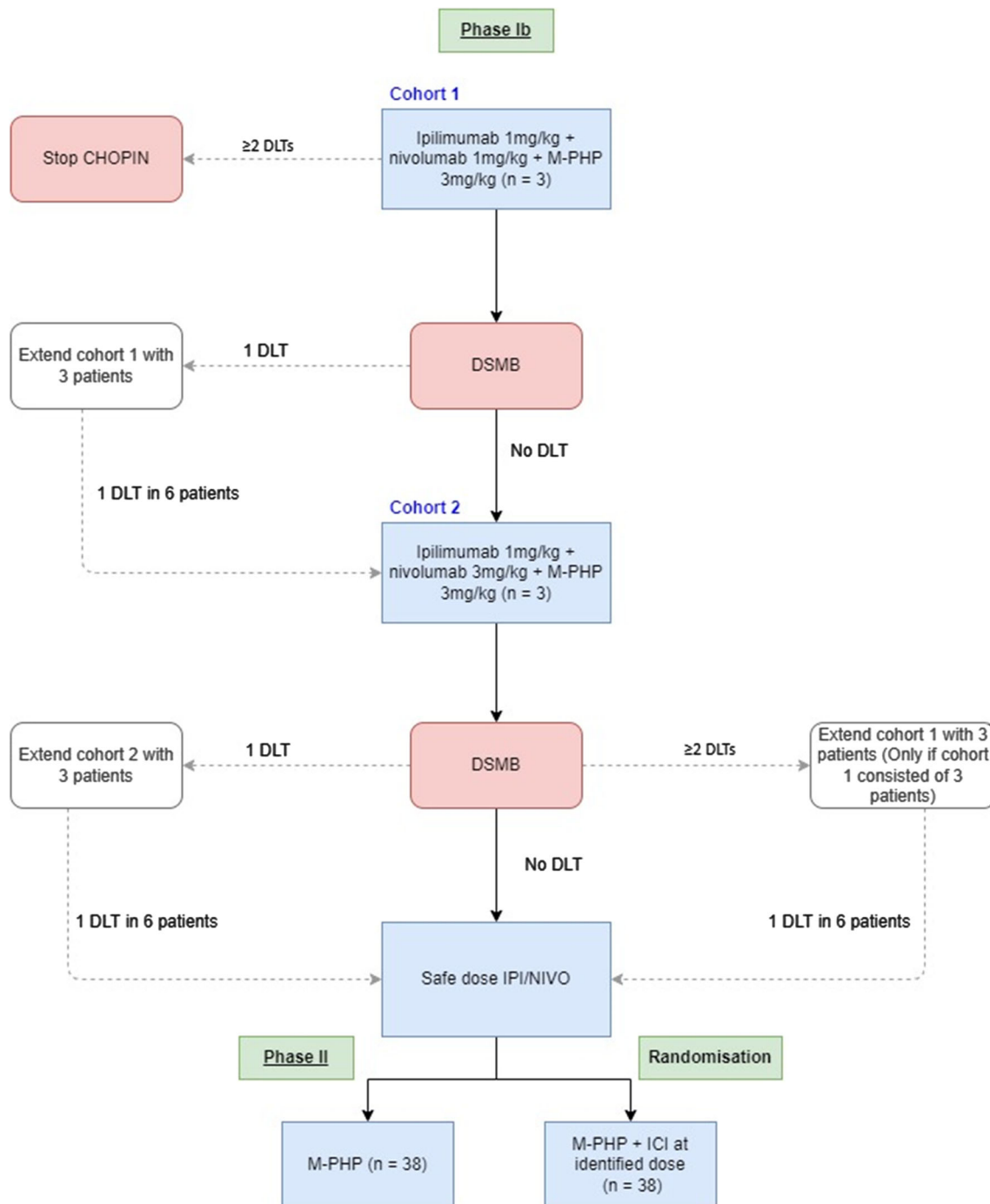


Fig. 1 Flowchart study inclusion and safety assessment. *DLT* dose-limiting toxicity. *DSMB* data safety monitoring board. *ICI* immune checkpoint inhibitor. *M-PHP* percutaneous hepatic perfusion with melphalan

Participants

We prospectively included patients with unresectable UM liver metastases. Main study inclusion and exclusion criteria have previously been reported [21]. Most importantly, patients between 18–75 years of age with a WHO performance score 0/1 with no prior systemic treatment were

included. Patients with limited extrahepatic disease were eligible for inclusion. Key exclusion criteria were cerebral metastases and ongoing use of immunosuppressive therapy, except for topical steroids and ≤ 10 mg prednisolone or equivalent. All patients were discussed in a multidisciplinary tumor board.

Interventions

The treatment schedule has previously been reported [21] and the protocol is attached as supplementary material. Screening procedures included a liver tumor biopsy, contrast-enhanced computed tomography (ceCT) of abdomen and chest and contrast-enhanced magnetic resonance imaging (ceMRI) of the liver. At week 0, patients received the first intravenous infusion of nivolumab 1 mg/kg for 30 min (cohort 1) or 3 mg/kg for 60 min (cohort 2), followed by ipilimumab for 30 min. The following infusions were in week 3, 6 and 9. M-PHP procedures were scheduled in week 1 and 7 (Supplementary material: Fig. 1). The pre-procedural work-up and M-PHP procedure have previously been described [22–24]. In short, all patients underwent angiography prior to M-PHP. If necessary, hepatico-enteric anastomoses were embolized in order to prevent unwanted melphalan leakage during the procedure. M-PHP was performed in an angiographic suite under general anesthesia. At the start of the procedure, an initial heparin dose of 300 U/kg was administered and an activated clotting time (ACT) of ≥ 450 s was maintained throughout the procedure. An infusion catheter was placed in the hepatic artery and a double-balloon catheter was positioned with the tip in the right atrium. Blood was aspirated through the catheter fenestrations in a segment between the two balloons and actively filtered using the second-generation Delcath extracorporeal filtration system. Melphalan was administered transarterial at a dose of 3 mg/kg of body weight (maximum of 220 mg). The coagulation was corrected with protamine sulfate 3 mg/kg at the end of the procedure. Patients received granulocyte colony-stimulating factor (G-CSF) 48 h after M-PHP. In case of grade 3/4 hematologic toxicity after the first M-PHP, melphalan dose was reduced to 75% of the initial dose for the second procedure. If progressive disease occurred after the first M-PHP and 2 courses of immunotherapy, treatment was discontinued.

Objectives and Endpoints

Primary objective was defining a safe treatment dose of IPI/NIVO plus M-PHP. Toxicity was assessed according to CTCAEv4.03. Secondary objectives were determination of response rate, progression-free survival (PFS) and OS. The primary study endpoint of the phase Ib trial was the assessment of a safe IPI/NIVO dose when applied in combination with M-PHP, based on dose-limiting toxicities (DLT). The DLT observation period ranged from week 0 until 12 after the first infusion of IPI/NIVO. DLTs were defined as unexpected serious adverse events (SAE) and adverse events (AE) deemed related to the

investigational combination treatment. Toxicity was assessed according to Common Terminology Criteria for Adverse Events version 4.03 (CTCAEv4.03) [25]. Adverse events (AEs) were classified as related to immunotherapy, M-PHP, both or due to other causes. The secondary endpoints analyzed in this phase Ib study were best overall response (BOR), PFS and OS.

Response Assessment

Follow-up imaging consisted of ceCT of chest and abdomen and ceMRI at 6 weeks after the first and second M-PHP, and then every 3 months in the first follow-up year and 4-monthly thereafter. BOR was assessed according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) [26]. Response was also evaluated according to immune-related RECIST (irRECIST) and modified RECIST (mRECIST) criteria [27, 28]. Objective response rate (ORR) was defined as the percentage of patients with complete response (CR) or partial response (PR), while disease control rate (DCR) was the percentage of patients with CR, PR or stable disease (SD). Duration of response was calculated as the time period in between the first objective response assessment, to the date of PD or the end of follow-up.

Survival Assessment

PFS was measured as the time between study inclusion until objective disease progression on follow-up imaging, or death, whichever occurred first. OS was defined as the time interval between the start of treatment and the date of death due to any cause.

Statistical Analysis

Descriptive statistics were used to describe the population characteristics. The AE data are presented on a patient basis. Response and survival analyses were performed with SPSS version 25.0. Change in tumor measurements was plotted with GraphPad Prism 9.0.1.

Results

Patient Characteristics

Between December 2019 and August 2020, seven patients were enrolled; 4 men and 3 women [median age 63.6 years (range 50–74)]. Detailed baseline characteristics are presented in Tables 1 and 2.

Safety and Tolerability

Three patients were included in cohort 1. All 3 patients completed treatment according to the study scheme and no DLTs occurred. The second cohort also consisted of 3 patients, initially. However, one patient developed cholecystitis and an extensive allergic reaction to iodine contrast medium after CT scan in week 6 which was a contraindication for the second M-PHP. Both events were not declared to be related to the treatment combination, and as such not classified as DLTs. Study treatment was

discontinued after 1 M-PHP and 2 courses of IPI/NIVO. The safety and response assessments of this patient are also included in this report. After consulting with the data safety monitoring board (DSMB), a fourth patient was included in cohort 2 and completed treatment according to the study schedule. No DLTs were registered in cohort 2.

Adverse Events

All grade ≥ 3 AEs are specified per patient and per cohort in Table 3. Grade 1/2 AEs were seen in all patients (Supplementary material: Table 1) and 71.4% experienced grade 3/4 toxicities. In detail, immunotherapy-mediated hepatitis (2 patients in cohort 2), hypothyroidism grade 1/2 (3 patients in total), dermatitis (3 patients in total) and vitiligo grade 2 in 2 patients were observed. In addition to these, 1 patient experienced grade 2 myalgia in the arms and legs, for which treatment with prednisone was started, followed by methotrexate for flairs-ups. One patient experienced localized grade 1 myalgia, which was treated with prednisone. Three other patients experienced myalgia in the chest area, on the back and the extremities, respectively, for which no treatment was required (all grade I/II).

Post-M-PHP AEs were mostly nausea, fatigue and vomiting. All patients experienced transient M-PHP-related anemia grade 1 or 2 after the first or second M-PHP. In the first cohort, 2 out of 3 patients experienced grade 3/4 AEs. One patient developed a Systemic Inflammatory Response Syndrome (SIRS)-like reaction. This patient was readmitted with grade 2 hypotension and grade 3 fever. During admission, bacteremia due to a splenic abscess was diagnosed, for which the patient was adequately treated with antibiotics and a drainage catheter. For the other patient, the melphalan dose was decreased to 75% of the initial dose for the second M-PHP due to grade 4 neutropenia after the first procedure.

Table 1 Baseline patient characteristics

	N	%
Number of patients	7	
Gender		
Male	4	57.1
Female	3	42.9
Age [median, years (range)]	63.6 (50–74)	
WHO Performance score		
0	3	42.9
1	4	57.1
Treatment primary UM		
Brachytherapy	3	42.9
Proton therapy	2	28.6
Surgery/enucleation	2	28.6
Prior treatment metastases		
Yes	0	0
No	7	100
Extrahepatic disease		
Yes	0	0
No	7	100
Sum target lesions [median, mm (range)]	32 (28–99)	
Baseline LDH [median (range)]	184.0 (150–309)	

WHO world health organization; UM uveal melanoma; LDH lactate dehydrogenase; Mm millimeters

Table 2 Individual patient characteristics

Patient No	Treatment primary UM	Interval primary UM—metastases (months)	Number of metastases	Sum of target lesions (mm)	Baseline LDH (U/L)
1	Brachytherapy	38	> 10	51	309
2	Proton therapy	8	< 5	32	184
3	Brachytherapy	14	> 10	53	213
4	Enucleation	46	5–10	28	160
5	Brachytherapy	16	> 10	28	150
6	Proton therapy	57	> 10	28	192
7	Enucleation	82	> 10	99	166

UM uveal melanoma; Mm millimeters; LDH lactate dehydrogenase

Table 3 Adverse events grade ≥ 3 per patient

	Cohort 1: IPI 1 mg/kg NIVO 1 mg/kg			Cohort 2: IPI 1 mg/kg NIVO 3 mg/kg			
Grade ≥ 3 AE	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Hematological							
Leukopenia		X					
Thrombopenia		X					
Neutropenia		X					
Hepatic							
Increased AST				X		X	
Increased ALT				X			
Gastrointestinal							
Cholecystitis					X		
General disorders							
Fever	x						
Hypotension					X		
Infections							
Febrile neutropenia		X					
SIRS-like reaction*	x*						

*Followed by splenic abscess with bacteremia and pleural empyema AE adverse event; AST aspartate aminotransferase; ALT alanine aminotransferase; IPI ipilimumab; NIVO nivolumab; Pt Patient; SIRS systemic inflammatory response syndrome

Table 4 Response to treatment

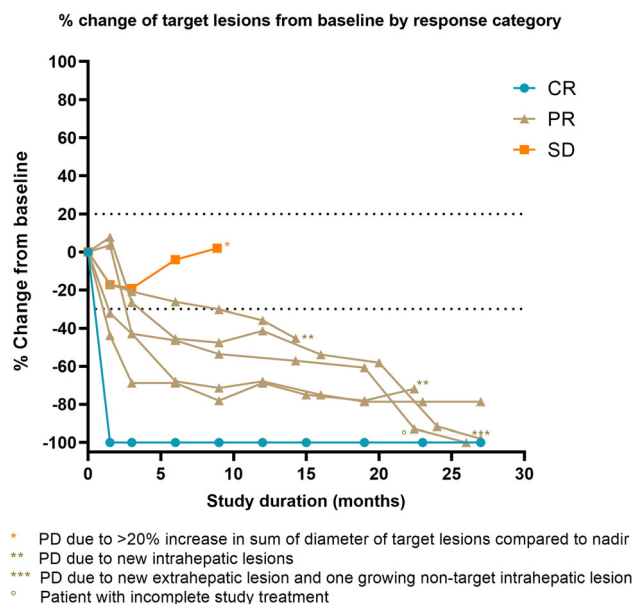
RECIST 1.1	irRECIST	mRECIST
N	7	7
Best overall response, n (%)		
CR	1 (14)	4 (57)
PR	5 (71)	1 (14)
SD	1 (14)	2 (29)
PD	0	0

CR complete response; PR partial response; PD progressive disease; SD stable disease; RECIST 1.1 Response Evaluation Criteria in Solid Tumors 1.1; irRECIST immune-related RECIST; mRECIST modified RECIST

Efficacy

BOR according to irRECIST was in accordance with RECIST 1.1, consisting of 1 (14%) CR, 5 (71%) PR and 1 (14%) SD. ORR and DCR were thus 85.7% and 100%, respectively.

With a median FU of 29.1 months (range 8.9 – 30.2), 1/1 CR and 2/5 PR are ongoing. Hepatic disease control as measured by mRECIST criteria revealed CR in 4 patients (57%), PR in 1 patient (14%), and SD in 2 patients (29%) (Table 4). In Fig. 2, the change in sum of diameter of target lesions over time is depicted.

**Fig. 2** Spider plot depicting change in target lesion sum of diameters over time. CR complete response. PR partial response. SD stable disease

Four patients experienced PD after 8.9, 14.3, 22.4 and 29.1 months. The median duration of response was 27.1 months (range 7.4 – 28.5). Three of four patients who experienced PD went on with treatment in the form of repeated M-PHP cycle. One patient that underwent a new cycle of two M-PHP procedures again experienced PD, for

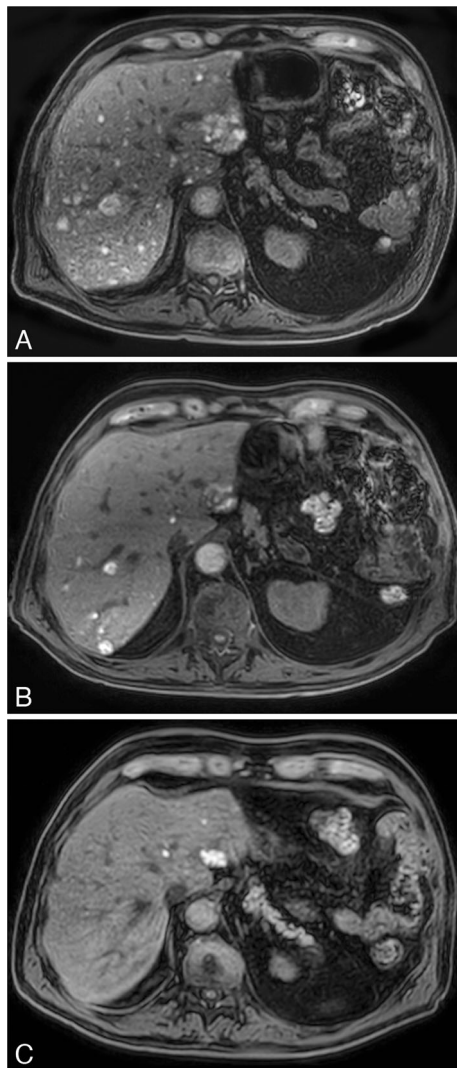


Fig. 3 **A** Baseline MRI of a 74-year-old patient with metachronous bilobar liver metastases from uveal melanoma, showing hyperintense multiple metastases in both liver lobes on the unenhanced images. The patient was treated with 2 courses of M-PHP together with IPI/NIVO 1 mg/kg each. In panel **B**, follow-up MRI shows partial response of baseline lesions. In panel **C**, 2 years and 3 months after baseline imaging, most lesions disappeared indicating sustained partial response. Yet, CT of the chest (not shown) demonstrated a new metastasis of the sixth rib on the right side consistent with progressive disease

which treatment with Temodal was started. In Fig. 3, the baseline and follow-up MRIs are shown of a study patient with partial response.

Survival

At the cut-off date of November 15, 2022, the median follow-up was 29.1 months (range 8.9–30.2). Median PFS was 29.1 months (95% CI 11.9–46.3). All patients are still alive.

Discussion

In the current reported phase Ib study, we demonstrate that the combination of M-PHP and IPI/NIVO is safe. Since no deaths or DLTs occurred, IPI 1 mg/kg with NIVO 3 mg/kg was declared to be the safe dose to commence the randomized phase II part of the CHOPIN trial. The majority of AEs observed were mild and well manageable, and this treatment combination did not lead to unexpected or more severe (S)AEs as compared to treatment with either M-PHP or IPI/NIVO alone [7–9]. The median PFS was 29.1 months, and no deaths occurred.

Metastatic UM is a relatively treatment-refractory disease. According to our observations and the available literature, liver-directed therapies can provide long-lasting disease control in the liver, but extrahepatic disease progression is a major problem. Conversely, IPI/NIVO treatment shows a trend toward control of extrahepatic lesions, but hepatic disease progression regularly occurs [9, 18, 20]. With this trial, we aim to control hepatic disease, as well as prevent extrahepatic disease in follow-up.

UM is characterized by a different set of driver mutations and lower mutational load compared to CM, leading to limited neoantigen presentation and lower efficacy of ICI. Additionally, there is lower PD-1 and PD-L1 expression in patients with metastatic UM compared to metastatic CM [11]. By combining M-PHP with IPI/NIVO, we aim to increase the efficacy of ICI by turning a ‘cold tumor’ into a ‘hot tumor’. A more recent study also demonstrates the importance of combining IPI/NIVO with liver-directed therapies [29]. To date, little is known about the immunomodulatory effects of M-PHP. Current available evidence comes from studies on isolated limb perfusion (ILP) and isolated hepatic perfusion (IHP), which is the surgical counterpart of M-PHP [30, 31]. These data show that ILP and IHP can lead to T-cell activation following the procedures. We hypothesize that this is also the case for M-PHP, leading to an improved activation of the immune system together with ICI. The combination of locoregional therapies with ICI has gained interest over recent years, but it is currently unknown which locoregional therapy has the best immunomodulatory effect. Theoretically, thermal ablation has the advantage of inducing a stronger inflammatory response as compared to M-PHP. In the SECIRA-UM trial thermal ablation was combined with IPI monotherapy in patients with mUM, but clinical activity was limited in this trial [20].

In this trial evaluating the combination of M-PHP with IPI/NIVO, two treatment modalities that can both be hepatotoxic when applied individually were studied. Therefore, defining the toxicity of the treatment combination was essential. Landmark studies on metastatic CM often

applied IPI 3 mg/kg and NIVO 1 mg/kg [32, 33]; however, IPI 1 mg/kg combined with NIVO 3 mg/kg yielded a lower amount of severe AEs while still maintaining treatment efficacy [34]. Previous studies, combining Yttrium⁹⁰ with either IPI alone or IPI/NIVO, have shown that IPI in high dose leads to excessive hepatic and non-hepatic toxicity in patients [20, 35]. In contrast to these studies, our application of low dose IPI might be the reason that both cohort doses were tolerated and no DLT's occurred. We did observe low-grade immune-related toxicities and PHP-related hematological toxicities in the treated groups. Hematological toxicity is a common AE after M-PHP, affecting approximately three-quarters of patients. All 7 patients in our study experienced grade 1/2 anemia. One patient developed a splenic abscess, which may have been related to transient leukocytopenia. To prevent severe leukopenia/neutropenia, G-CSF is administered within 48 h after M-PHP in our center. The phase II part of the CHOPIN study will provide more information on both hepatic and systemic toxicity associated with the combination therapy.

In addition to safety, the first results from our trial indicate promising efficacy with a median PFS of 29.1 months, ORR of 85.7% and DCR of 100%. Until now, all trials testing systemic therapy including ICI, chemo- and targeted therapy as monotherapy have failed to show clinical benefit [36, 37]. Studies investigating M-PHP treatment only report ORRs up to 72% (18). While tebentafusp has shown a low ORR and DCR of 9% and 46%, respectively, it is the first treatment that has improved 1-year overall survival (OS) in the treatment arm (73%), compared to the control arm (59%). However, only a subgroup of patients can benefit from this treatment, namely HLA-A2 patients [10]. Different trials combining locoregional and immunotherapy are ongoing. These include IPI/NIVO combined with immuno-embolization (NCT03472586) and radio-embolization (NCT02913417) [38]. Despite the promising results of our phase Ib study, the results should be interpreted with caution because of the small sample size. The current randomized phase II part of the CHOPIN trial, comparing M-PHP with M-PHP plus IPI/NIVO, will include another 76 patients (38 per arm) and will provide more insight in the efficacy.

Conclusion

In this phase Ib dose-escalation study combining M-PHP with IPI/NIVO, the safe treatment dose was established at IPI 1 mg/kg and NIVO 3 mg/kg. The PFS of 29.1 months is promising, but results of the phase II part of the CHOPIN study need to be awaited before conclusions can be drawn on the efficacy of the combination therapy.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00270-022-03338-1>.

Acknowledgements The authors thank Gerrit Kracht for his help in producing the figures.

Funding Contribution in kind by Bristol Myers Squibb and Delcath Systems Inc. Bristol Myers Squibb contributes to the study with the supply of ipilimumab and nivolumab. Delcath Systems contributes to the study by supplying the kits for the percutaneous hepatic perfusion procedure.

Declarations

Conflict of interest EK and MB have received consultancy fees from Delcath Systems. EK has consultancy/advisory relationships with Bristol Myers Squibb, Novartis, Merck, Pierre Fabre, and received research grants from Bristol Myers Squibb and Pierre Fabre. CB has an advisory role for MSD, Roche, Novartis, GSK, AZ, Pfizer, Lilly, GenMab, Pierre Fabre, Third Rock Ventures, receives research funding from BMS, Novartis, NanoString and 4SC, has stockownership in Immagine BV and a pending patent for WO 2021/177822 A1. The other authors declare no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

References

1. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011;118(9):1881–5.
2. van der Kooij MK, Joosse A, Speetjens FM, Hospers GA, Bisschop C, de Groot JW, et al. Anti-PD1 treatment in metastatic uveal melanoma in the Netherlands. *Acta Oncol*. 2017;56(1):101–3.
3. Rossi E, Pagliara MM, Orteschi D, Dosa T, Sammarco MG, Caputo CG, et al. Pembrolizumab as first-line treatment for metastatic uveal melanoma. *Cancer Immunol Immunother*. 2019;68(7):1179–85.
4. Algazi AP, Tsai KK, Shoushtari AN, Munhoz RR, Eroglu Z, Piulats JM, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer*. 2016;122(21):3344–53.
5. Kelderman S, van der Kooij MK, van den Eertwegh AJM, Soetekouw PMMB, Jansen RLH, van den Brom RRH, Hospers GAP, Haanen JBAG, Kapiteijn E, Blank CU. Ipilimumab in pretreated metastatic uveal melanoma patients. Results of the dutch working group on immunotherapy of oncology (WIN-O). *Acta Oncologica*. 2013;52(8):1786–8. <https://doi.org/10.3109/0284186X.2013.786839>.
6. Heppt MV, Amaral T, Kähler KC, Heinzerling L, Hassel JC, Meissner M, et al. Combined immune checkpoint blockade for

- metastatic uveal melanoma: a retrospective, multi-center study. *J Immunother Cancer*. 2019;7(1):299.
7. Najjar YG, Navrazhina K, Ding F, Bhatia R, Tsai K, Abbate K, et al. Ipilimumab plus nivolumab for patients with metastatic uveal melanoma: a multicenter, retrospective study. *J Immunother Cancer*. 2020;8(1):e000331.
 8. Piulats JM, Espinosa E, de la Cruz ML, Varela M, Alonso Carrion L, Martin-Algarra S, et al. Nivolumab plus ipilimumab for treatment-naïve metastatic uveal melanoma: an open-label, multicenter, phase II trial by the spanish multidisciplinary melanoma group (GEM-1402). *J Clin Oncol*. 2021;39(6):586–98.
 9. Pelster MS, Gruschus SK, Bassett R, Gombos DS, Shephard M, Posada L, et al. Nivolumab and ipilimumab in metastatic uveal melanoma: results from a single-arm phase II study. *J Clin Oncol*. 2021;39(6):599–607.
 10. Nathan P, Hassel JC, Rutkowski P, Baurain J-F, Butler MO, Schlaak M, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med*. 2021;385(13):1196–206.
 11. Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol*. 2005;123(12):1639–43.
 12. Rowcroft A, Loveday BPT, Thomson BNJ, Banting S, Knowles B. Systematic review of liver directed therapy for uveal melanoma hepatic metastases. *HPB*. 2020;22(4):497–505.
 13. Gonsalves CF, Adamo RD, Eschelman DJ. Locoregional therapies for the treatment of uveal melanoma hepatic metastases. *Semin Intervent Radiol*. 2020;37(5):508–17.
 14. Pingpank JF, Libutti SK, Chang R, Wood BJ, Neeman Z, Kam AW, et al. Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. *J Clin Oncol*. 2005;23(15):3465–74.
 15. Hughes MS, Zager J, Faries M, Alexander HR, Royal RE, Wood B, et al. Results of a randomized controlled multicenter phase iii trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. *Ann Surg Oncol*. 2016;23(4):1309–19.
 16. de Leede EM, Burgmans MC, Meijer TS, Martini CH, Tijl FGJ, Vuyk J, et al. Prospective clinical and pharmacological evaluation of the delcath system's second-generation (GEN2) hemofiltration system in patients undergoing percutaneous hepatic perfusion with melphalan. *Cardiovasc Intervent Radiol*. 2017;40(8):1196–205.
 17. Meijer TS, Burgmans MC, Fiocco M, de Geus-Oei LF, Kapiteijn E, de Leede EM, et al. Safety of Percutaneous hepatic perfusion with melphalan in patients with unresectable liver metastases from ocular melanoma using the delcath systems' second-generation hemofiltration system: a prospective non-randomized phase II trial. *Cardiovasc Intervent Radiol*. 2019;42(6):841–52.
 18. Meijer TS, Burgmans MC, de Leede EM, de Geus-Oei LF, Boekstijn B, Handgraaf HJM, et al. Percutaneous Hepatic Perfusion with Melphalan in Patients with Unresectable Ocular Melanoma Metastases Confined to the Liver: A Prospective Phase II Study. *Ann Surg Oncol*. 2021;28(2):1130–41.
 19. Karydis I, Chan PY, Wheeler M, Arriola E, Szlosarek PW, Ottensmeier CH. Clinical activity and safety of Pembrolizumab in Ipilimumab pre-treated patients with uveal melanoma. *Oncoimmunology*. 2016;5(5):e1143997.
 20. Rozeman EA, Prevoo W, Meier MAJ, Sikorska K, Van TM, van de Wiel BA, et al. Phase Ib/II trial testing combined radiofrequency ablation and ipilimumab in uveal melanoma (SECIRA-UM). *Melanoma Res*. 2020;30(3):252–60.
 21. Tong TML, van der Kooij MK, Speetjens FM, van Erkel AR, van der Meer RW, Lutjeboer J, et al. Combining hepatic percutaneous perfusion with ipilimumab plus nivolumab in advanced uveal melanoma (CHOPIN): study protocol for a phase Ib/randomized phase II trial. *Trials*. 2022;23(1):137.
 22. Burgmans MC, de Leede EM, Martini CH, Kapiteijn E, Vahrmeijer AL, van Erkel AR. Percutaneous isolated hepatic perfusion for the treatment of unresectable liver malignancies. *Cardiovasc Intervent Radiol*. 2016;39(6):801–14.
 23. de Leede EM, Burgmans MC, Martini CH, Tijl FG, van Erkel AR, Vuyk J, et al. Percutaneous hepatic perfusion (PHP) with melphalan as a treatment for unresectable metastases confined to the liver. *J Vis Exp*. 2016;113:e53795.
 24. Meijer TS, Geus-Oei LF, Martini CH, Tijl FGJ, Sitsen ME, Erkel ARV, et al. Embolization of variant hepatic arteries in patients undergoing percutaneous hepatic perfusion for unresectable liver metastases from ocular melanoma. *Diagn Interv Radiol*. 2019;25(6):451–8.
 25. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed 1 September 2021.
 26. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Europ J Cancer*. 2009;45(2):228–47. <https://doi.org/10.1016/j.ejca.2008.10.026>.
 27. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekas S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143–52.
 28. Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30(01):052–60.
 29. Blomen CL, Kött J, Hartung TI, Torster LK, Gebhardt C. Combination of immune checkpoint inhibitors and liver-specific therapies in liver-metastatic uveal melanoma: can we thus overcome its high resistance? *Cancers*. 2021;13(24):6390. <https://doi.org/10.3390/cancers13246390>.
 30. Johansson J, Kiffin R, Andersson A, Lindnér P, Naredi PL, Olofsson Bagge R, et al. Isolated limb perfusion with melphalan triggers immune activation in melanoma patients. *Front Oncol*. 2018;8:570.
 31. Johansson J, Siarov J, Kiffin R, Molne J, Mattsson J, Naredi P, et al. Presence of tumor-infiltrating CD8(+) T cells and macrophages correlates to longer overall survival in patients undergoing isolated hepatic perfusion for uveal melanoma liver metastasis. *Oncoimmunology*. 2020;9(1):1854519.
 32. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(13):1270–1.
 33. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381(16):1535–46.
 34. Lebke C, Meyer N, Mortier L, Marquez-Rodas I, Robert C, Rutkowski P, et al. Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV checkmate 511 Trial. *J Clin Oncol*. 2019;37(11):867–75.
 35. Minor DR, Kim KB, Tong RT, Wu MC, Kashani-Sabet M, Orloff M, et al. A pilot study of hepatic irradiation with yttrium-90 microspheres followed by immunotherapy with Ipilimumab and nivolumab for metastatic uveal melanoma. *Cancer Biother Radiopharm*. 2022;37(1):11–6.

36. Rantala ES, Hernberg M, Kivela TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma Res.* 2019;29(6):561–8.
37. Khoja L, Atenafu EG, Suci S, Leyvraz S, Sato T, Marshall E, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. *Ann Oncol.* 2019;30(8):1370–80.
38. Aedo-Lopez V, Gérard CL, Boughdad S, Moura BG, Berthod G, Digkila A, Homicsko K, Schaefer N, Duran R, Cuendet MA, Michielin O. Safety and efficacy of ipilimumab plus nivolumab and sequential selective internal radiation therapy in hepatic and extrahepatic metastatic uveal melanoma. *Cancers.* 2022;14(5):1162. <https://doi.org/10.3390/cancers14051162>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.