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



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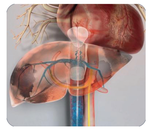
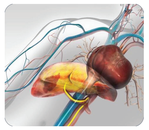
## Background

- 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

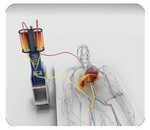
**Liver Isolated Via Double Balloon Catheter in Inferior Vena Cava**



**Melphalan Infused Directly Into Liver Via Catheter In Hepatic Artery**



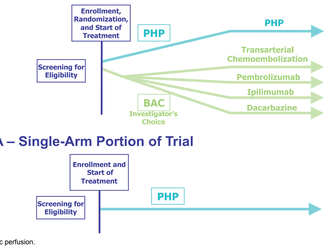
**Blood Exiting the Liver Filtered by Proprietary Extracorporeal Filters**



## 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

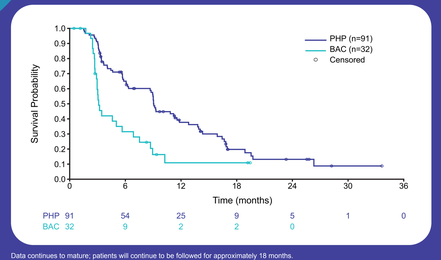
### Key Exclusion Criteria

- 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

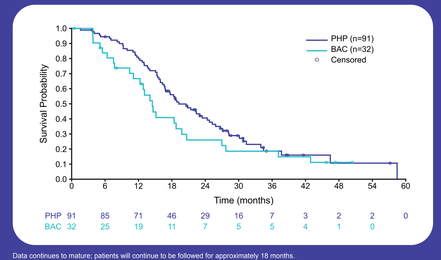
- A total of 144 patients were enrolled overall; 102 were assigned to PHP (301: n=43; 301A: n=59) and 42 were assigned to BAC; 91 patients received PHP treatment (301: n=40; 301A: n=51) and 32 patients received BAC (Table 1; Figure 1)
- ORR among treated PHP patients was 36.3% and among treated BAC patients 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**



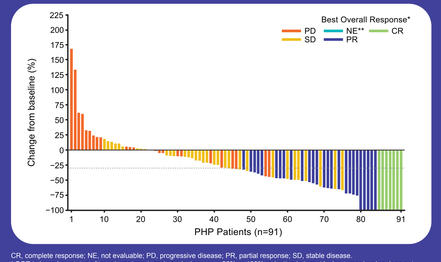

Data continues to mature; patients will continue to be followed for approximately 18 months.

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



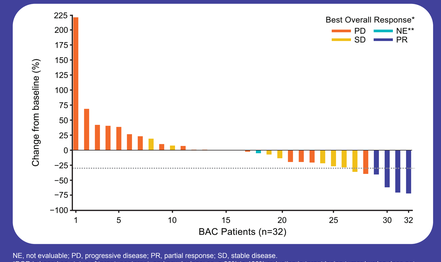

Data continues to mature; patients will continue to be followed for approximately 18 months.

**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.