FOCUS Phase 3 Trial Results: Percutaneous Hepatic Perfusion (PHP) With Melphalan for Patients With Ocular Melanoma Liver Metastases (PHP-OCM-301/301A)

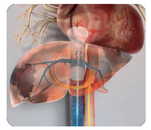
Jonathan S. Zager,[1] Marlana Orloff,[2] Pier Francesco Ferrucci,[3] Evan S. Glazer,[4] Aslam Ejaz,[5] Erika Richtig,[6] Sebastian Ochsenreither,[7] Michael C. Lowe,[8] Sunil A. Reddy,[9] Georgia M. Beasley,[10] Anja Gesierich,[11] Reinhard Dummer,[12] Ana Arance,[13] Stephen William Fenwick,[14] Matthew Wheater,[15] Christian H. Ottensmeier[16]

[1]Moffitt Cancer Center, Tampa, FL; [2]Thomas Jefferson University, Philadelphia, PA; [3]IEO–Istituto Europeo di Oncologia, IRCCS, Milan, Italy; [4]The University of Tennessee Health Science Center, Memphis, TN; [5]The Ohio State University, Columbus, OH; [6]Medical University of Graz, Graz, Austria; [7]Charité Hospital Berlin, Berlin, Germany; [8]Emory University School of Medicine, Atlanta, GA; [9]Stanford University, Stanford, CA; [10]Duke University, Durham, NC; [11]University Hospital Würzburg, Würzburg, Germany; [12]University Hospital Zürich, Zürich, Switzerland; [13]Hospital Clínic Barcelona, Barcelona, Spain; [14]Liverpool University Hospital, Liverpool, UK; [15]University Hospital Southampton, Southampton, UK; [16]University of Liverpool & The Clatterbridge Cancer Center, Liverpool, UK

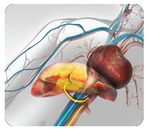
Background

- Ocular melanoma, the most common intraocular malignancy, frequently metastasizes to the liver[1]
- Liver metastasis is the most common cause of death for patients with metastatic ocular melanoma[2]
- Percutaneous hepatic perfusion (PHP) uniquely treats the entire liver by isolating liver circulation to deliver a high concentration of chemotherapy (melphalan) and then filters the blood removing most of the chemotherapy extracorporeally before the blood is returned to the patient via veno-veno bypass

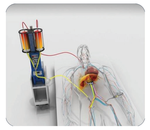
Liver Isolated Via Double Balloon Catheter in Inferior Vena Cava



Melphalan Infused Directly Into Liver Via Catheter In Hepatic Artery



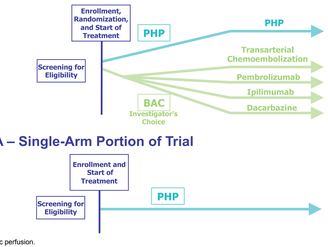
Blood Exiting the Liver Filtered by Proprietary Extracorporeal Filters



Methods

- Focus trial began as a randomized trial with eligible patients with hepatic-dominant ocular melanoma randomized 1:1 to receive PHP or best alternative care (BAC; investigator's choice of transarterial chemoembolization [TACE], pembrolizumab, ipilimumab, or dacarbazine)
- Due to slow enrollment and patient reluctance to receive BAC treatment, the trial design was amended to a single arm design with all eligible patients receiving PHP after discussion with FDA
- PHP patients could receive up to 6 PHP treatments
- PHP was repeated every 6-8 weeks
- Melphalan dosed at 3.0 mg/kg ideal body weight (IBW)
- Patients with hepatic or extrahepatic progressive disease (PD) were discontinued from study treatment and all patients are followed until death
- Patients were imaged every 12 (±2) weeks
- Primary endpoint, objective response rate (ORR; per RECIST v1.1), was assessed by Independent Review Committee (IRC)

Figure 1. FOCUS Trial



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

Key Inclusion Criteria

- 50% or less liver involvement from metastatic ocular melanoma
- Liver disease must be measurable by CT and/or MRI
- Evidence of limited extrahepatic disease at baseline is acceptable if the life-threatening component of progressive disease is in the liver
- ECOG performance status of 0-1 at screening
- Prior chemotherapy, radiotherapy, chemoembolization, radioembolization, or immunoembolization is allowed with a washout period of 30 days
- Patients receiving PD-1 immunotherapy, such as pembrolizumab or nivolumab, or anti–CTLA-4 immunotherapy, such as ipilimumab, should wait 8 weeks before receiving PHP treatment

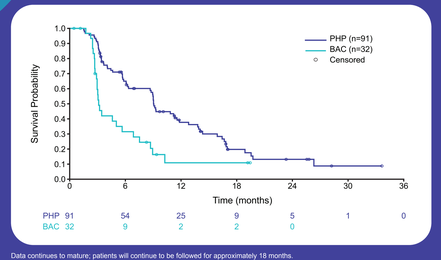
Key Exclusion Criteria

- Patients with Child-Pugh Class B or C cirrhosis or with evidence of portal hypertension
- Patients with New York Heart Association functional classification II, III or IV active cardiac conditions, or any cardiac conditions precluding the use of general anesthesia
- Clinically significant pulmonary disease that precludes the use of general anesthesia
- Patients with prior Whipple procedure
- Patients taking immunosuppressive drugs or who are unable to 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

Results

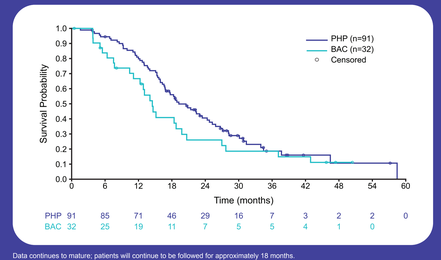
- A total of 144 patients were enrolled overall; 102 were assigned to PHP (301: n=43; 301A: n=59) and 42 were assigned to BAC; 91 patients received PHP treatment (301: n=40; 301A: n=51) and 32 patients received BAC (Table 1; Figure 1)
- ORR among treated PHP patients was 36.3% and among treated BAC patients was 12.5% (Table 4)
- Median DOR was 14 months for PHP patients and not calculable for BAC patients (Table 5)
- DCR among PHP patients was 73.6% and among BAC patients was 37.5% (Table 4)
- PFS was 9.03 months among PHP patients and was 3.12 months among BAC patients (Table 6; Figure 2)
- OS among treated PHP patients was 19.25 months and among treated BAC patients was 14.49 months (Table 7; Figure 3)
- With the last treatment occurring in May 2021, the OS, DOR, and PFS data continue to mature as patients are still being followed for survival
- Among the 94 patients assessed for safety after treatment with PHP, 42.6% of patients experienced a serious treatment-emergent adverse event (TEAE), the majority of which were hematological, transient in nature, and resolved without sequelae (Table 8)
- There were no treatment-related deaths in the trial

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



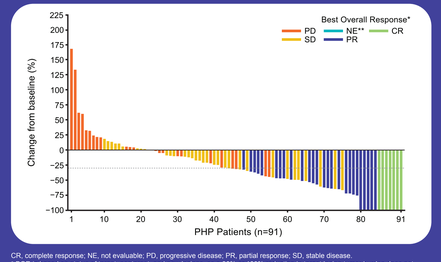
Data continues to mature; patients will continue to be followed for approximately 18 months.

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



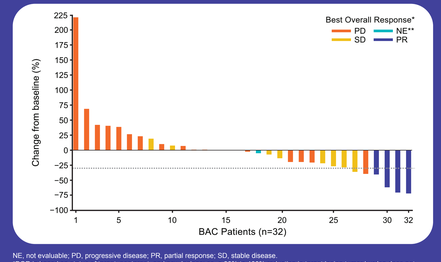
Data continues to mature; patients will continue to be followed for approximately 18 months.

Figure 4. Best Percent Change in Target Lesion Tumor Burden in Patients Who Received PHP per IRC



CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
* BOR is based on status of target, nontarget, and new lesions, so a 30% or 100% reduction in target lesion tumor burden does not necessarily indicate BOR of PR or CR.
** Target lesions were not evaluable for 1 patient after baseline, and 1 patient had no imaging after baseline; these patients are represented with a 0% change from baseline.

Figure 5. Best Percent Change in Target Lesion Tumor Burden in Patients Who Received BAC per IRC



NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
*BOR is based on status of target, nontarget, and new lesions; so, a 30% to 100% reduction in target lesion tumor burden does not necessarily indicate a BOR of PR or CR.
**Target lesions were not evaluable for two patients after baseline, and one patient had no imaging after baseline; these patients are represented with 0% change from baseline. One patient had a 4.6% reduction in target lesion tumor burden, but BOR was NE because the only post-baseline imaging was acquired too soon after first treatment (<4 weeks) to qualify for SD.

Additional Information

Table 1. Study Participant Disposition by Enrollment and Treatment

	Enrolled (N=144)	Treated (N=123)
PHP arm	102	91
BAC arm	42	32
Dacarbazine	1	0
Ipilimumab	7	1
Pembrolizumab	8	6
TACE	26	25

Table 2. Demographics for Participants in the ITT Population

	PHP (n=102)	BAC (n=42)
Age at baseline, years		
Mean	58.1	61.7
Median	62.0	62.0
Min, Max	20.0, 79.0	31.0, 82.0
Sex, n (%)		
Male	52 (51.0)	17 (40.5)
Female	50 (49.0)	25 (59.5)
Time since diagnosis of liver metastases, months		
Median	5.65	2.53
Min, Max	0.2, 109.3	0.4, 26.0

ITT, intent to treat; max, maximum; min, minimum.

Table 3. Best Overall Response in the Treated Population

	PHP (n=91)	BAC (n=32)
Complete response, n (%)	7 (7.7)	0
Partial response, n (%)	26 (28.6)	4 (12.5)
Stable disease, n (%)	34 (37.4)	8 (25.0)
Progressive disease, n (%)	23 (25.3)	18 (56.3)
Not evaluable, n (%)	1 (1.1)	2 (6.3)
p-value (Fisher's exact test) between the two arms	0.0133	
p-value (Chi-square test) between the two arms	0.0117	

Table 4. ORR and DCR in the Treated Population

Efficacy Endpoint	PHP (n=91)	BAC (n=31)	*p* Value*
ORR, n (%)	33 (36.3)	4 (12.5)	0.0117
[95% CI]	[26.44 – 47.01]	[3.51 – 28.99]	
DCR, n (%)	67 (73.6)	12 (37.5)	0.0002
[95% CI]	[63.35 – 82.31]	[21.10 – 56.31]	

DCR, disease control rate; ORR, objective response rate.
*Chi-square test.

Table 5. DOR in the Treated Population

	PHP (n=91)	BAC (n=32)
Median DOR, months	14	NC
[95% CI]	[8.31 – 17.74]	[6.93 – NC]
Patients with confirmed CR or PR	33 (7 CR, 26 PR)	4 (all PR)
Patients with subsequent PD, n (%)	16 (48.5)	1 (25.0)
Censored, n (%)	17 (51.5)	3 (75.0)

CR, complete response; DOR, duration of response; NC, not calculable; PD, progressive disease; PR, partial response.
Data continues to mature; patients will continue to be followed for approximately 18 months.

Table 6. PFS in the Treated Population

Secondary Endpoint	PHP (n=91)	BAC (n=32)	*p* Value*
Median PFS, months	9.03	3.12	0.0003
[95% CI]	[6.34 – 11.56]	[2.89 – 5.65]	
PFS status, n (%) Events	67 (73.6)	25 (78.1)	
Censored	24 (26.4)	7 (21.9)	
Hazard ratio estimate	0.38		0.0001
[95% CI]	[0.232 – 0.628]		

PFS, progression-free survival.
Data continues to mature; patients will continue to be followed for approximately 18 months.

Table 7. Exploratory Comparison of OS in the Treated Population

Secondary Endpoint	PHP (n=91)	BAC (n=32)	*p* Value*
Median OS, months	19.25	14.49	0.1479
[95% CI]	[16.72 – 24.35]	[11.10 – 19.78]	
OS status, n (%) Events	67 (73.6)	25 (78.1)	
Censored	24 (26.4)	7 (21.9)	
Hazard ratio estimate	0.700		0.1437
[95% CI]	[0.434 – 1.129]		

*Chi-square test.
Data continues to mature; patients will continue to be followed for approximately 18 months.

Table 8. Serious TEAEs Occurring in >5% of PHP Patients

Category	Focus Trial (n=94)
Bone marrow suppression, n (%)	21 (22.3)
Thrombocytopenia, %	14.9
Neutropenia, %	10.9
Leukopenia, %	4.2
Respiratory and thoracic disorders, including hemothorax, pulmonary edema, and pleural effusion, n (%)	6 (6.4)
Cardiac disorders, including arrhythmias and cardiac arrest, n (%)	5 (5.3)

References

1. Jovanovic P, et al. *Int J Clin Exp Pathol*. 2013;6(7):1230-1244.
2. Bakalian S, et al. *Clin Cancer Res*. 2008;14(4):951-956.

Conclusions

- PHP demonstrates superior ORR, DCR, PFS, and OS in comparison with BAC in the treatment of hepatic metastases from ocular melanoma
  - ORR was nearly 3 times better in PHP vs. BAC (36.3% vs 12.5%)
  - DCR was approximately doubled in favor of PHP vs. BAC (73.6% vs 37.5%)
  - PFS was nearly tripled in PHP vs BAC (9.03 mos vs. 3.12 mos)
  - The PHP arm showed a statistically significant advantage over BAC in ORR, DCR, and PFS
  - PHP patients had a durable response of 14 mos
  - Adverse events were well-described and manageable
- This therapy offers a potential option for patients with this rare indication that is associated with a poor prognosis and few treatment options

Disclosures

Jonathan S. Zager has received medical advisory board, research, and grant funding from Delcath Systems Inc; International Lead PI FOCUS Trial.

Presented at the ASCO Annual Meeting; June 3-7, 2022; Chicago, IL.

Acknowledgments

Medical writing and editorial support were provided by Chantel Cadwell, PhD, and Michele Salernitano of Ashfield MedComms, an Ashfield Health company, and were funded by Delcath Systems, Inc.