Percutaneous Hepatic Perfusion with Administration of Melphalan Hydrochloride

ICD-10 Coordination and Maintenance Committee Meeting

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Ocular Melanoma

- Ocular melanoma (OM) is a very rare form of cancer that affects melanocytes in the eye. Approximately 5% of all melanomas are ocular. The majority (95%) of OMs have a uveal origin. The US incidence is approximately 1500 to 1600 cases per year[1]
- Most common treatment options for primary OM include surgery, plaque brachytherapy, and/or particle beam radiotherapy.[2] There are no local or systemic chemotherapeutic agents that treat primary OM or adjuvant treatments that prevent recurrence or metastatic disease following resection of the primary tumor.
- Approximately half of the patients with OM will develop metastatic disease, primarily due to the inability to treat early micro-metastases of the primary tumor. The metastases occur predominantly in the liver (approximately 90% of patients)[3], often with a diffuse or miliary pattern, and less commonly to the lungs and bones

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Metastatic Ocular Melanoma (mOM)

- Patients diagnosed with OM require periodic surveillance for metastatic recurrence. Once a patient develops metastatic OM (mOM), the prognosis and outcomes are poor, with a median survival of 10 to 12 months[4,5]
- OM frequently disseminates to the liver through the blood circulation. Approximately half of all metastatic disease is detected within 5 years of primary diagnosis although patients may die from metastasis several decades after successful treatment of the primary tumor.
- Treatment of mOM is challenging since available therapy rarely produces durable responses or significant survival benefits. Liver-directed therapies are often incorporated in treatment regimens since liver failure is most often the cause of death for patients with mOM[6]

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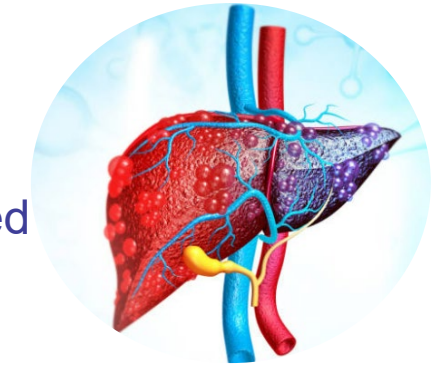
Current Treatment Overview



- Current treatment options for patients with liver-dominant mOM are either liver directed therapies such as trans arterial chemo embolization (TACE) and selective internal radioembolization (SIRT) using Yttrium-90 (Y90) spheres or systemic delivery of chemotherapeutic, immunotherapy, or biologic agents alone or in combination.
- Tumors in the liver tend to grow rapidly and are diffuse, thus, an effective treatment should ideally treat the entire liver as well as allow for retreatment. Neither TACE nor SIRT/Y90 fulfill these requirements.
- Prior to 2022, there were no FDA-approved systemic therapies for uveal melanoma in the adjuvant or metastatic settings, and no therapy was shown to improve overall survival (OS).[7] Consequently, there was no standard-of-care therapy, and participation in a clinical trial was prioritized for patients with metastatic disease.
- KIMMTRAK™ (tebentafusp-tebn), a bispecific immunotherapeutic agent, was approved in January 2022 for the treatment of a subset of patients with uveal melanoma: HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma
- Based on tebentafusp's mechanism of action it can be used in the treatment of only approximately **45% of the target patients in the US**, that is, patients who have the HLA-A*02:01 genotype.

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HEPZATO™ KIT (melphalan hydrochloride for injection/Hepatic Delivery System)- Percutaneous Hepatic Perfusion treatment for patients with mOM

- HEPZATO™ KIT (melphalan hydrochloride for injection/Hepatic Delivery System) is a single source drug/device combination product.
  - 505(b)(2) NDA re-submission, fast track designation and orphan drug designation
- Melphalan, the drug constituent part of the combination product, confers the primary mode of action.
  - Currently melphalan hydrochloride is approved at 0.25 mg/kg via IV infusion for patients with Multiple Myeloma and is not substitutable for the melphalan hydrochloride in the Hepzato Kit
  - Hepzato brand melphalan hydrochloride is seeking approval at 3.0 mg/kg via intraarterial delivery for patients with metastatic Ocular Melanoma
- Melphalan is administered via hepatic artery, has broad efficacy as an anticancer chemotherapeutic agent against a variety of tumor histologies, limited liver toxicity, a high hepatic extraction rate, a very short half-life, and an immediate effect on tumor cells.
- The Hepatic Delivery System (HDS) is the device part of the combination product. The HDS consists of an
  - Extracorporeal filtration circuit (EFC)
  - Arterial infusion catheter to deliver melphalan hydrochloride to the hepatic artery
  - Femoral access set

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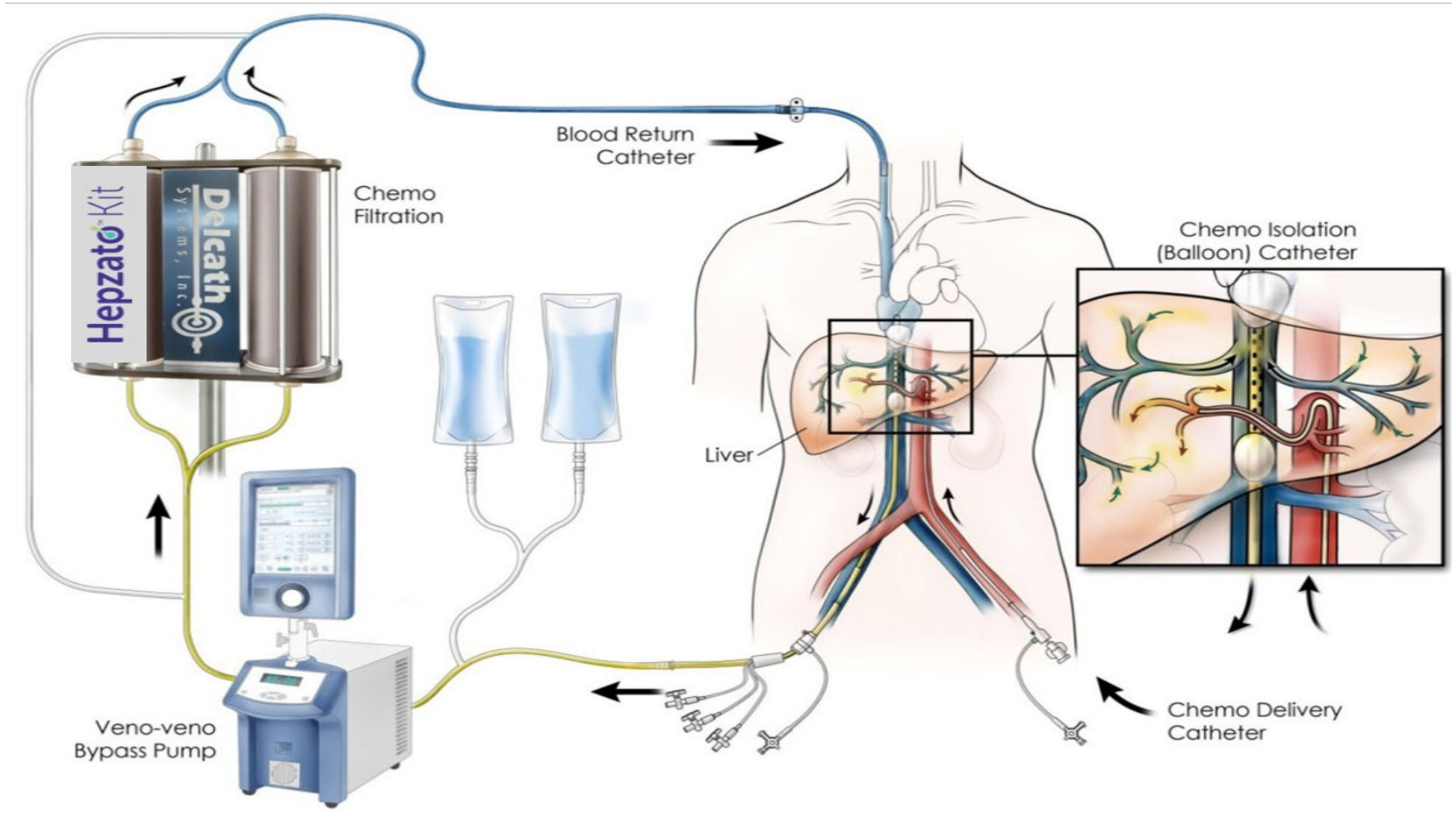
PHP Melphalan procedure description

HEPZATO™ KIT is a melphalan chemosaturation drug delivery system



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Procedural Steps

1. General anesthesia is initiated in interventional radiology suite or formal operating room. Procedure is not performed in chemotherapy suite.

2. Venous/Arterial Access

2a. The patient has an arterial line (placed for monitoring of arterial pressure), triple lumen catheter (central venous pressure), and foley catheter (for fluid management).
2b. Contralateral internal jugular vein accessed with a 10F venous return sheath.
2c. Common femoral artery (CFA) is accessed with a 5F sheath.
2d. Common femoral vein (CFV) is accessed with a 18F sheath.
2e. 5F infusion catheter placed into the hepatic artery for chemotherapy procedure.
2f. After all lines placed, patient is anticoagulated with 300 units/kg of heparin and an activated clotting time (ACT) of ≥ 400 seconds is maintained throughout the procedure.
2g. Double-balloon catheter inserted via the CFV under fluoroscopic guidance into the inferior vena cava (IVC).

3. Double Balloon Catheter Placement

3a. Double-balloon catheter is connected to extracorporeal hemofiltration circuit. Connect the hemofiltration circuit venous return line to the stopcock of the 10F venous return sheath placed in the jugular vein, normal saline flush.
3b.Venous blood aspiration from the central lumen through fenestrations in the double balloon catheter.
3c.Venous blood flows through double balloon catheter into hemofiltration pump through a bypass line.
3d. Venous blood returns to the patient through the venous return sheath into IVC.
3e. Cephalad balloon of the catheter is inflated in the right atrium and retracted into the interior vena cava (IVC)
3f. A centrifugal pump is used to achieve appropriate flow rates. The hemofiltration filters are brought online and after the cartridges are completely filled with blood (in preparation to initiate hemofiltration following chemo).

4. Inferior Vena Cava (IVC) Occlusion

4a. Fluoroscopy/venogram to confirm correct balloon positions. Venous bypass lines will be occluded.
4b. Cephalad balloon to occlude the IVC above the highest hepatic vein.
4c. Caudal balloon to occlude the IVC below the lowest hepatic vein.

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Procedural Steps

5. When the hemofiltration circuit is running adequately and the patient is hemodynamically stable intra-hepatic arterial infusion of melphalan hydrochloride (HCl) is started (3 mg/kg correct for the patient's body weight) and infused for 30 minutes.

6. Following arterial infusion, hemofiltration is performed for 30 minutes.

7. Post Melphalan HCL hemofiltration procedure
   - 7a. Discontinue filtration
   - 7b. Protamine sulphate is infused to reverse heparinization
   - 7c. Blood products are transfused to replace clotting factors if needed.
   - 7d. Deflate caudal and then cephalad balloon
   - 7e. Once patient coagulation profile normalizes, vascular sheaths are removed
   - 7f. Pressure is held on all catheter sites for 45 minutes

Total Procedure Time: 4 hours

HEPZATO KIT Procedure

- Documentation
  - The procedure will likely be performed in the O.R. or interventional radiologist suite. O.R. documentation will be in operative reports, physician operative notes, and/or technical operating room minutes. Documentation in the interventional radiologist suite will occur in interventional radiologist reports, physician procedural notes, and technical radiologist summary logs.

- The devices used in this procedure are not permanent

- The HEPZATO™ KIT procedure is a standalone procedure

- It is expected in year one of commercialization that 25% of cases will be inpatient and 75% will be outpatient

- Average # of cycles: 4.1 in FOCUS trial

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FOCUS Trial
2nd Registration Clinical Trial for Patients with mOM

FOCUS

- Multinational, multicenter, single-arm trial
- Efficacy Endpoints:
  - » Primary: Objective Response Rate (ORR) compared to meta-analysis of IO therapy
  - » Secondary: Duration of Response (DOR), Disease Control Rate (DCR), Overall Survival (OS), Progression Free Survival (PFS)
- 102 subjects enrolled, 91 completed treatments at 23 centers in the US and EU
- All patients have been treated using research protocol which requires a stay the night prior to the procedure and discharge the day after the procedure according to trial protocol
- HEPZATO Tx every 6-8 weeks up to a maximum of 6 cycles
- Initially a Randomized Clinical Trial (RCT) against Best Alternative Care (BAC)
  - » Subsequently modified with FDA agreement to single-arm trial
  - » FDA will view the comparisons with the 32 patient BAC arm as supportive exploratory analyses

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FOCUS Trial Analysis: Prespecified Endpoint Met

ORR Advantage Coupled With Meaningful Duration of Response

ORR and DCR in the Treated Population

Efficacy Endpoint	PHP (n=91)	BAC (n=32)	*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.

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.

26.44% >> 8.3% prespecified threshold*
Exploratory comparison versus BAC supportive

14 Month Duration of Response
7 Complete Responses

* Meta-analysis of checkpoint inhibitors (476 patients,16 publications) calculated a 95% Confidence Interval for ORR of 3.6% - 8.3%"

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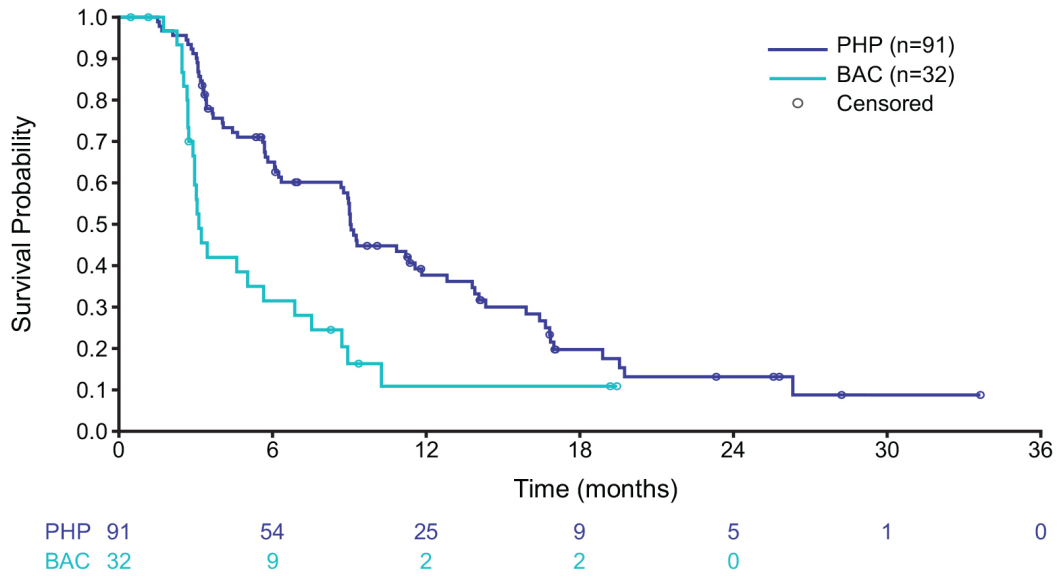
Progression Free Survival

Kaplan Meier Curves in Treated Populations

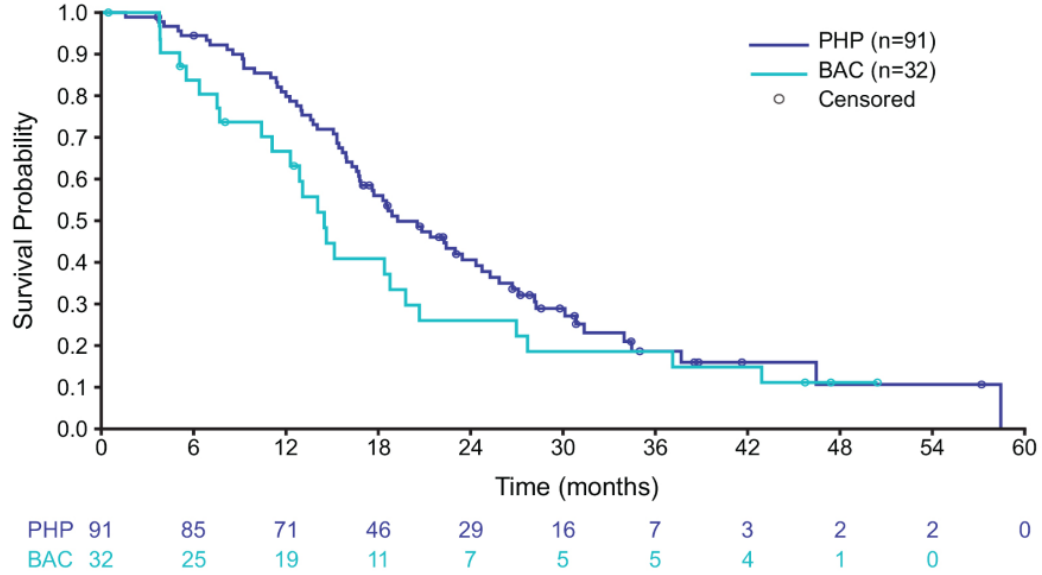


Secondary Endpoint	PHP (n=91)	BAC (n=32)	*p* Value*
Median PFS, months	9.03	3.12	0.0003
[95% CI]	[6.34 – 11.56]	[2.89 – 5.65]	
PFS status, n (%) Events	67 (73.6)	25 (78.1)	
Censored	24 (26.4)	7 (21.9)	
Hazard ratio estimate	0.38		0.0001
[95% CI]	[0.232 – 0.628]		

PFS, progression-free survival.

Exploratory comparison versus BAC supportive

Overall Survival



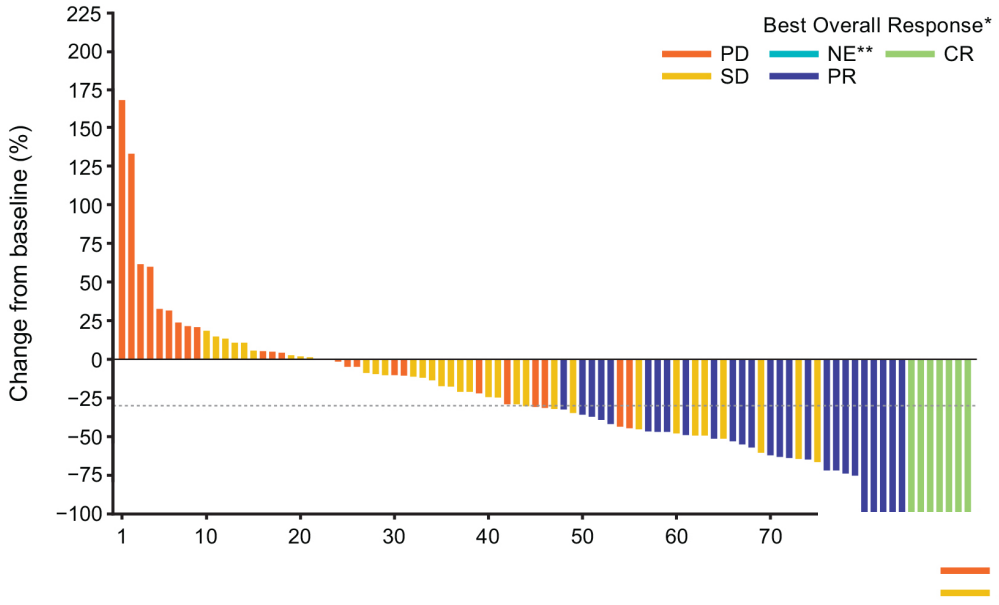
Secondary Endpoint	PHP (n=91)	BAC (n=32)	*p* Value*
Median OS, months	19.25	14.49	0.1479
[95% CI]	[16.72 – 24.35]	[11.10 – 19.78]	
OS status, n (%) Events	67 (73.6)	25 (78.1)	
Censored	24 (26.4)	7 (21.9)	
Hazard ratio estimate	0.700		0.1437
[95% CI]	[0.434 – 1.129]		

*Chi-square test.

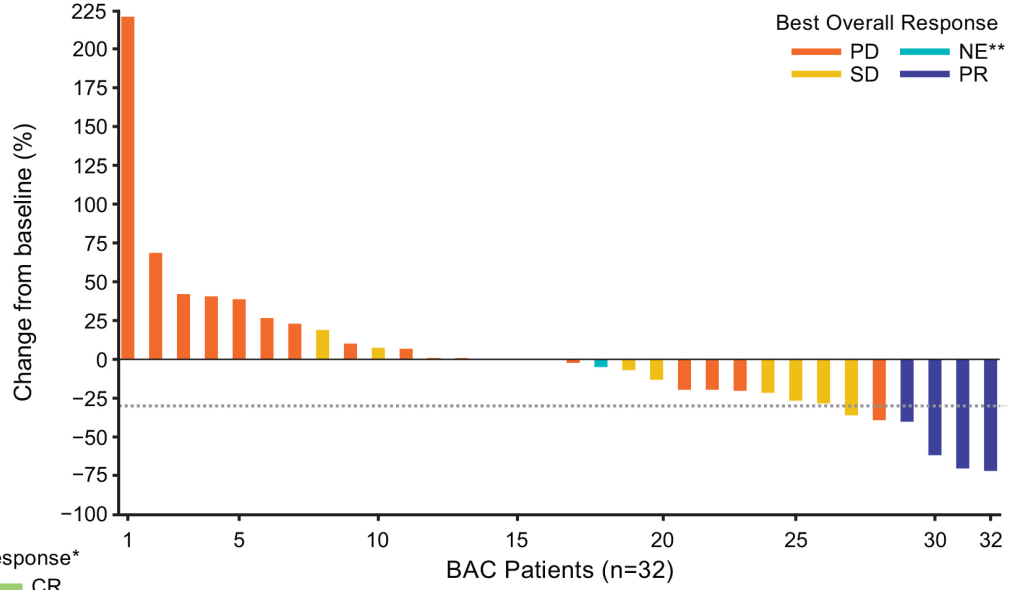
Best Percent Change in Target Lesion Tumor Burden Greater with PFS than with BAC

- 7.7 % Complete Response in the FOCUS trial

PHP Patients (n=91)



BAC Patients (n=32)



Best Overall Response*
PD
NE**
CR
SD
PR

Exploratory comparison versus BAC supportive

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

* Best Overall Response (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.

** Not evaluable target lesions are represented with a 0% change from baseline.

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Adverse Events Are Predictable and Manageable

- The AEs that do occur are predictable, well-known and are manageable by the treating physicians who are familiar with these types of events that occur with melphalan (chemotherapeutic agents).
- There is a fraction of melphalan that does enter the circulation; however, this systemic exposure is approximately 80% lower than equivalent IV dose (ie, 3 mg/kg) and similar to the labeled dose for Alkeran ((melphalan hydrochloride) for injection) indicated for multiple myeloma (0.5 mg/kg).

Serious TEAEs Occurring in >5% of PHP Patients

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

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References

1. Rossi E, Croce M, Reggiani F, Schinzari G, Ambrosio M, Gangemi R, Tortora G, Pfeffer U, Amaro A. Uveal Melanoma Metastasis. Cancers (Basel). 2021 Nov 13;13(22):5684. doi: 10.3390/cancers13225684. PMID: 34830841; PMCID: PMC8616038.
2. Savan et al 2020
3. Nathan P, Hassel JC, Rutkowski P, Baurain JF, Butler MO, Schlaak M, Sullivan RJ, Ochsenreither S, Dummer R, Kirkwood JM, Joshua AM, Sacco JJ, Shoushtari AN, Orloff M, Piulats JM, Milhem M, Salama AKS, Curti B, Demidov L, Gastaud L, Mauch C, Yushak M, Carvajal RD, Hamid O, Abdullah SE, Holland C, Goodall H, Piperno-Neumann S; IMCgp100-202 Investigators. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021 Sep 23;385(13):1196-1206. doi: 10.1056/NEJMoa2103485. PMID: 34551229.
4. Khoja L, Atenafu EG, Suciu S, Leyvraz S, Sato T, Marshall E, Keilholz U, Zimmer L, Patel SP, Piperno-Neumann S, Piulats J, Kivelä TT, Pfoehler C, Bhatia S, Huppert P, Van Iersel LBJ, De Vries IJM, Penel N, Vogl T, Cheng T, Fiorentini G, Mouriaux F, Tarhini A, Patel PM, Carvajal R, Joshua AM. 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 Aug 1;30(8):1370-1380. doi: 10.1093/annonc/mdz176. PMID: 31150059.
5. Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. Melanoma Res. 2019 Dec;29(6):561-568. doi: 10.1097/CMR.0000000000000575. PMID: 30664106; PMCID: PMC6887637.
6. Wilson et al 2001
7. Carvajal RD, Nathan P, Sacco JJ, Orloff M, Hernandez-Aya LF, Yang J, Luke JJ, Butler MO, Stanhope S, Collins L, McAlpine C, Holland C, Abdullah SE, Sato T. Phase I Study of Safety, Tolerability, and Efficacy of Tebentafusp Using a Step-Up Dosing Regimen and Expansion in Patients With Metastatic Uveal Melanoma. J Clin Oncol. 2022 Jun 10;40(17):1939-1948. doi: 10.1200/JCO.21.01805. Epub 2022 Mar 7. PMID: 35254876; PMCID: PMC9177239.
8. Tulokas S, Mäenpää H, et al. Selective internal radiation therapy (SIRT) as treatment for hepatic metastases of uveal melanoma: a Finnish nation-wide retrospective
9. Shibayama Y, Namikawa K, Sone M, et al. Efficacy and toxicity of transarterial chemoembolization therapy using cisplatin and gelatin sponge in patients with liver metastases from uveal melanoma in an Asian population. Int J Clin Oncol. 2017 Jun;22(3):577-584. doi: 10.1007/s10147-017-1095-0. Epub 2017 Jan 31. PMID: 28144882
10. Van Iersel LB, Verlaan MR, Vahrmeijer AL, et al. Hepatic artery infusion of high-dose melphalan at reduced flow during isolated hepatic perfusion for the treatment of colorectal metastases confined to the liver: a clinical and pharmacologic evaluation. Eur J Surg Oncol. 2007;33:874–81.
11. Meta-analysis: Data on file

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