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Percutaneous Hepatic Perfusion vs. Best Alternative Care for Patients with Melanoma Liver Metastases: Efficacy Update of the Phase 3 Trial (NCT00324727)

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Background

- There is no standard of care for liver-dominant metastatic melanoma
- Regional therapies provide a way of delivering intensified treatment to the whole organ while limiting unwanted systemic toxicity
  - chemosaturation with percutaneous hepatic perfusion (CS-PHP) can deliver repeated high doses of chemotherapy to the liver using a minimally invasive approach
- A phase 3 multicenter randomized trial compared CS-PHP with melphalan to best alternative care (BAC) in patients ocular or cutaneous melanoma with metastases of the liver[1]
- We report the updated results from this study

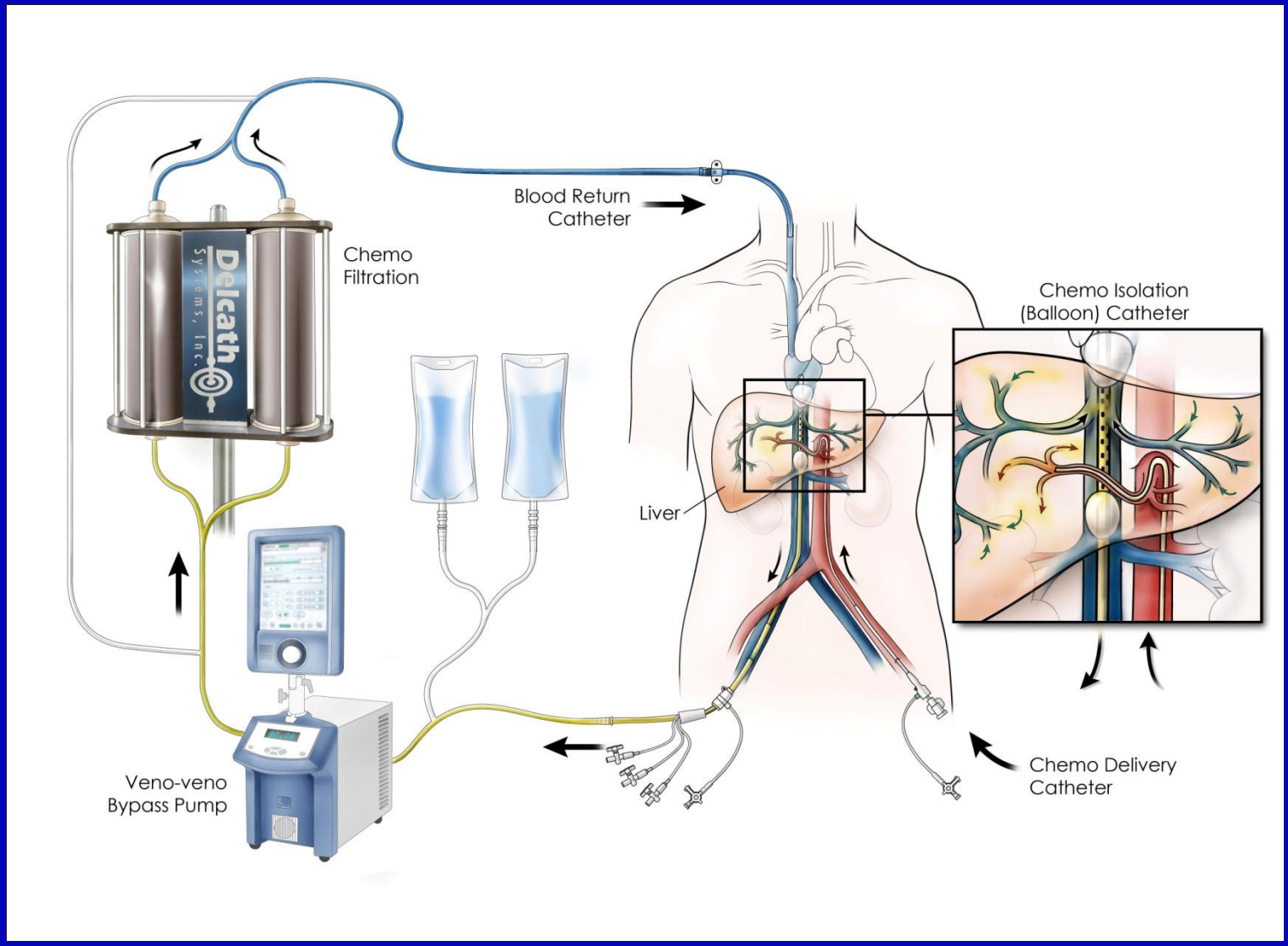
1. Pingpank J, et al. ASCO 2010;LBA 8512

Chemosaturation-PHP

- CS-PHP isolates the liver from the systemic circulation using a purpose-designed system of catheters and filters (Delcath Systems Inc, New York, NY)
- It allows direct infusion of high-dose chemotherapy into the liver via the hepatic artery, delivering a saturating dose of chemotherapy to the entire organ
- The procedure can be repeated, as it does not require a major operative procedure
- Extracorporeal filtration of the hepatic venous blood reduces systemic exposure to chemotherapy by 77% after intrahepatic delivery[2]

2. Pingpank J, et al. JCO 2005;23:3465–74

Chemosaturation-PHP procedure



Study design and endpoints

- Randomized, open-label, multicenter phase 3 study
- Primary study endpoint:
  - hepatic progression-free survival (hPFS)
- Secondary endpoints included:
  - hepatic objective response rate
  - overall survival
  - safety

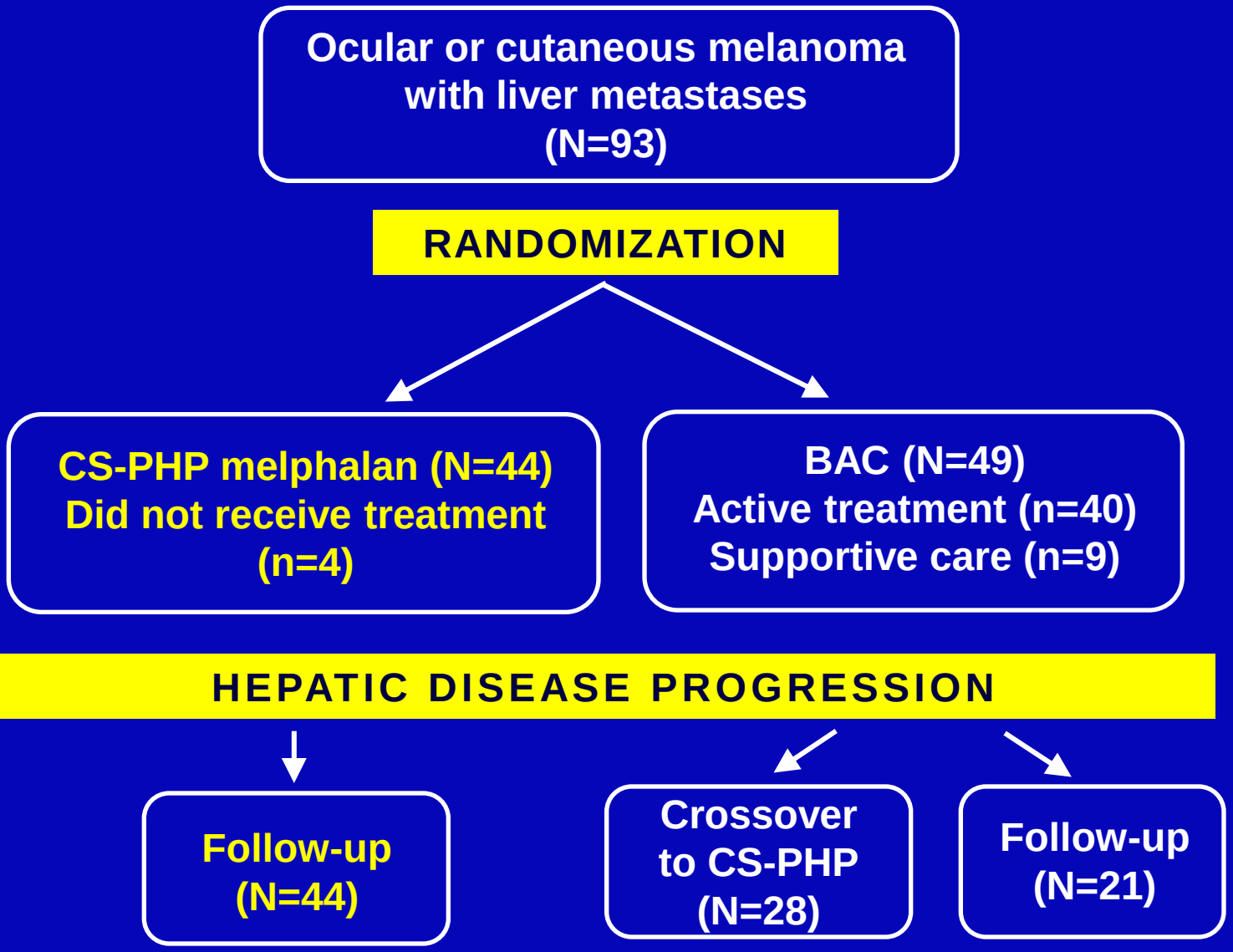
Patient population

- Proven ocular or cutaneous metastatic melanoma predominantly in the liver parenchyma
- Limited extrahepatic disease
- Adequate hepatic 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

- **CS-PHP with melphalan**
  - **melphalan 3.0 mg/kg as a 30-minute infusion via CS-PHP**
  - **an additional 30 minutes of extracorporeal filtration after each infusion was performed**
  - **CS-PHP given while patients under general anesthesia**
  - **up to six treatments repeated every 4–8 weeks**
- **Best alternative care (BAC)**
  - **investigator's choice of systemic, regional or other appropriate therapy**
  - **crossover to CS-PHP permitted after hepatic progression if patients continued to meet study eligibility criteria**

Patient flowchart



Results

Patient characteristics

- Between February 2006 and October 2009, 93 patients were enrolled at 12 US centers
  - most (88%) had ocular melanoma
  - metastases were generally confined to the liver (71%)

Baseline characteristics (ITT population)

Characteristic	CS-PHP (N=44)	BAC (N=49)	P value
Median age, years	55	56	NS
Primary tumor site, %			
Ocular	89	88	NS
Cutaneous	11	12	NS
Hepatic tumor burden, %			
<50%	77	78	NS
≥50%	18	22	NS
Unknown	5	0	
Extrahepatic sites, %	28	33	NS
Previous treatment, %			
Radiation therapy	52	53	NS
Surgery/procedure	55	65	NS
Chemotherapy	16	14	NS

ITT, intent-to-treat; NS, not significant

Treatment exposure

- Median of 3 (range, 1–6) CS-PHP treatments
- Median melphalan dose 187 mg (range, 85-220 mg)
- BAC constituted active treatment (n=40) or supportive care (n=9)
- Active BAC treatments:
  - single-agent chemotherapy (n=25, mostly temozolomide)
  - chemoembolization (n=5)
  - intrahepatic infusional chemotherapy (n=5)
  - selective internal radiation therapy (n=2)
  - other (n=3)

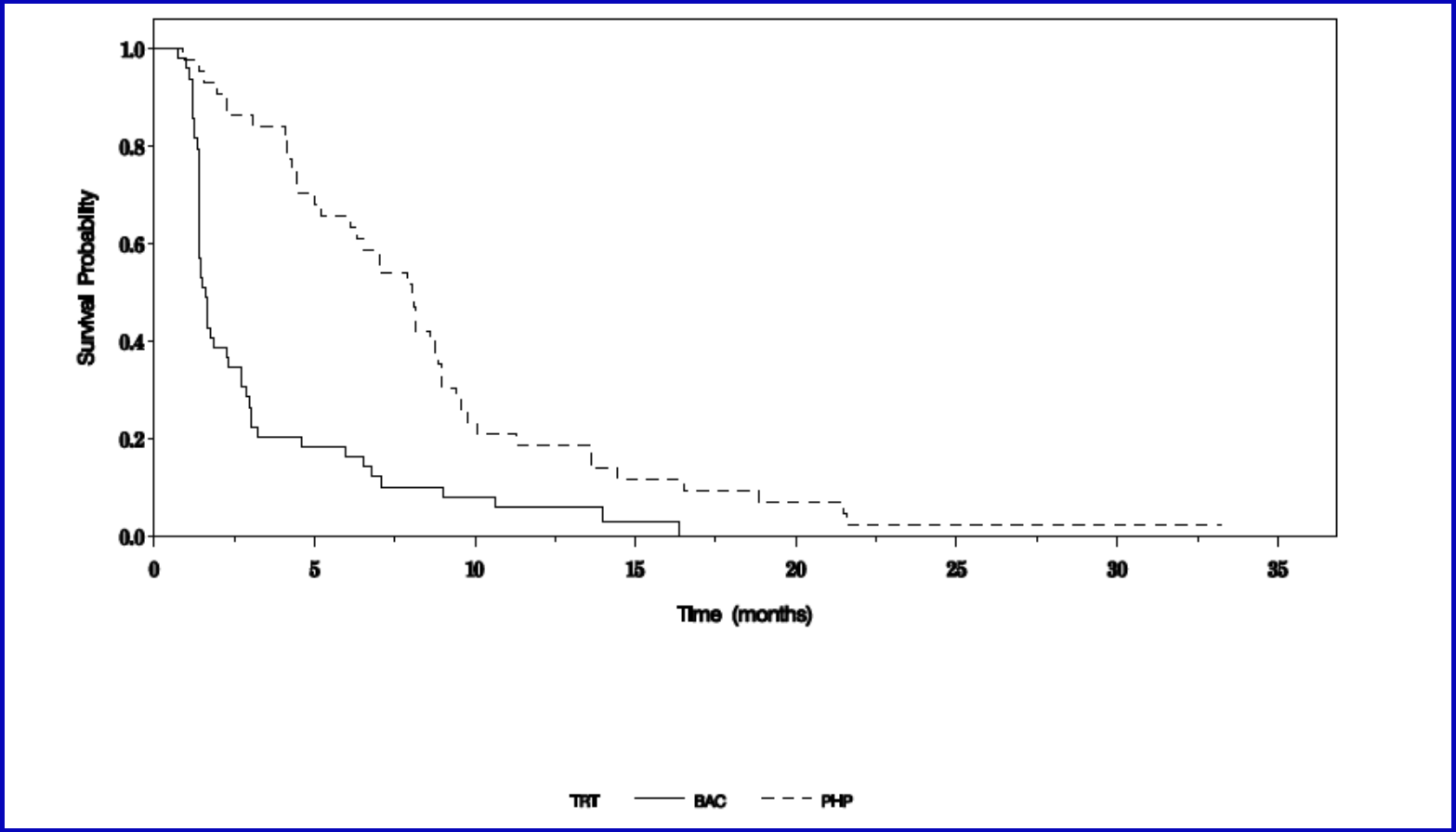
Efficacy (ITT population)

Endpoint	CS-PHP (N=44)	BAC (N=49)	Hazard ratio (95% CI)	P value
hPFS (investigator)				
Median, months	8.0	1.6	0.35 (0.23–0.54)	<0.0001
hPFS (IRC)				
Median, months	7.0	2.3	0.61 (0.40–0.94)	0.0236
Overall survival				
Median, months	9.8	9.9	1.08 (0.69–1.68)	0.740
Hepatic response rate, %	29.5	2.0	–	0.0002

IRC, independent review committee; ITT, intent-to-treat; hPFS, hepatic progression-free survival

Hepatic progression-free survival

Investigator-assessed hPFS



Intent-to-treat population

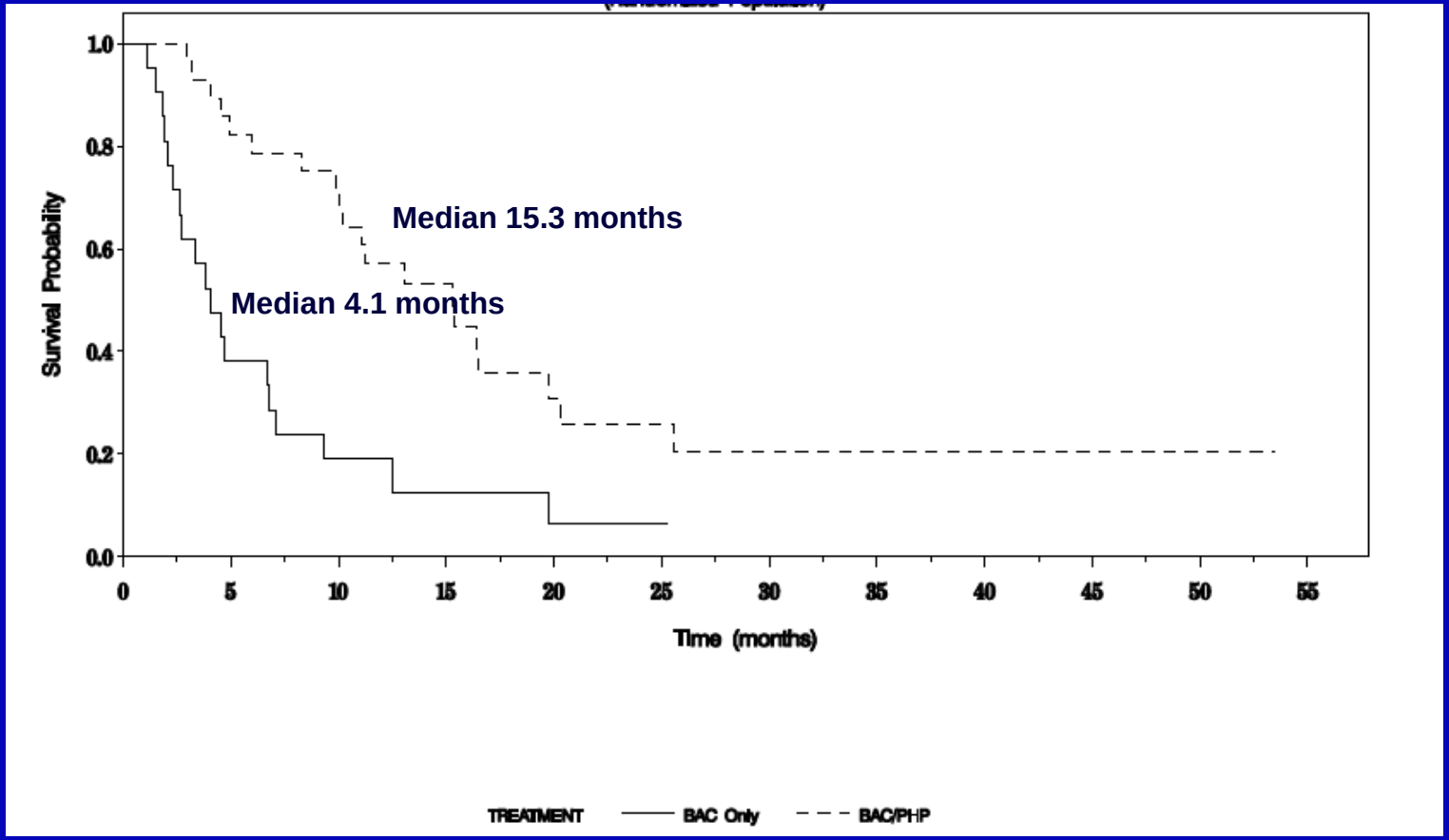
Hepatic progression-free survival

IRC-assessed hPFS

Intent-to-treat population

Overall survival: exploratory analysis

BAC alone (n=21) vs. BAC with crossover to CS-PHP melphalan (n=28)



Safety

- The most common grade 3/4 adverse events associated with CS-PHP melphalan were thrombocytopenia, anemia and hypoalbuminemia
- Reductions in neutrophil and white blood cell counts during the post-procedural period were also common
  - febrile neutropenia documented in 6 (15%) patients
- Hepatic laboratory abnormalities affected 10 to 30% of patients, and included transient peri-procedural transaminitis and hyperbilirubinemia
- Non-hematological toxicities occurred infrequently
- Three patients in the CS-PHP group died of treatment-related events:
  - hepatic failure, n=1
  - abdominal infection, n=1
  - pancytopenia, n=1

Most common adverse events (n=40)

No. of patients (%)	Grade 3/4 events	
	Peri-procedural*	Cycle toxicity†
Neutrophil count decreased	<?> (<?>)	37 (93)
Platelet count decreased	29 (73)	33 (83)
Hemoglobin decreased	22 (55)	22 (55)
White blood cell count decreased	<?> (<?>)	23 (58)
Blood albumin decreased	15 (38)	3 (8)
Febrile neutropenia	<?> (<?>)	6 (15)
AST increased	12 (30)	5 (13)
Blood alkaline phosphatase increased	<?> (<?>)	5 (13)
aPTT prolonged	12 (30)	<?> (<?>)
Blood calcium decreased	8 (20)	<?> (<?>)
ALT increased	4 (10)	4 (10)
Blood bilirubin increased	4 (10)	7 (18)
Fatigue	<?> (<?>)	<?> (<?>)

*Day of treatment through to day 3 post-treatment
†Day 4 post-treatment through to end of treatment cycle

Adverse events of special interest (n=40)

No. of patients (%)	Grade 3/4 events	
	Peri-procedural*	Cycle toxicity†
Any bleeding event	20 (50)	22 (55)
Any gastrointestinal event	0 (0)	3 (8)
Abdominal pain	0 (0)	2 (5)
Nausea	0 (0)	1 (3)
Edema	<?> (<?>)	2 (5)
Febrile neutropenia	0 (0)	6 (15)
Hypersensitivity	0 (0)	1 (3)
Any hematological event	<?> (<?>)	<?> (<?>)

*Day of treatment through to day 3 post-treatment
†Day 4 post-treatment through to end of treatment cycle

Conclusions

- Melphalan delivered via CS-PHP significantly prolonged hPFS compared with BAC in patients with liver-dominant metastatic melanoma, thereby meeting the study primary objective
  - investigator analysis of hPFS was confirmed by IRC analysis
  - CS-PHP melphalan also significantly improved hepatic response rate
  - overall survival was similar in both groups, but was confounded by crossover to CS-PHP
- Adverse events were mainly hematological and managed effectively with supportive measures
- CS-PHP with melphalan is a new treatment option for unresectable metastatic melanoma in the liver