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# Percutaneous Hepatic Perfusion (PHP) with Melphalan versus Best Alternative Care (BAC) in Patients with Unresectable Hepatic Metastases from Melanoma: A *Post-hoc* Analysis of PHP-randomized vs BAC-to-PHP Crossover vs BAC-only Patients

H. Richard Alexander, Jr. on behalf of the CS-PHP Investigators (University of Maryland School of Medicine, Baltimore, MD)

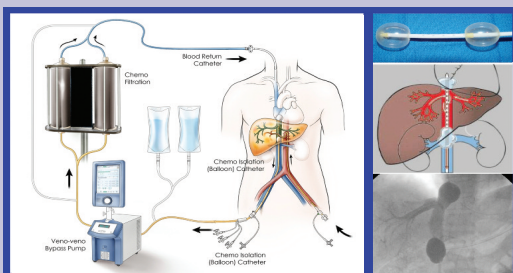
## Background

- The prognosis for patients with liver-dominant metastatic melanoma is dismal with a survival time of approximately 2 months.<sup>1</sup>
- Recently introduced drugs are limited by toxicity, long induction periods (e.g., ipilimumab) or applicability (e.g., vemurafenib):
  - vemurafenib is an inhibitor of BRAF mutations, but these mutations do not occur in ocular melanoma and are evident in only a subset of patients with cutaneous melanomas (40% to 60%).<sup>2</sup>
- There are no agents that meaningfully alter the natural history of metastatic melanoma.
- Regional therapies deliver high-dose chemotherapy to the whole organ while limiting unwanted systemic toxicity.

## Chemosaturation-PHP\*

- Isolates the liver from the systemic circulation using a system of special catheters introduced percutaneously.
- Infusion via the proper hepatic artery allows perfusion of the entire hepatic parenchyma.
- The procedure allows for considerable dose escalation to the cancer-burdened organ and provides treatment for both established and micrometastatic disease.
- Hepatic venous effluent is captured via a double-balloon catheter positioned in the retrohepatic vena cava, filtered to remove chemotherapeutic agents, and then returned to the systemic circulation.<sup>3</sup>
- The procedure is minimally invasive and repeatable.

\*Delcath Systems, Inc., NY, NY



## Purpose

- A prospective randomized multicenter study compared melphalan PHP versus BAC in patients with unresectable hepatic metastases from ocular or cutaneous melanoma and showed a highly significant advantage for PHP in terms of the primary endpoint, hepatic PFS, and multiple secondary endpoints.<sup>4</sup>
- We present an exploratory *post-hoc* analysis of patients assigned to BAC who crossed over to PHP after disease progression (BAC-to-PHP crossover) versus those who did not (BAC-only) versus PHP-randomized patients.

## Patient population

- Proven ocular or cutaneous metastatic melanoma predominantly in the liver parenchyma.
- Limited extra-hepatic disease.
- Adequate liver function:
  - total serum bilirubin <3.0 mg/dL
  - prothrombin time within 2 seconds of ULN
  - liver function tests ≤10 x ULN.
- No portal hypertension.

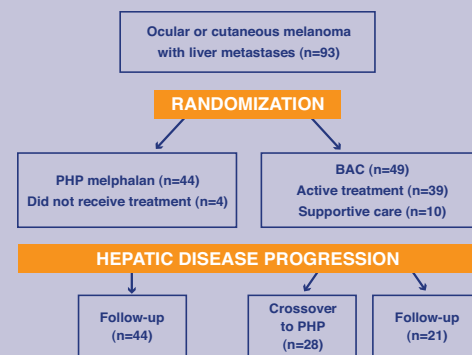
## Study treatments

- Melphalan PHP:
  - 3.0 mg/kg as a 30-minute intra-arterial infusion<sup>3</sup>
  - an additional 30 minutes of extracorporeal filtration at end of infusion (washout)
  - under general anesthesia
  - allowed up to 6 treatments, repeated every 4–8 weeks.
- Best alternative care (BAC):
  - investigator's choice of systemic, regional or other appropriate therapy
  - crossover to PHP permitted after hepatic progression (if patients still met eligibility criteria).

## Study design and endpoints

- Randomized, open-label, multicenter phase 3 study.
- Study endpoints:
  - Primary**
    - hepatic progression-free survival (hPFS) (RECIST)
    - defined as time from randomization to hepatic disease progression or death.
  - Secondary**
    - hepatic objective response rate
    - overall survival
    - safety.

## Patient flowchart



## Baseline characteristics

Characteristic	PHP-randomized (n=44)	BAC (n=49)		
		Total (n=49)	BAC-to-PHP crossover (n=28)	BAC only (n=21)
Median age, years	55	56	56	57
Primary tumor site, %				
Ocular	89	88	82	95
Cutaneous	11	12	18	5
Hepatic tumor burden, %				
<50%	77	78	86	67
≥50%	18	22	14	33
Unknown	5	0	0	0
Extrahepatic sites, %	27	33	36	29
Previous treatment, %				
Radiation therapy	52	53	54	52
Surgery/procedure	55	65	64	67
Chemotherapy	16	14	14	14

Intent-to-treat population

## BAC treatments

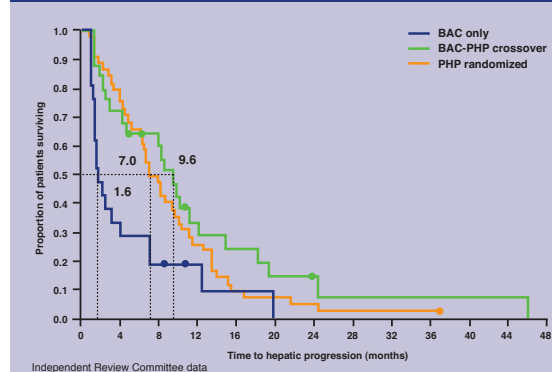
- BAC constituted:
  - active treatment (n=39)
  - supportive care/watchful waiting (n=10).
- Active treatments:
  - Temozolomide (n=20)
  - Chemoembolization (n=10)
  - Yttrium microspheres (n=3)
  - Systemic chemotherapy (n=6).

## Exploratory analysis

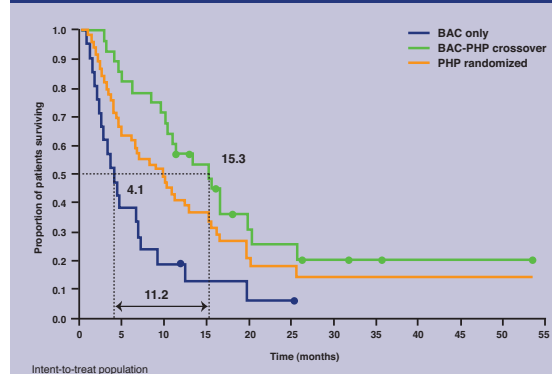
Endpoint	PHP-randomized (n=44)	BAC only (n=21)	BAC-to-PHP crossover (n=28)
Median hPFS (investigator), months	8.0	1.6	8.8
HR (crossover vs BAC-only)			0.32
Median hPFS (IRC), months	7.0	1.6	9.6
HR (crossover vs BAC-only)			0.44
Median overall survival, months	9.8	4.1	15.3
HR (crossover vs BAC-only)			0.33
Still alive as of 31 March 2011	4	3*	7
Follow-up: 9.7–53.5 months			

\*1 patient crossed over but never received PHP; Intent-to-treat population; Data as of 31 March 2011 IRC, independent review committee

## Exploratory analysis: hPFS



## Exploratory analysis: Overall survival



## Most common peri-procedural\* grade 3/4 AEs

Percentage of patients	PHP-randomized (n=40)	BAC-to-PHP crossover (n=25)
Platelet count decreased	73	80
Hemoglobin decreased	63	60
aPTT prolonged	30	16
AST increased	30	8
Blood calcium decreased	20	8
ALT increased	10	8
Blood bilirubin increased	10	8
Back pain	10	0

\*Day of treatment through to day 3 post-treatment; Safety population

## Most common in-cycle\* grade 3/4 AEs

Percentage of patients	PHP-randomized (n=40)	BAC-to-PHP crossover (n=25)
Neutrophil count decreased	93	92
Platelet count decreased	83	84
White blood cell count decreased	58	32
Hemoglobin decreased	55	60
Blood bilirubin increased	18	8
Febrile neutropenia	15	8
AST increased	13	12
Blood alkaline phosphatase increased	13	0
ALT increased	10	8
Blood albumin decreased	8	8

\*Day 4 post-treatment through to end of treatment cycle; Safety population

## Conclusions

- Efficacy of melphalan PHP in BAC-to-PHP crossover patients was consistent with that seen in PHP-randomized patients with hepatic metastases from melanoma.
- Crossover from BAC to PHP after hepatic disease progression led to a median 11-month survival advantage vs BAC alone.
- The safety profile of melphalan PHP in BAC-to-PHP crossover patients was similar to that seen in PHP-randomized patients.
- PHP delivery of melphalan is a new treatment option for unresectable metastatic melanoma in the liver.

## Study investigators

Marybeth Hughes, National Cancer Institute, Bethesda, MD  
 Charles W. Nutting, Swedish Medical Center, Englewood, CO  
 Jonathan S. Zager, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL  
 Mark Faries, John Wayne Cancer Institute, Santa Monica, CA  
 Gary Siskin, Albany Medical Center Hospital, Albany NY  
 Sanjiv Agarwala, St Luke's Cancer Center, Easton, PA  
 Eric Whitman, Atlantic Melanoma Center, Morristown, NJ  
 Richard Royal, University of Texas, MD Anderson Cancer Center, Houston, TX  
 James Pingpank, University of Pittsburgh, Hillman Cancer Center, Pittsburgh, PA

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