Chemosaturation Therapy with Percutaneous Hepatic Perfusions of Melphalan Versus Standard of Care in Patients with Hepatic Metastases from Melanoma: A Randomized Multicenter Phase 3 Study

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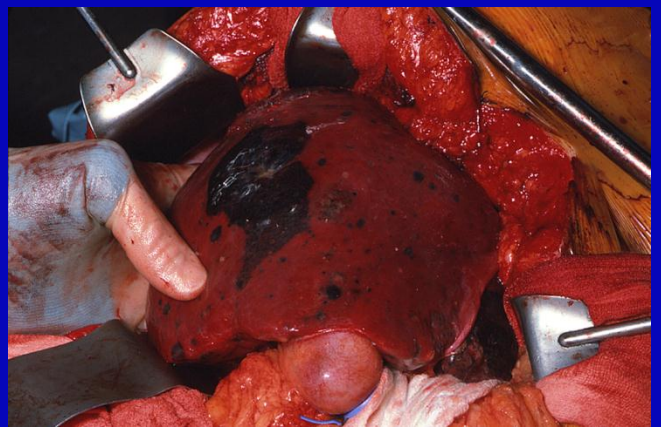
Disclosures

- **Nutting: PI**
- **Zager: PI**

Background

- There is no standard of care for liver-dominant metastatic melanoma; if untreated, the prognosis is dismal
- Recently introduced drugs are limited by tolerability, long induction periods, and applicability
- Regional therapies deliver high chemotherapy doses to the whole organ while limiting unwanted systemic toxicity



Chemosaturation-PHP*

- Percutaneously isolates the liver from the systemic circulation using a system of special catheters
- Directly infuses high-dose chemotherapy into the liver via the hepatic artery, allowing saturation of the entire organ
- Saturation of the entire organ exposes both visible and invisible (micro)metastases to chemotherapy
- Extracorporeal filtration of the hepatic venous blood reduces systemic exposure to chemotherapy[1]
- The procedure is minimally invasive and repeatable

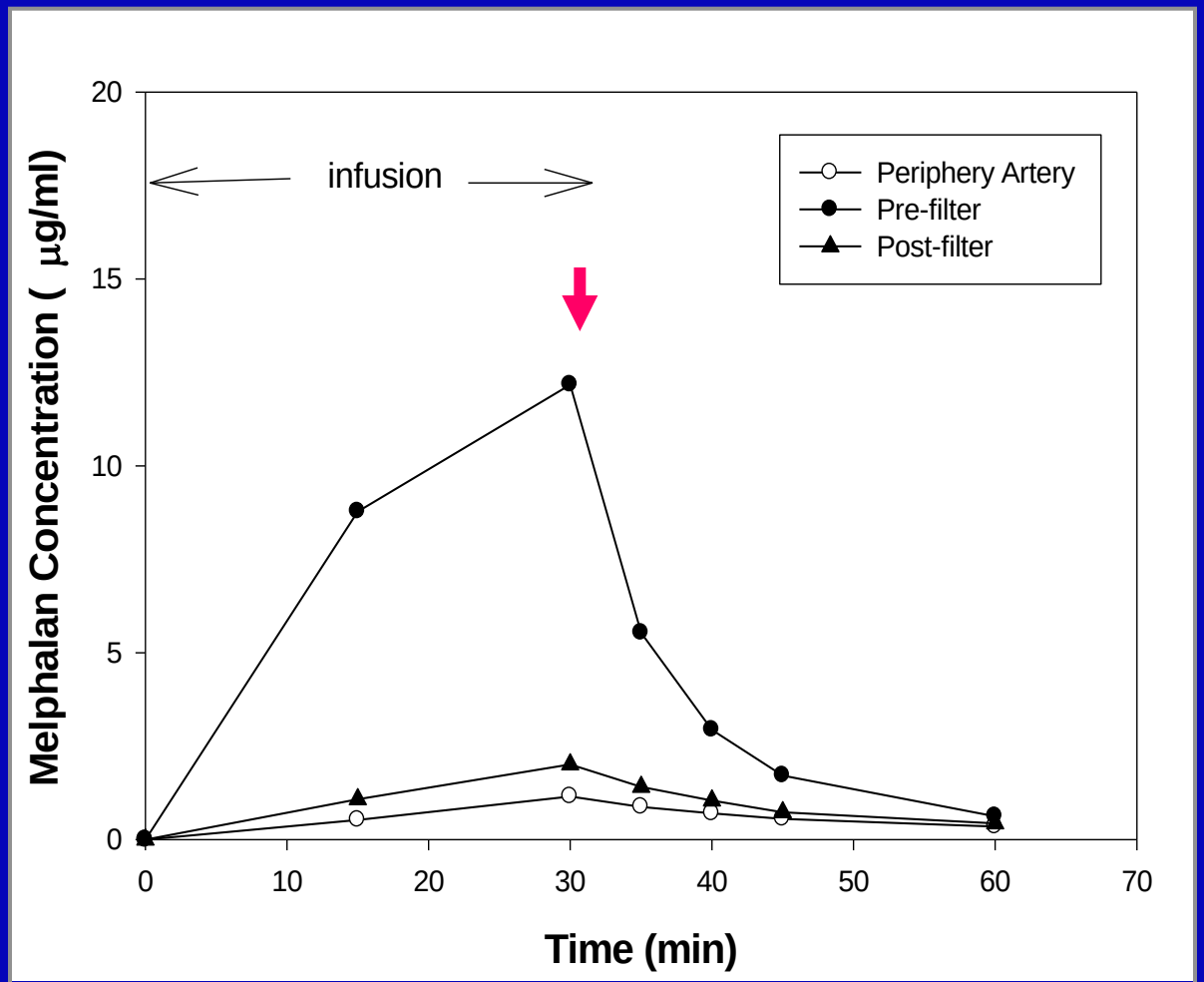
*Delcath Systems, Inc., NY, NY

1. Pingpank et al. JCO 2005;23:3465–74

Chemotherapy Levels During Therapy

Chemosaturation with PHP

Percutaneous Hepatic Perfusion



3.0 mg/kg

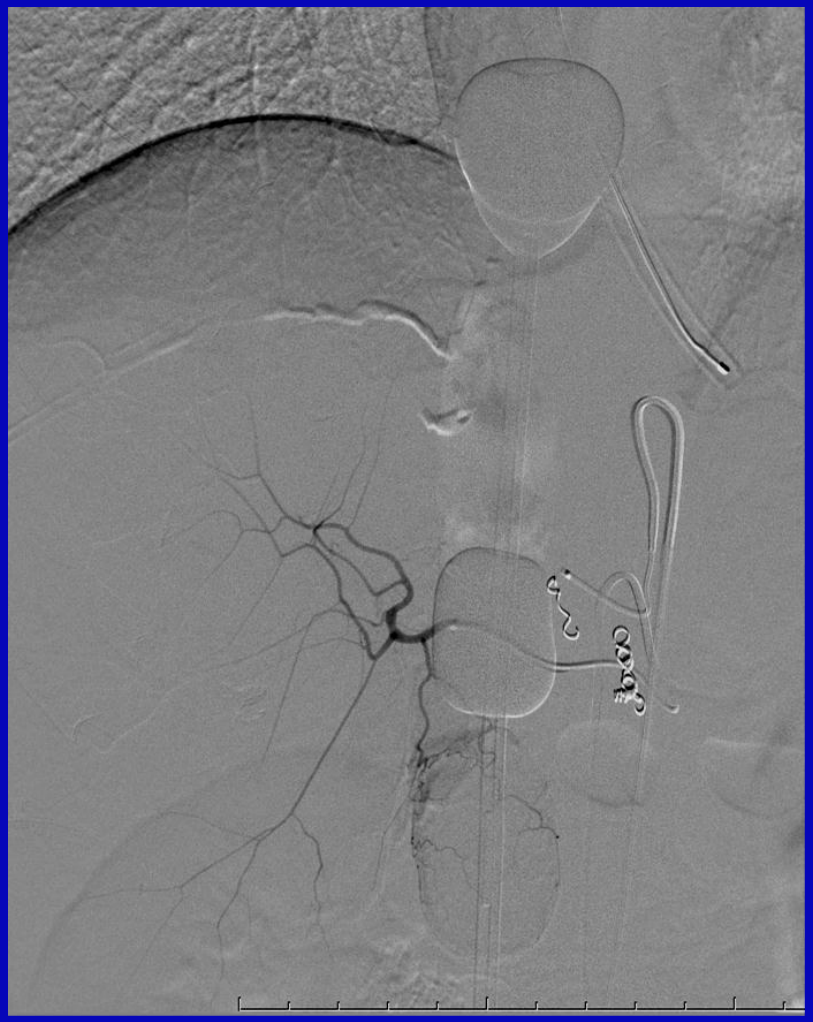
Melphalan Dosing Levels

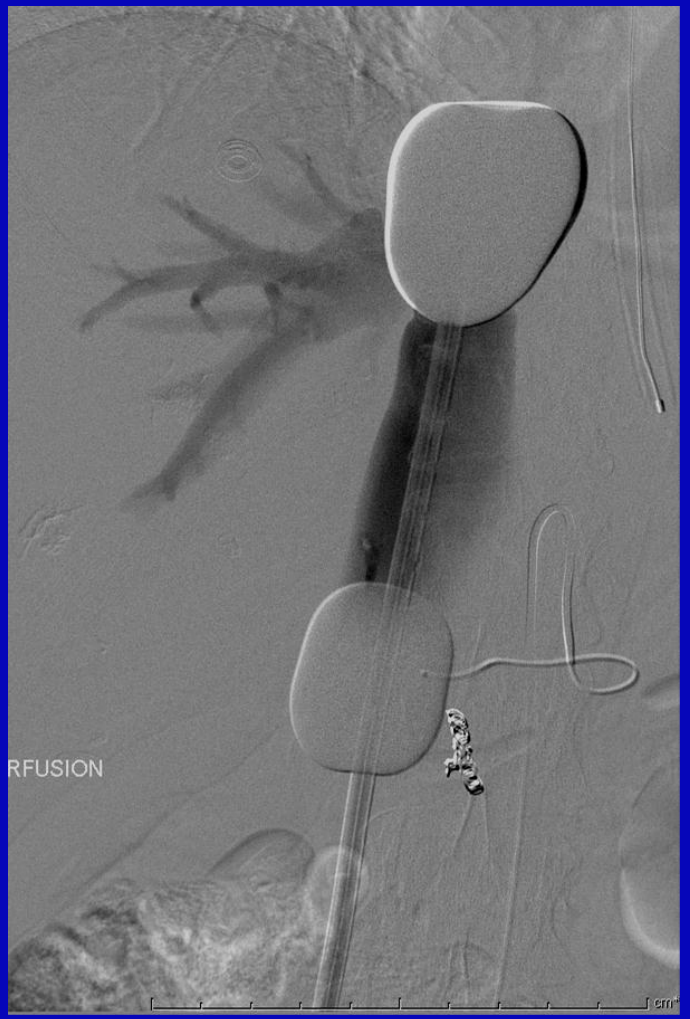
Multiple Myeloma (label)	0.25 mg/kg[1]
Chemoembolization	0.62 mg/kg[2]
Surgical Isolated Hepatic Perfusion	1.5 mg/kg[3]
Percutaneous Hepatic Perfusion (PHP™)	3.0 mg/kg
Myeloablation	2.5-3.5 mg/kg

- Drug dosing 10x higher than FDA approved dose via traditional chemotherapy
- Dose delivered to tumor is estimated at 100x that of systemic chemotherapy
- Filters remove drug from blood, significantly reducing systemic toxicities

1. Cancer PPO, p. 335, 2005 2. Hepatogastro 50(54):1919-1926, 2003 3. Clin Can Res 9:6343-6349, 2003

Angiographic considerations





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

- **CS-PHP with melphalan**
  - **3.0 mg/kg as a 30-minute intra-arterial infusion**
  - **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 CS-PHP permitted after hepatic progression (if patients still met eligibility criteria)**

Study design and endpoints

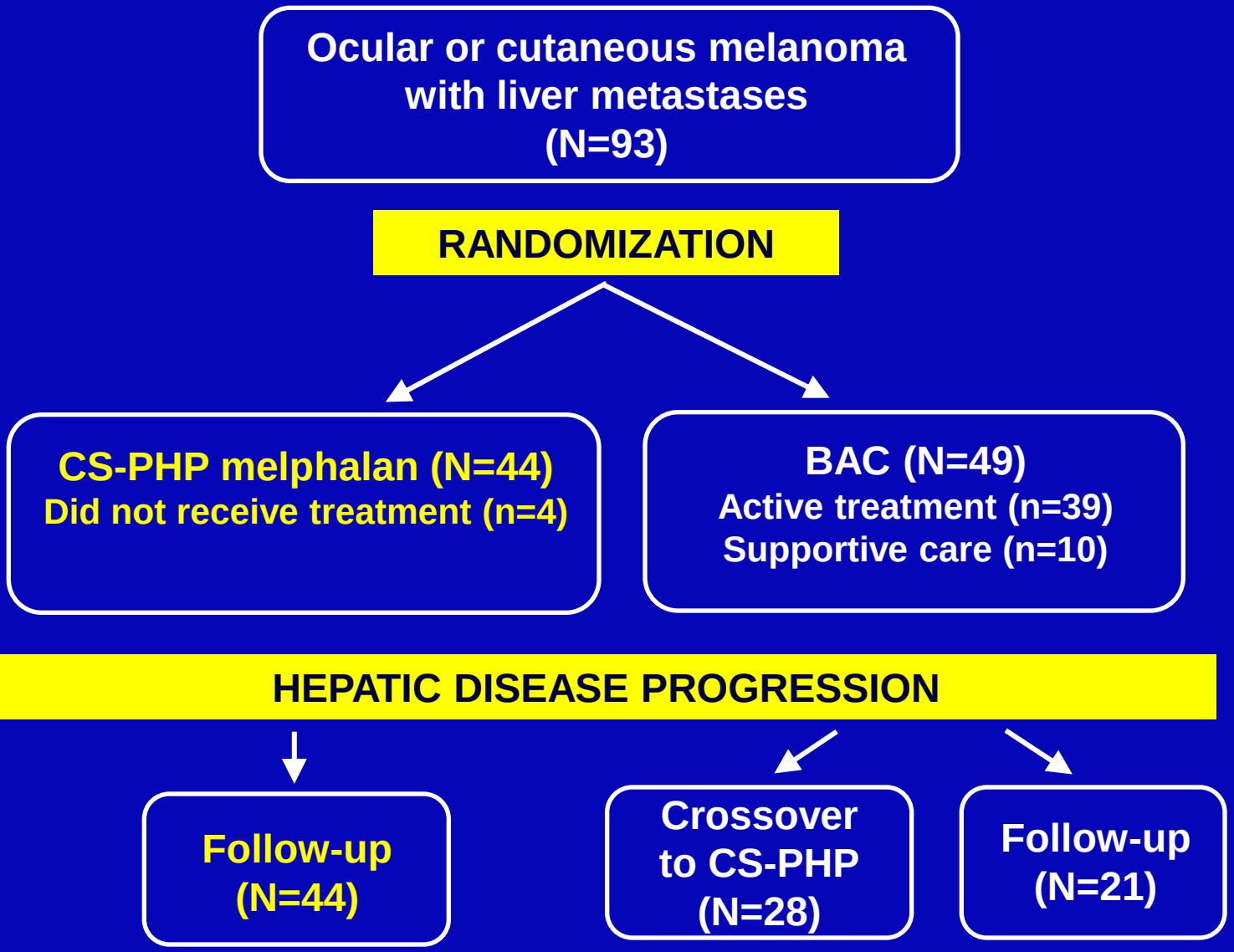
- Randomized, open-label, multicenter phase 3 study
- Study endpoints
  - Primary
    - hepatic progression-free survival (hPFS) (RECIST)
    - defined as time from randomization to hepatic disease progression or death
  - Secondary
    - hepatic objective response rate
    - overall survival
    - safety

Efficacy analysis

- **Primary analysis**
  - **Conducted after 73 hepatic progression events (per protocol)**
  - **Performed April 30 2010[1]**
- **Survival update**
  - **Updated findings as of 31 March 2011 presented**
- **Exploratory *post-hoc* analysis**
  - **BAC patients who crossed over to CS-PHP vs BAC only**

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

Patient flowchart



Results

Patient characteristics

- Between February 2006 and October 2009, 93 patients were enrolled at 10 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)
Median age, years	55	56
Primary tumor site, %		
Ocular	86	90
Cutaneous	11	10
Unknown	2	0
Hepatic tumor burden, %		
<50%	82	80
≥50%	18	20
Extrahepatic sites, %	28	33
Previous treatment, %		
Radiation therapy	52	53
Surgery/procedure	55	65
Chemotherapy	16	14

ITT, intent-to-treat

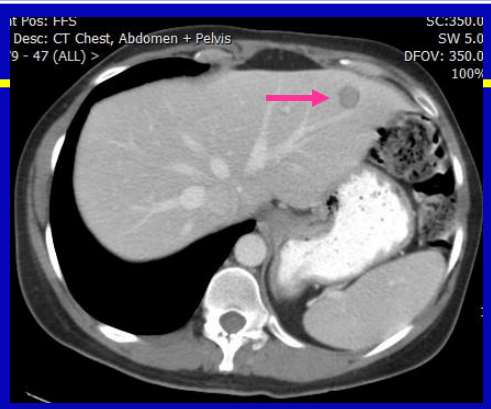
Baseline characteristics (BAC group, n=49)

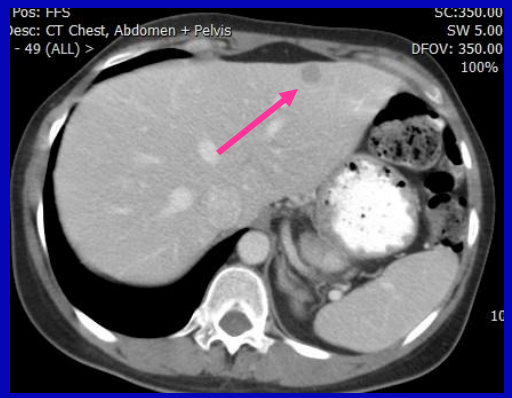
Characteristic	Crossover to CS-PHP (N=28)	Follow-up (N=21)
Median age, years	56	57
Primary tumor site, %		
Ocular	82	95
Cutaneous	18	5
Hepatic tumor burden, %		
<50%	86	67
≥50%	14	33
Extrahepatic sites, %	36	28
Previous treatment, %		
Radiation therapy	54	52
Surgery/procedure	64	67
Chemotherapy	14	14

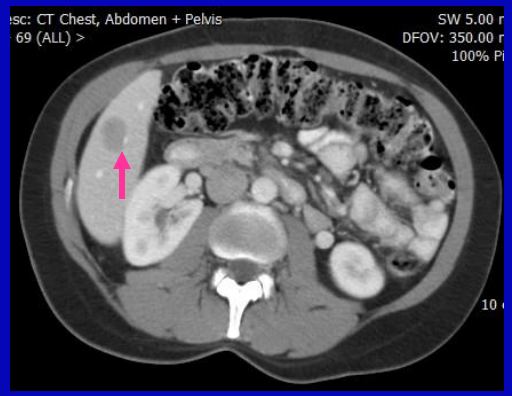
Treatment exposure

- Median of 3 (range, 1–6) CS-PHP treatments
- Median melphalan dose 187 mg (range, 85–220 mg)
- BAC constituted active treatment (n=39) or supportive care/watchful waiting (n=10)
- Active BAC treatments
  - Temozolomide (n=20)
  - Chemoembolization (n=10)
  - Yttrium microspheres (n=3)
  - Systemic chemotherapy (n=6)

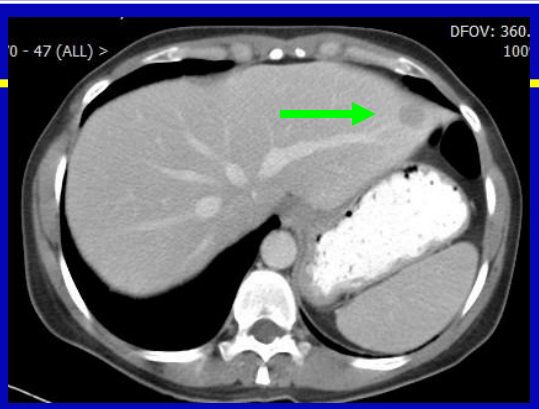
Phase III PHP results

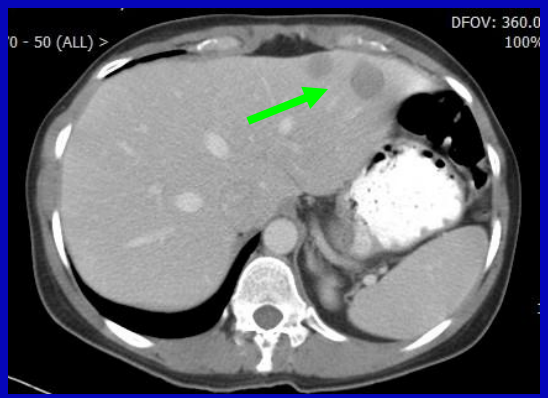


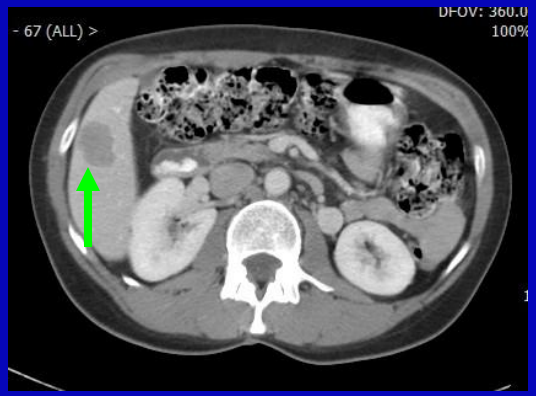




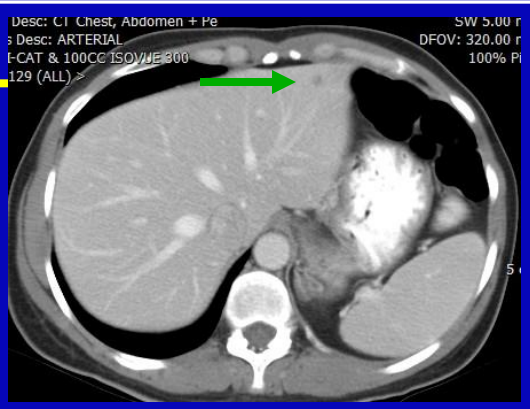
Baseline (7-24-2006)

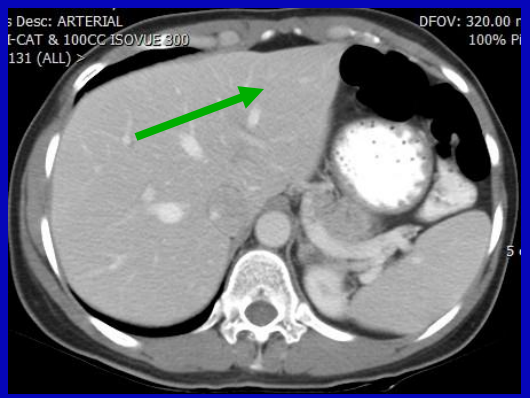


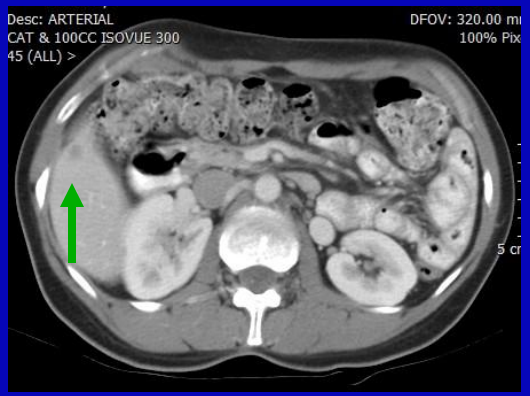




Crossover (3-13-2007)







Post treatment (4-11-2008)

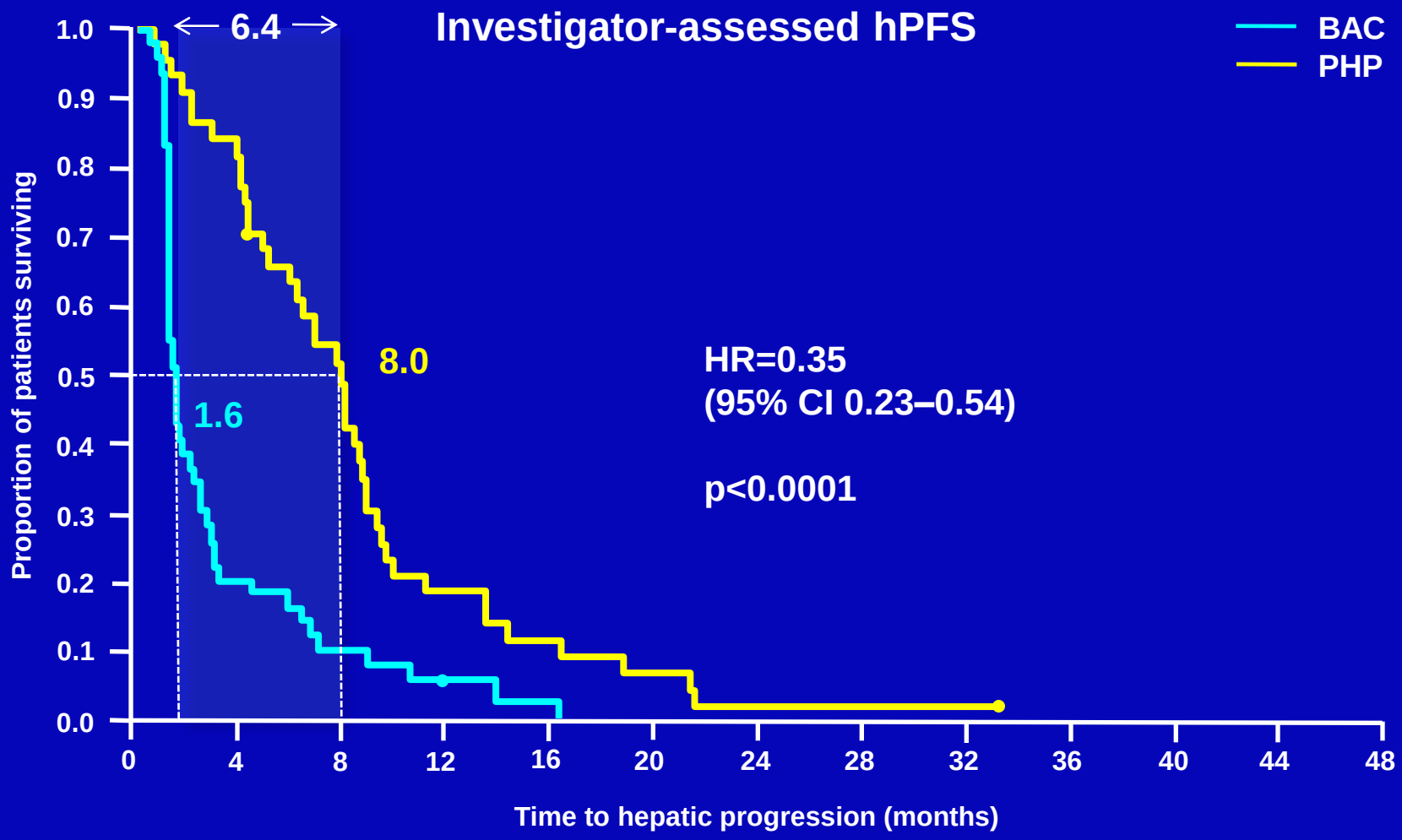
Efficacy (patients randomized to CS-PHP vs randomized to BAC)

Endpoint	CS-PHP (N=44)	BAC (N=49)	HR (95% CI)	P value
Median hPFS, months	8.0	1.6	0.35 (0.23–0.54)	p<0.0001
Median OS, months	9.8	9.9	1.08 (0.69–1.68)	p=0.7403
ORR, %	32	2	–	p=0.0001

ITT population

Data as of 31 March 2011

Hepatic progression-free survival



Intent-to-treat population

Efficacy (CS-PHP and by BAC subset)

Endpoint	CS-PHP randomized (N=44)	BAC only (N=21)	BAC-to-PHP crossover (n=28)
Median hPFS, months	8.0	1.6	8.8
HR (crossover vs BAC-only)		0.32	
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			

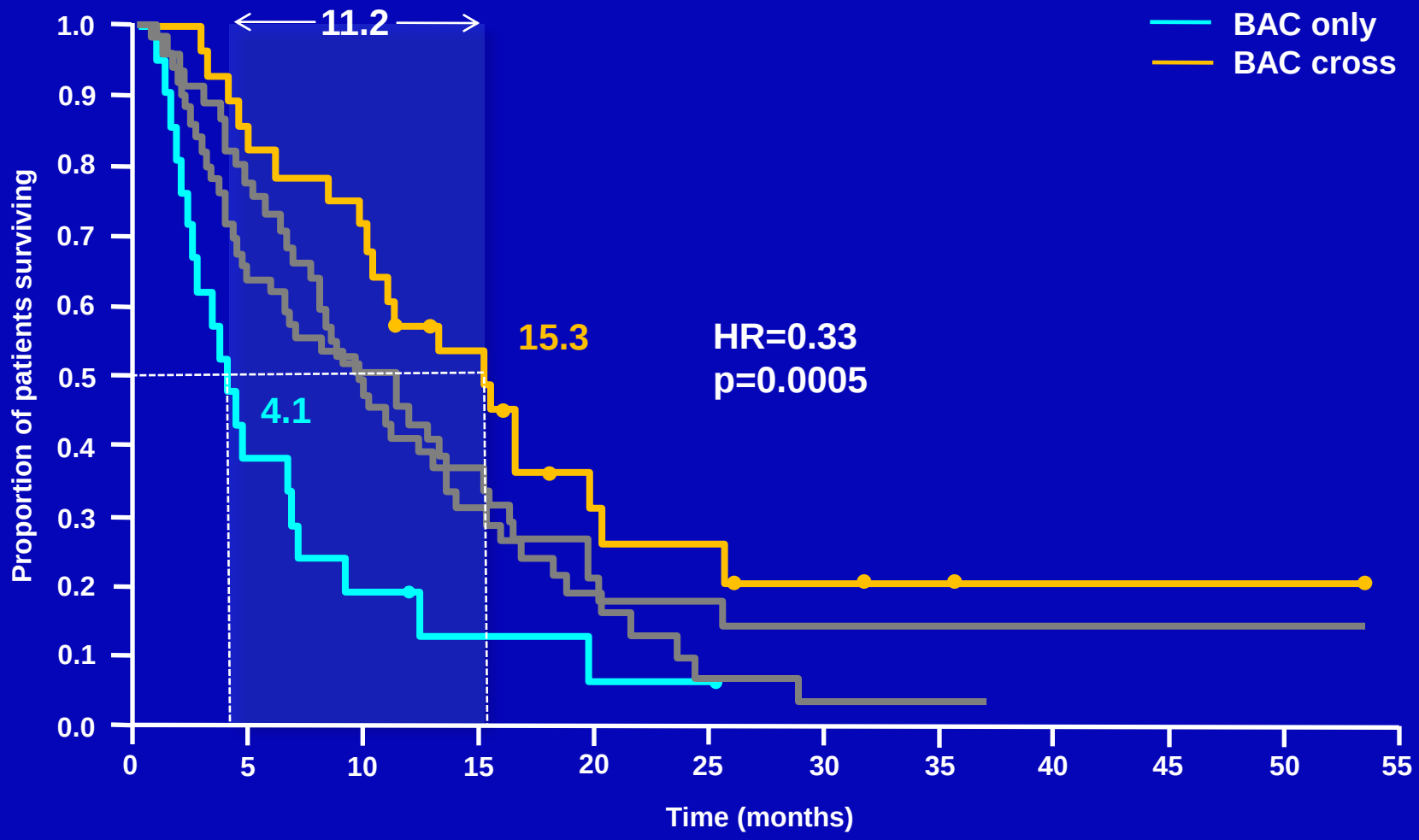
*1 patient crossed over but never received PHP

BAC-only patients: chemoembolization, HAI nab-paclitaxel, temozolomide

ITT population

Data as of 31 March 2011

Exploratory cross-over analysis: OS



Intent-to-treat population

Most common peri-procedural* grade 3/4 AEs (n=40)

	No. of pts	%
Platelet count decreased	29	73
Hemoglobin decreased	22	55
Blood albumin decreased	15	38
AST increased	12	30
aPTT prolonged	12	30
Blood calcium decreased	8	20
ALT increased	4	10
Blood bilirubin increased	4	10

*Day of treatment through to day 3 post-treatment

Most common in-cycle* grade 3/4 AEs (n=40)

	No. of pts	%
Neutrophil count decreased	37	93
Platelet count decreased	33	83
White blood cell count decreased	23	58
Hemoglobin decreased	22	55
Blood bilirubin increased	7	18
Febrile neutropenia	6	15
AST increased	5	13
Blood alkaline phosphatase increased	5	13
ALT increased	4	10
Blood albumin decreased	3	8

*Day 4 post-treatment through to end of treatment cycle

Safety of CS-PHP melphalan

- Most common grade 3/4 AEs were thrombocytopenia and anemia
- Low neutrophils, common during in-cycle period
  - febrile neutropenia in 6 patients (15%)
- Hepatic laboratory abnormalities in 10 to 30% of patients
  - Transient peri-procedural transaminitis
  - Hyperbilirubinemia
- Non-hematological toxicities infrequent
- Three treatment-related deaths ≤30 days of last melphalan dose:
  - hepatic failure in patient with >75% liver tumor burden, n=1
  - streptococcal sepsis, n=1
  - gastric perforation, n=1 (BAC-crossover)

Conclusions

- CS-PHP significantly prolonged hPFS compared with BAC in patients with liver-dominant metastatic melanoma
- Study primary objective met
  - Investigator analysis confirmed by IRC and secondary endpoints
- CS-PHP significantly improved hepatic response rate
- Overall survival similar in both groups, as expected
  - Confounded by crossover
  - Most long-term survivors received CS-PHP
    - Efficacy similar in BAC-crossover and CS-PHP-randomized pts
- Hematological AEs managed effectively with supportive care
- CS-PHP with melphalan is a new treatment option for unresectable metastatic melanoma in the liver