Melphalan/Hepatic Delivery System versus Best Available Care in Patients with Unresectable Metastatic Uveal Melanoma: Randomized FOCUS Trial Results

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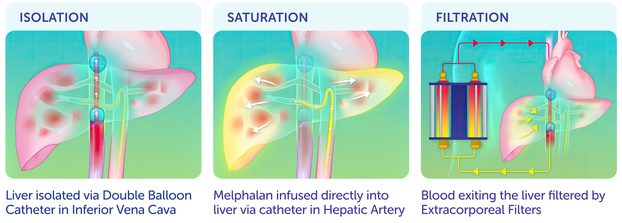
Background

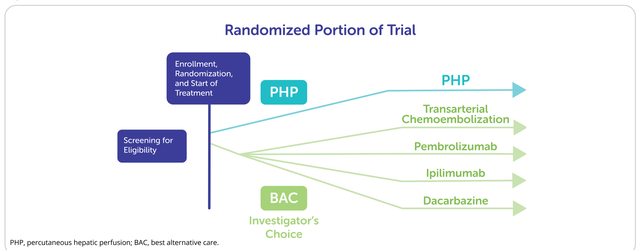
- Metastatic uveal melanoma (mUM) has a poor prognosis, with liver metastases typically presenting a therapeutic challenge.[1]
- Liver metastasis is the most common cause of death for patients with mUM.[2]
- Melphalan/Hepatic Delivery System (melphalan/HDS) is a drug/device combination used in the percutaneous hepatic perfusion (PHP) procedure for liver-directed treatment of unresectable metastatic tumors in mUM patients.
- The PHP procedure uniquely treats the entire liver by isolating liver circulation, saturating the entire liver with a high dose of melphalan, and then filtering the blood extracorporeally to remove up to 85% of the administered melphalan prior to returning the blood to systemic circulation.



Methods

- The FOCUS trial was initiated as a controlled, two arm study; patients were randomized 1:1 to receive PHP or best alternative care (BAC).
- PHP-randomized patients were treated with melphalan at 3 mg/kg ideal body weight (maximum dose: 220 mg per treatment) every 6-8 weeks for up to 6 cycles.
- Tumor response was assessed by CT or MRI every 12 (±2) weeks using RECIST 1.1 criteria. Patients with hepatic or extrahepatic progressive disease (PD) were discontinued from study treatment. All patients were followed until death.
- The primary endpoint was overall survival (OS) with a planned study size of 240 patients.
- Due to slow enrollment and patient reluctance to receive BAC treatment, after discussion with FDA the trial design was amended to single arm with all eligible patients receiving PHP.
- Here we report exploratory efficacy results from the randomized portion of the trial only.

Figure 1. FOCUS Trial



PHP, percutaneous hepatic perfusion; BAC, best alternative care.

Key Inclusion Criteria

- 50% or less liver involvement from metastatic uveal melanoma.
- Liver disease must be measurable by CT and/or MRI.
- Limited extrahepatic disease at baseline permitted if life-threatening component of disease is in liver.
- ECOG performance status of 0-1 at screening.
- Prior chemotherapy, radiotherapy, chemoembolization, radioembolization, or immunoembolization permitted after washout period of 30 days.
- Prior PD-1 immunotherapy, such as pembrolizumab or nivolumab, or anti–CTLA-4 immunotherapy, such as ipilimumab, permitted after washout period of 8 weeks.

Key Exclusion Criteria

- Child-Pugh Class B or C cirrhosis or evidence of portal hypertension.
- New York Heart Association functional classification II, III or IV active cardiac conditions, or any cardiac conditions precluding use of general anesthesia.
- Clinically significant pulmonary disease that precludes use of general anesthesia.
- Prior Whipple procedure.
- Patients on immunosuppressive drugs or who cannot be temporarily removed from chronic anticoagulation therapy
- Patients with active bacterial infections with systemic manifestations (eg, malaise, fever, leukocytosis) are not eligible until completion of appropriate therapy.

REFERENCES

1. Kaštelan S, et al. Front Biosci (Landmark Ed). 2022 Feb 21;27(2):72.
2. Bakalian S, et al. Clin Cancer Res. 2008;14(4):951-956.

Key Results

- A total of 85 patients were enrolled: 43 were randomized to PHP and 42 were randomized to BAC. 40 patients received PHP treatment and 32 patients received BAC therapy.
- Key efficacy results (all analyses are exploratory):
  - Median OS was 18.5 months for PHP patients and 14.5 months for BAC patients.
  - Median PFS was 9.1 months for PHP patients and 3.3 months for BAC patients.
  - ORR was 27.5% for PHP patients and 9.4% for BAC patients.
  - Median DOR was 14.0 months for PHP patients and 5.6 months for BAC patients.
  - DCR was 80.0% for PHP patients and 46.9% for BAC patients.
- Key safety results:
  - SAEs were experienced by 51.2% of PHP patients and 21.9% of BAC patients.
  - AEs were experienced by 100.0% of PHP patients and 93.8% of BAC patients.
  - There were no treatment-related deaths.

Figure 2. Kaplan-Meier Plot for PFS in the Treated Population

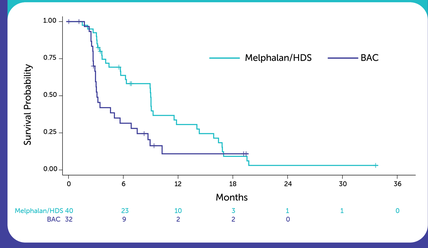


Figure 3. Kaplan-Meier Plot for OS in the Treated Population

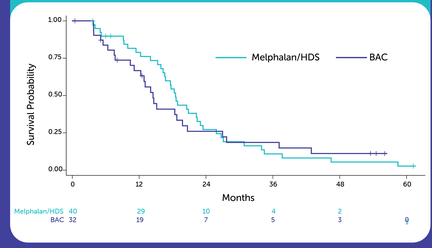
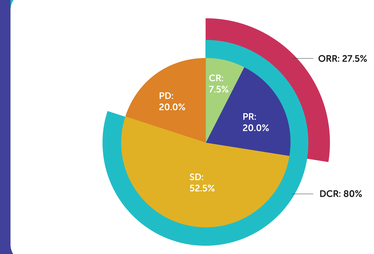
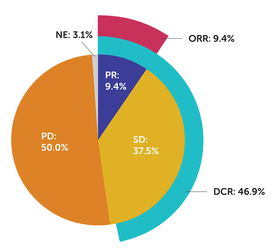


Figure 4. Overall Tumor Response in patients treated with PHP



BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate

Figure 5. Overall Tumor Response in patients treated with BAC



BOR, best overall response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate

Detailed Results

Table 1. Patient Disposition by Enrollment and Treatment

	Enrolled (N=85)	Treated (N=72)
PHP arm	43	40
BAC arm	42	32
Dacarbazine	1	0
Ipilimumab	7	1
Pembrolizumab	8	6
TACE	26	25

Table 2. Demographics

	PHP (n=40)	BAC (n=32)
Age at baseline, years		
Median (range)	63.0 (20-78)	61.0 (31-82)
Extent of liver involvement, n (%)		
1-25%	31 (77.5)	24 (75.0)
26-50%	9 (22.5)	8 (25.0)
Received prior therapy for mUM, n (%)	19 (47.5)	14 (43.8)
Sex, n (%)		
Male	20 (50.0)	14 (43.8)
Female	20 (50.0)	18 (56.3)
Time since diagnosis of liver metastases, months		
Median	5.36	2.48
Min, Max	0.5, 40.4	0.3, 26.0

Max, maximum; min, minimum.

Table 3. Progression Free Survival

Secondary Endpoint	PHP (n=40)	BAC (n=32)	*p* Value*
Median PFS, months	9.07	3.25	0.0036
[95% CI]	[6.37 – 11.83]	[2.89 – 5.91]	
PFS status, n (%) Events	32 (80.0)	29 (90.6)	
Censored	8 (20.0)	3 (9.4)	
Hazard ratio estimate**	0.35		0.0002
[95% CI]	[0.20 – 0.61]		

PFS, progression-free survival.
* Log-rank test.
** Hazard ratio estimate includes region (US vs. outside US) and extent of liver involvement (1-25% vs. 26-50%) as covariates.

Table 4. Overall Survival

Secondary Endpoint	PHP (n=91)	BAC (n=32)	*p* Value*
Median OS, months	18.53	14.49	0.7135
[95% CI]	[16.30 – 22.41]	[11.10 – 19.78]	
OS status, n (%) Events	36 (90.0)	25 (78.1)	
Censored	4 (10.0)	7 (21.9)	
Hazard ratio estimate**	0.91		0.7281
[95% CI]	[0.54 – 1.54]		

OS, overall survival.
* Log-rank test.
** Hazard ratio estimate includes region (US vs. outside US) and extent of liver involvement (1-25% vs. 26-50%) as covariates.

All data above is for treated patients. Response assessments are based on investigator assessments.

Table 5. Adverse Events of Any Severity Occurring in >15% of Patients in Either Arm

Adverse Event, n (%)	PHP (n=41)	BAC (n=32)
Any Adverse Event	41 (100.0)	30 (93.8)
Nausea	29 (70.7)	19 (59.4)
Thrombocytopenia*	28 (68.3)	1 (3.1)
Anemia**	27 (65.9)	2 (6.3)
Fatigue	23 (56.1)	11 (34.4)
Vomiting	18 (43.9)	11 (34.4)
Leukopenia***	17 (41.5)	2 (6.3)
Neutropenia****	16 (39.0)	1 (3.1)
Upper abdominal pain	13 (31.7)	6 (18.8)
ALT increased	11 (26.8)	3 (9.4)
Back pain	11 (26.8)	3 (9.4)
INR increased	11 (26.8)	0 (0.0)
Diarrhea	9 (22.0)	1 (3.1)
Dyspnea	9 (22.0)	1 (3.1)
Contusion	8 (19.5)	0 (0.0)
Headache	8 (19.5)	4 (12.5)
Abdominal pain	7 (17.1)	8 (25.0)
aPTT prolonged	7 (17.1)	0 (0.0)
AST increased	7 (17.1)	3 (9.4)
Asthenia	7 (17.1)	4 (12.5)
Blood alkaline phosphatase increased	7 (17.1)	4 (12.5)
Decreased appetite	7 (17.1)	4 (12.5)
Hypophosphatemia	7 (17.1)	0 (0.0)
Pain in extremity	7 (17.1)	1 (3.1)
Pyrexia	4 (9.8)	5 (15.6)

* Thrombocytopenia includes thrombocytopenia, platelet count decreased.
** Anemia includes anemia, febrile bone marrow aplasia, normochromic normocytic anemia, red blood cell count decreased.
*** Leukopenia includes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.
**** Neutropenia includes neutropenia, neutrophil count decreased.

Table 6. Serious Adverse Events Occurring in >5% of Patients in Either Arm

Adverse Event, n (%)	PHP (n=41)	BAC (n=32)
Thrombocytopenia*	19.5	0
Neutropenia**	9.8	0
Leukopenia***	9.8	0
Febrile neutropenia	7.3	0
Cholecystitis	0	6.3
Nausea	0	6.3
Vomiting	0	6.3

* Thrombocytopenia includes thrombocytopenia, platelet count decreased.
** Neutropenia includes neutropenia, neutrophil count decreased.
*** Leukopenia includes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.

Conclusions

- PHP with melphalan/HDS shows numerical improvements in ORR, DCR, PFS and OS when compared to BAC in patients with mUM.
- Safety profile of PHP with melphalan/HDS is less favorable than that of BAC, consistent with prior experience and the nature of the procedure.
- Overall, the benefit-risk profile appears to favor PHP with melphalan/HDS over BAC.
- PHP with melphalan/HDS is a novel and promising treatment option for mUM patients, a patient population with poor prognosis and limited therapeutic options.

Melphalan/HDS was approved by the FDA for the treatment of unresectable mUM patients in Aug 2023.

For questions/comments, contact
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