

Melblez Kit for Ocular Melanoma

**FDA Oncologic Drugs
Advisory Committee Meeting**

Delcath Systems, Inc.

Context for Use of Melblez Kit in Liver Metastases of Ocular Melanoma

- **Very rare and rapidly fatal disease**
- **No approved therapies**
- **Clinically meaningful hPFS benefit balanced against considerable toxicities**
- **Restricted to very specialized centers and physicians with expertise in liver-directed therapies**
- **Only suitable for a subset of patients**

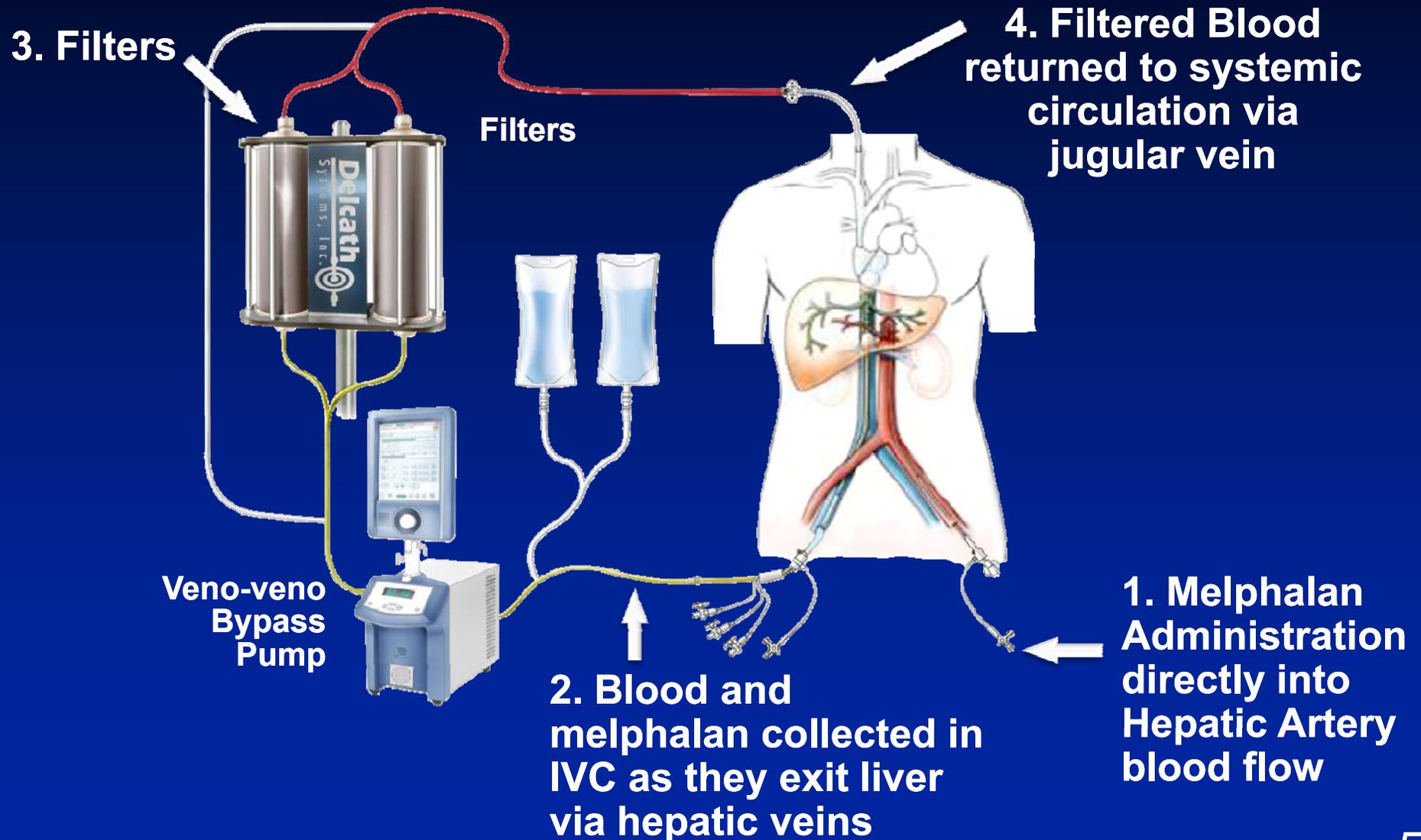
Proposed Indication for Melblez Kit

- **For the treatment of patients with unresectable metastatic ocular melanoma in the liver**

The Melblez Kit

- **Combination drug/device product**
 - Melphalan hydrochloride
 - Delcath Hepatic Delivery System
- **Purpose**
 - Administers high dose melphalan to tumor
 - Maximize efficacy in liver
 - Filters blood and returns it to systemic circulation
 - Controls systemic exposure to melphalan

How the Combination Product Works



Filters Utilized During Clinical Development

Asahi Filter

**Gen 1 Filter
(Clark)**

Phase I

**N=29 Pt
N=83 Tx**

Phase II

**N=10 Pt N=44 Pt
N=25 Tx N=102 Tx**

Phase III

**N=65 Pt
N=177 Tx**

Experience Outside Clinical Trials

EU Commercial Experience (7 countries, 9 sites)

Patients treated	35
Total cycles	40
OM patients treated	17
Total cycles in OM	23

Compassionate Use/Expanded Access in OM

Patients treated	12
Total cycles	19

Current Clinical Safety Data Collection

- **EU Retrospective Registry – ongoing**
- **US EAP/Compassionate Use – ongoing**
- **EU Prospective Registry – Implemented 3Q13**
- **US Post-approval Registry – under discussion**

Regulatory History

June 2001	Melphalan IND opened
April 2005	End of Phase 2 meeting and Fast Track designation for malignant melanoma
February 2006	Special Protocol Assessment (SPA) for the phase 3 study DSI MEL 2005-001
November 2008	Orphan Drug designations for ocular and cutaneous melanoma
March 2010	Pre-NDA meeting
December 2010	Rolling NDA submission completed
February 2011	Refusal to File: incomplete hospitalization data and unclear death information
April 2011	Type A meeting: remonitoring plan agreed
January 2012	Pre-NDA meeting
August 2012	NDA resubmission

Presentation Overview

Introduction

John Purpura

EVP Regulatory Affairs, Delcath Systems, Inc.

Medical Need

Steven O'Day, MD

Director, Clinical Research
The Beverly Hills Cancer Center

Procedure, Phase 1 Study

Richard Alexander, MD, FACS

Professor of Surgery, Associate Chairman for
Clinical Research, Univ. of Maryland Medical Center

Phase 3 Efficacy

Krishna Kandarpa, MD, PhD

Chief Scientific Officer, Delcath Systems, Inc.

Safety, Risk Management & REMS

Krishna Kandarpa, MD, PhD

Clinical Perspective

Richard Alexander, MD, FACS

Responders and Experts

Delcath Systems, Inc.

Bill Appling	SVP, Medical Device R&D
Daniel Johnston, PhD	VP, Pharmaceutical R&D
Johnny John, MD	Director, Clinical Operations
Jennifer Simpson, PhD	EVP, Global Head of Business Operations

Consultants

Richard Alexander, MD	Associate Chairman, Clinical Research, Surgery, University of Maryland School of Medicine
Steven O'Day, MD	Director, Clinical Research, Beverly Hills Cancer Center
Erin Gardner, PhD	Clinical Pharmacologist
David Donley, PhD	Statistician
Mary Chen, MD	Cardiac Anesthesiologist, St. John's Health Center
Michael Ewer, MD	Cardiologist, MD Anderson Cancer Center
Gregory Gores, MD	Hepatologist, Mayo Clinic

Medical Need

Steven O'Day, MD

*Director, The Los Angeles Skin Cancer Institute
The Beverly Hills Cancer Center*

Clinical Associate Professor of Medicine, USC

Member, The John Wayne Cancer Institute

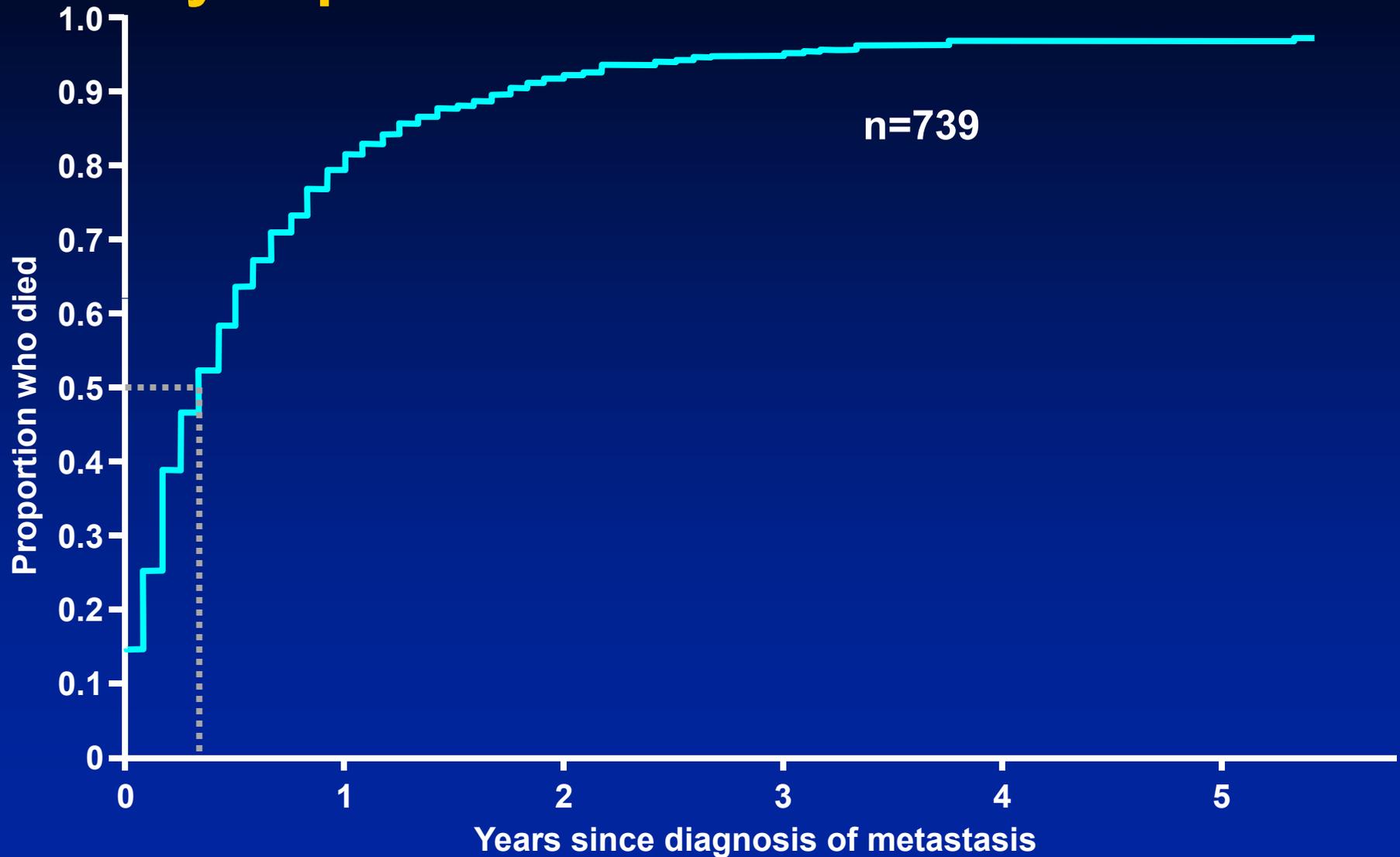
Epidemiology of Ocular Melanoma

- Rare, orphan disease
- Approximately 2,000 US cases/year
- Uveal pigmented cells
- 50% metastasize
- No FDA-approved therapies

Ocular Melanoma

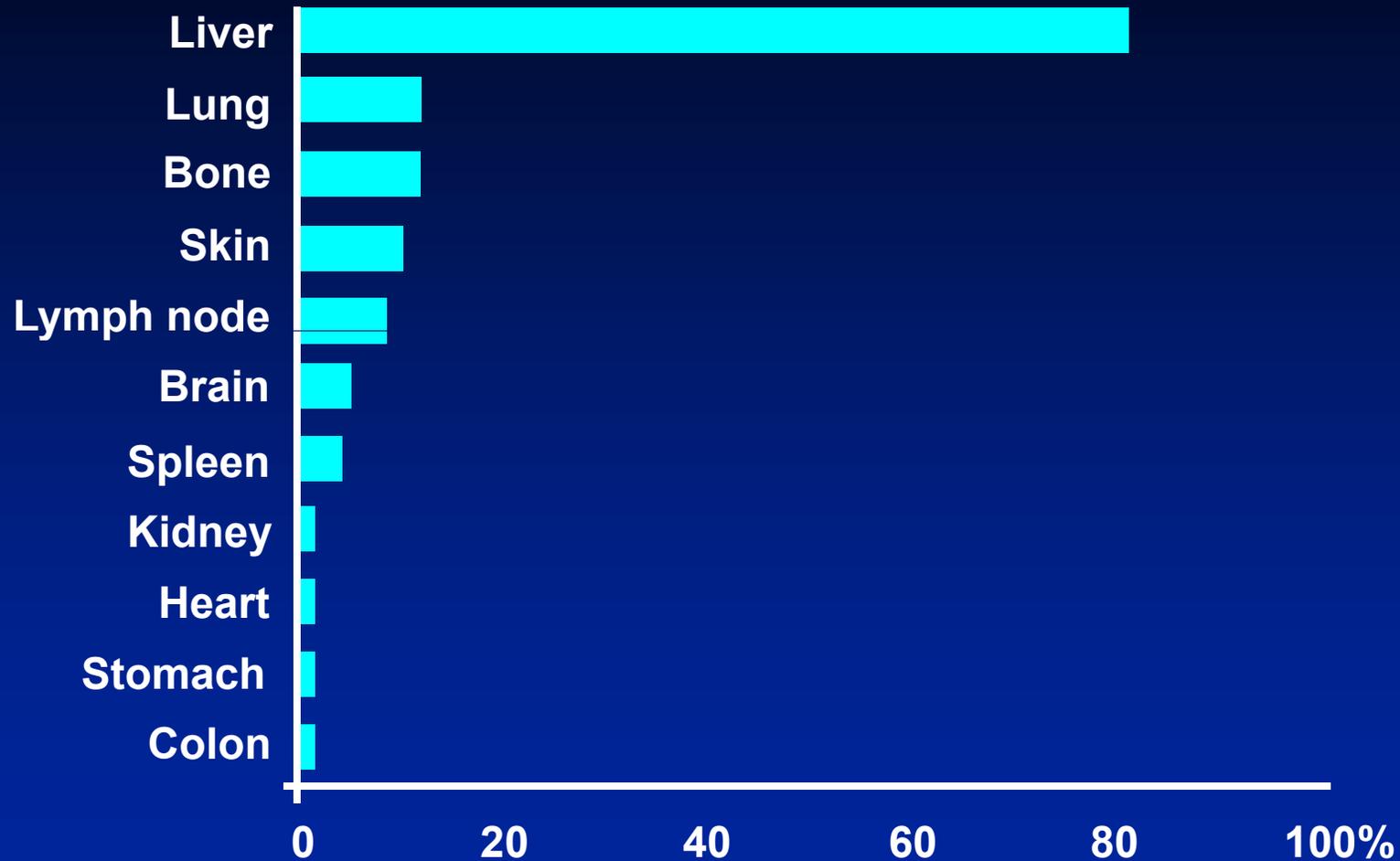
- 90% liver dominant metastases
- Cause of death – liver
- Rare CNS metastases
- Absence of BRAF, c-kit
- Median OS 4-6 months
- 1 year OS 10-15%
- 5 year survival <1%

Collaborative Oncology in Melanoma Study Report



Adapted from: Diener-West, M et al. Arch Ophthalmol 2001;119:961-5

Sites of Metastasis of Ocular Melanoma



Adapted from Sato, HemOnc Today Melanoma, 2012

Clinical Presentation: Liver Metastases

- **10% surgically resectable**
- **Majority multi-focal, multi-lobular**
- **Imaging underestimates extent of disease**

Liver Dominant Ocular Melanoma Management

- Systemic treatments ineffective
- Hepatic artery directed therapies
 - Hepatic perfusion
 - Chemoembolization
 - Immunoembolization
 - Radiospheres
 - Drug eluting beads
- Clinical trials

Ocular Melanoma: Optimal Therapy

- Overcome innate resistance
- Deliver multiple cycles
- Treat macro and microscopic liver disease
- Direct therapy to the entire liver

Ocular Melanoma: Unmet Medical Need

- **Unique biology and metastatic pattern**
- **Liver most frequent cause of death**
- **Rare and devastating**
- **No available standard of care**
- **<1000 patients are candidates per year**

Procedure (PHP)

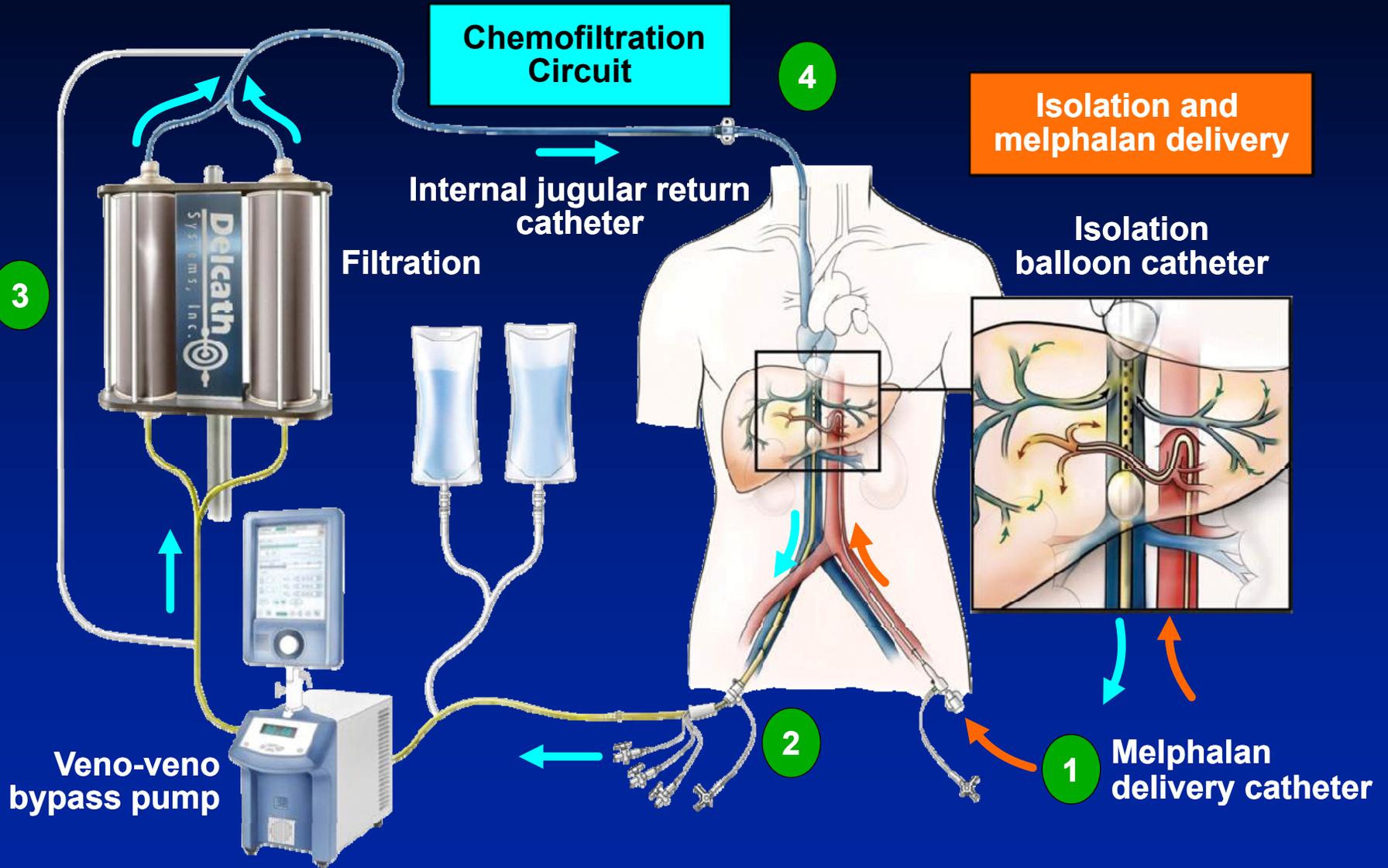
H. Richard Alexander, MD

*Professor of Surgery,
Associate Chairman for Clinical Research
University of Maryland Medical Center*

IHP: Surgical Procedure

- **One time only treatment**
- **Delivers high dose melphalan to liver**
- **Controls systemic exposure by complete surgical isolation**
- **Extensive abdominal surgery**
- **8 hours to complete**
- **2-3 days in ICU**
- **10-15 days in hospital**

PHP Procedure



Treatment Team

Team Member	Roles and Responsibilities
Medical or Surgical Oncologist	Patient's complete management
Interventional Radiologist	Training, coordination and communication
Anesthesiologist	Sedation, analgesia, hemodynamic support
Perfusionist	Establishing, monitoring and controlling the extracorporeal circuit
Certified HCP for Chemotherapy Delivery	Melphalan administration
Interventional Radiology Staff (RN/RT)	Assists in procedure and imaging
Pharmacist	Preparation of melphalan

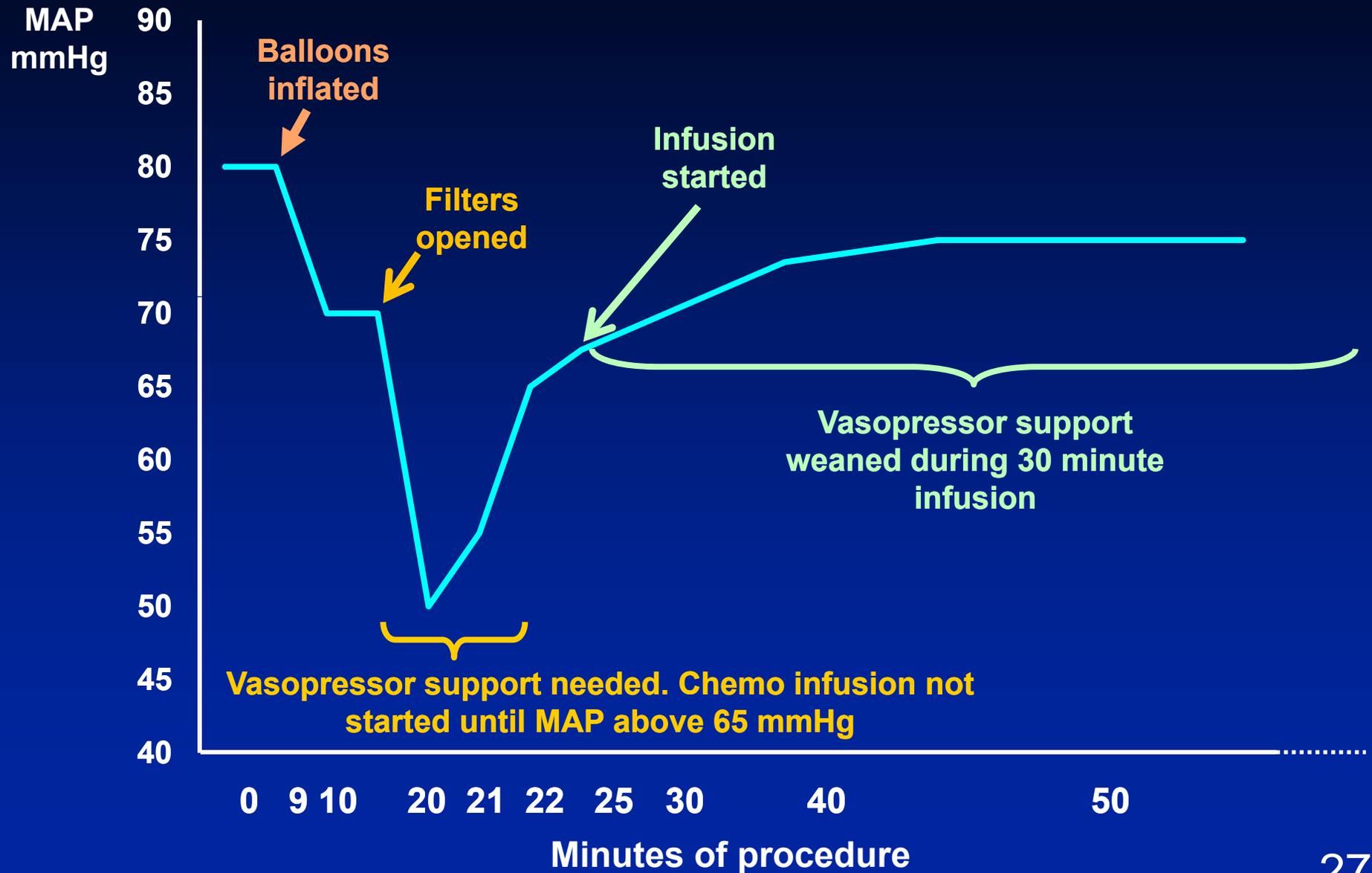
Pre-Procedural Patient Selection

- **Ensure adequate cardiac, hepatic, hematologic and renal function**
- **Complete CT/ MRI, pelvis, abdomen, chest, brain**
- **Exclude hepatic failure and portal hypertension**
 - Laparoscopy and biopsy if liver tumor >50% on imaging
 - Delay treatment if residual effects of prior therapy
- **Avoid GI complications**
 - Endoscopy for suspected peptic ulcer disease
 - Screen for prior surgeries to biliary/vascular anatomy
 - Visceral angiogram to rule out variant anatomy
- **Prevent bleeding**
 - Exclude active intracranial lesions via CT/MRI
 - Hormonal suppression for pre-menopausal women
- **Hypersensitivity to melphalan excluded**

Patient Experience and Support during PHP

- **Pre-procedure preparation**
 - Pre-hydration, embolization and medications (antibiotics, PPI, allopurinol)
- **Procedure (3 hours on table)**
 - General anesthetic, heparinization, hemodynamic support
 - Venous and arterial access, catheter placement
 - Monitoring, management of hepatic artery spasm (NTG)
 - Infusion and filtration, removal of catheters
- **Recovery/ICU (24 hours)**
 - Anticoagulation reversal, hemodynamic support
 - Transfusions, electrolytes as needed
- **Hospital recovery (4 days)**
 - Ambulation and diet
 - Monitor labs

Blood Pressure Management during PHP



NCI Phase I Study Design (01-C-0215)

Trial Design	Open-label, single-center, multiple-ascending-dose
Patients	Unresectable primary or metastatic hepatic malignancies from a non-liver primary site
Objectives	To determine DLT/MTD, toxicities, PK
Doses	2.0-3.5 mg/kg ideal body weight <ul style="list-style-type: none">• 0.5 mg/kg increments• Starting dose based on open surgical isolated perfusion experience
Cycle Length	4-week cycles for a maximum of 4 cycles

Adjudicated DLT and MTD Determination

	2.0 mg/kg N=14	2.5 mg/kg N=3	3.0 mg/kg N=10	3.5 mg/kg N=6
No. of patients with a DLT	0	0	1	2
Neutropenia	0	0	–	2
Leukopenia	0	0	1	1
Thrombocytopenia	0	0	1	2
Febrile neutropenia	0	0	1	1

Activity in Phase I Study

Hepatic Objective Response	Ocular Melanoma N=12	Cutaneous Melanoma N=3	Other Tumor Type N=19
Response	4 (33.3)	0	0
Complete Response	3 (25.0)	0	0
Partial Response	1 (8.3)	0	0
Stable Disease	3 (25.0)	1 (33.3)	7 (36.8)
hPFS (median, months)	8.9	2.1	2.9

Phase I Overall Conclusions

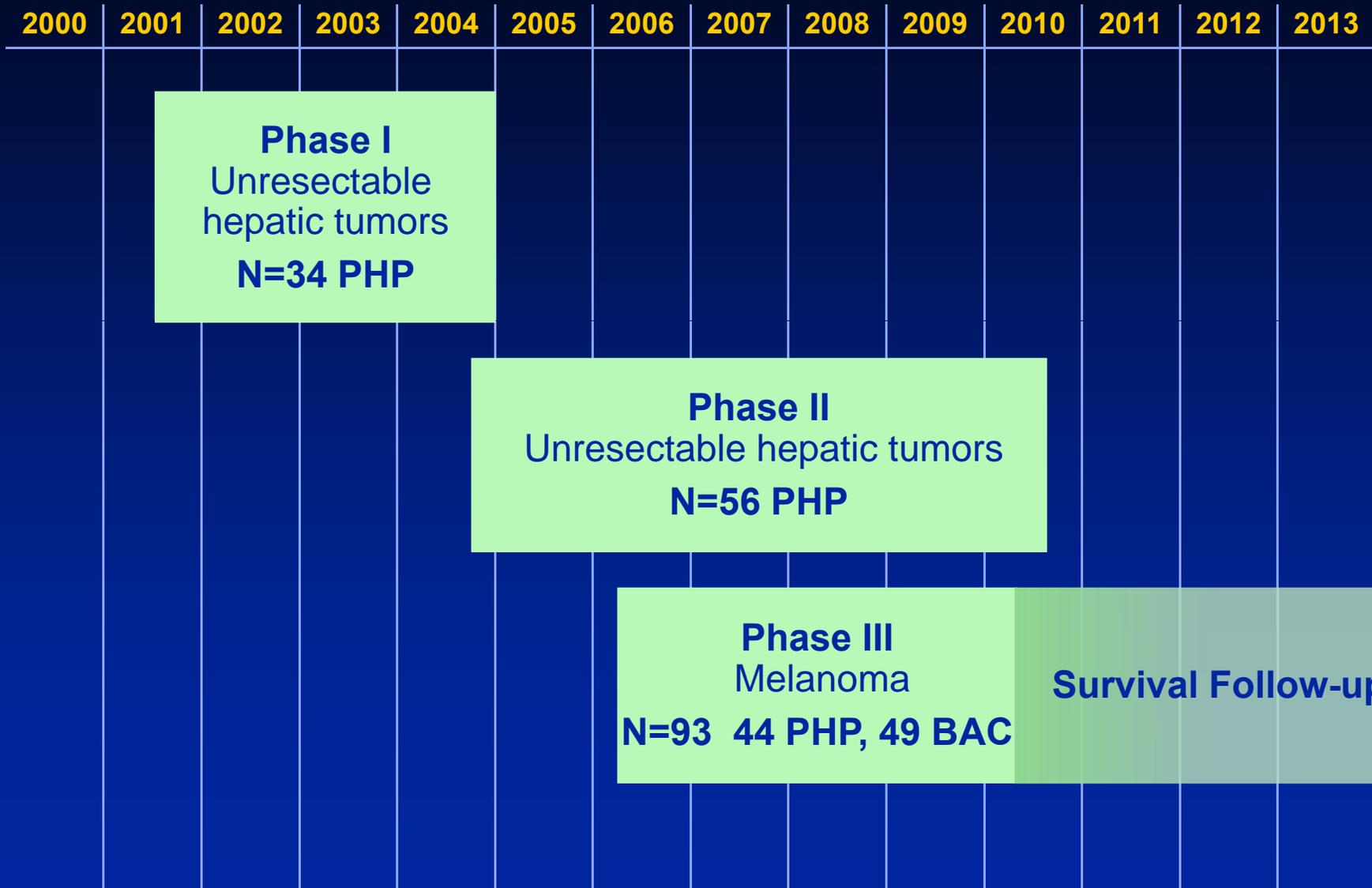
- **Defined MTD as 3.0 mg/kg**
- **DLTs were due to bone marrow suppression**
 - No deaths on study
- **Clinically meaningful hepatic responses in ocular melanoma**
 - 3 complete responses

**Phase III Efficacy
Study DSI MEL 2005-001**
February 2006-April 2010

Krishna Kandarpa, MD, PhD

*Chief Scientific Officer
Delcath Systems, Inc.*

Clinical Program



Phase I
Unresectable
hepatic tumors
N=34 PHP

Phase II
Unresectable hepatic tumors
N=56 PHP

Phase III
Melanoma
N=93 44 PHP, 49 BAC

Survival Follow-up

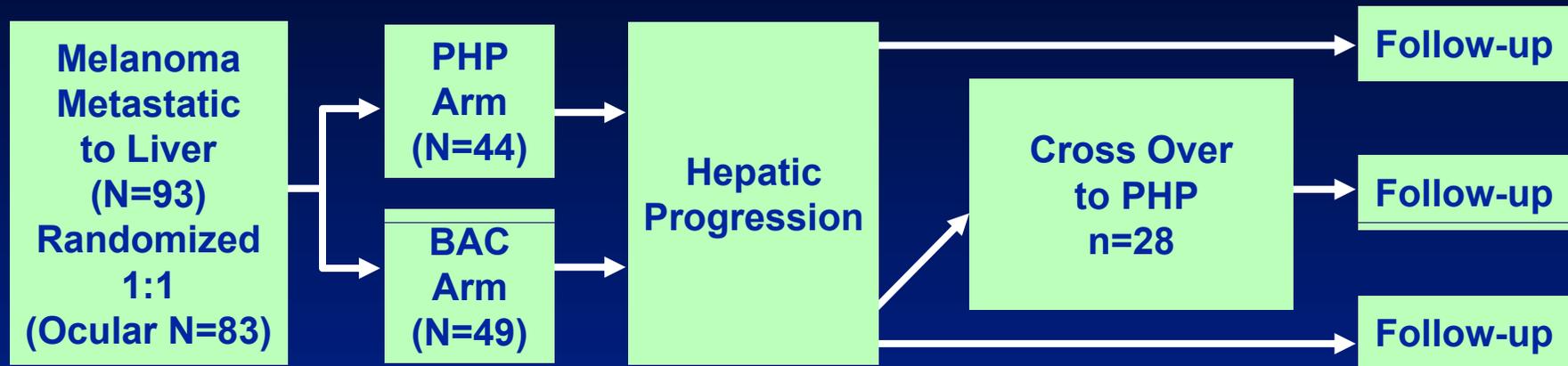
Pivotal Trial Design

- **Open-label, randomized, multi-center (US), PHP vs. Best Alternative Care (BAC)**
- **Primary endpoint: hPFS by IRC**
 - Assessed week 6, 12 then every 8 weeks both arms
- **Secondary endpoint:**
 - hPFS
 - hOR
 - Overall survival
 - xPFS, overall PFS, OOR
 - Safety
 - Pharmacokinetics

Statistical Analysis Plan

- **Planned sample size 92 patients**
 - 46 per treatment group
- **Powered for hPFS**
 - Analysis after 73 events
- **Primary hPFS analysis of ITT population**
 - 80% power to detect difference of 4 months at median
 - Log rank test with two-sided alpha = 0.05
- **Stratification factors**
 - NCI vs Other
 - Ocular, cutaneous

Phase III Study Schema



Melphalan Dosing

- **Starting dose 3.0 mg/kg ideal body weight**
 - Maximum melphalan dose 220 mg
 - Dose reduction permitted for severe toxicity
- **Cycle interval 4 weeks**
 - Up to 4-week delay for resolution of toxicity
- **Permanent discontinuation if persistent toxicity > grade 2 eight weeks after PHP**
- **Maximum 6 cycles**

Key Inclusion Criteria

- Surgically unresectable melanoma mets in the liver
- Histologically or cytologically-proven melanoma
 - Ocular or cutaneous
- Disease measurable by CT and/or MRI
- Limited unresectable extrahepatic disease
 - If life-limiting component in liver
- Acceptable extrahepatic disease included, but not limited to:
 - Up to 4 pulmonary nodules each <1 cm
 - Retroperitoneal lymph nodes <3 cm
 - Fewer than 10 (sub)cutaneous metastases and <1 cm
 - Asymptomatic bone metastases treatable with radiotherapy
 - Any resectable solitary metastasis

Baseline Patient Characteristics

	PHP N=44	BAC N=49
Median age, years (range)	55 (33-74)	56 (31-77)
Female, n (%)	21 (47.7)	27 (55.1)
Male, n (%)	23 (52.3)	22 (44.9)
White, n (%)	44 (100)	48 (98.0)
Black/African-American, n (%)	0	1 (2.0)
ECOG PS 0	28 (63.6)	42 (85.7)
ECOG PS 1	13 (29.5)	6 (12.2)
Prior systemic therapy, n (%)	14 (31.8)	15 (30.6)
Chemotherapy	8 (18.2)	10 (20.4)
Immunotherapy	8 (18.2)	8 (16.3)

Baseline Disease Characteristics

	PHP N=44	BAC N=49
Ocular melanoma	39 (88.6)	44 (89.8)
Cutaneous melanoma	5 (11.4)	5 (10.2)
Median time since diagnosis, months (range)	49.2 (3-292)	38.1 (1-162)
Median time since liver metastasis, months (range)	1.9 (0.0-44.1)	2.1 (0.1-28.9)

Baseline Tumor Characteristics

	PHP N=44	BAC N=49
Hepatic lesions only	27 (61.4)	28 (57.1)
Hepatic and extrahepatic lesions	17 (38.6)	21 (42.9)
1 extrahepatic lesion	10 (22.7)	14 (28.5)
≥ 2 extrahepatic lesions	7 (15.9)	7 (14.3)
Lung metastasis	8 (18.2)	13 (26.5)
<50% liver involvement	35 (79.5)	39 (79.6)
≥50% liver involvement	9 (20.5)	10 (20.4)
LDH > ULN	25 (56.8)	26 (53.1)

Best Alternate Care (BAC) Treatment Arm

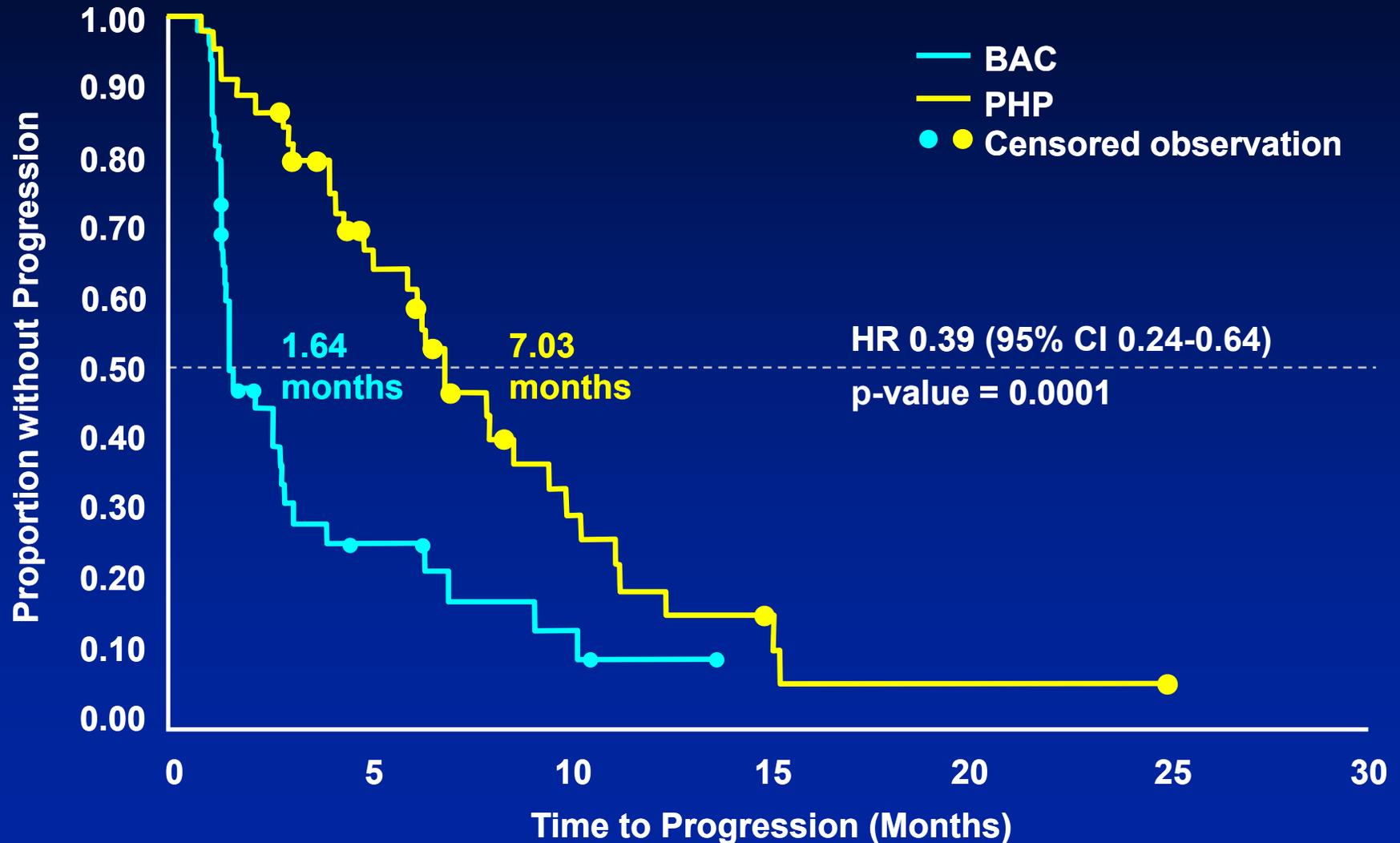
Selected Treatment	% Patients
Active treatment	81.6
Systemic chemotherapy	49.0
Temozolomide	41.0
Dacarbazine	2.0
Carboplatin plus paclitaxel	6.1
Chemoembolization	22.4
Radioembolization	6.1
Systemic chemo plus chemoembolization	2.0
Surgery	2.0
Supportive care only	18.4

Primary hPFS by IRC Analysis

- **Clinically meaningful improvement in hPFS**
- **Median hepatic progression-free survival**
 - 7.03 months PHP vs. 1.64 months BAC
 - 5.5 month extension
 - $p=0.0001$ (log-rank)
- **HR=0.39 (95% CI 0.24-0.64)**
 - 61% hazard reduction

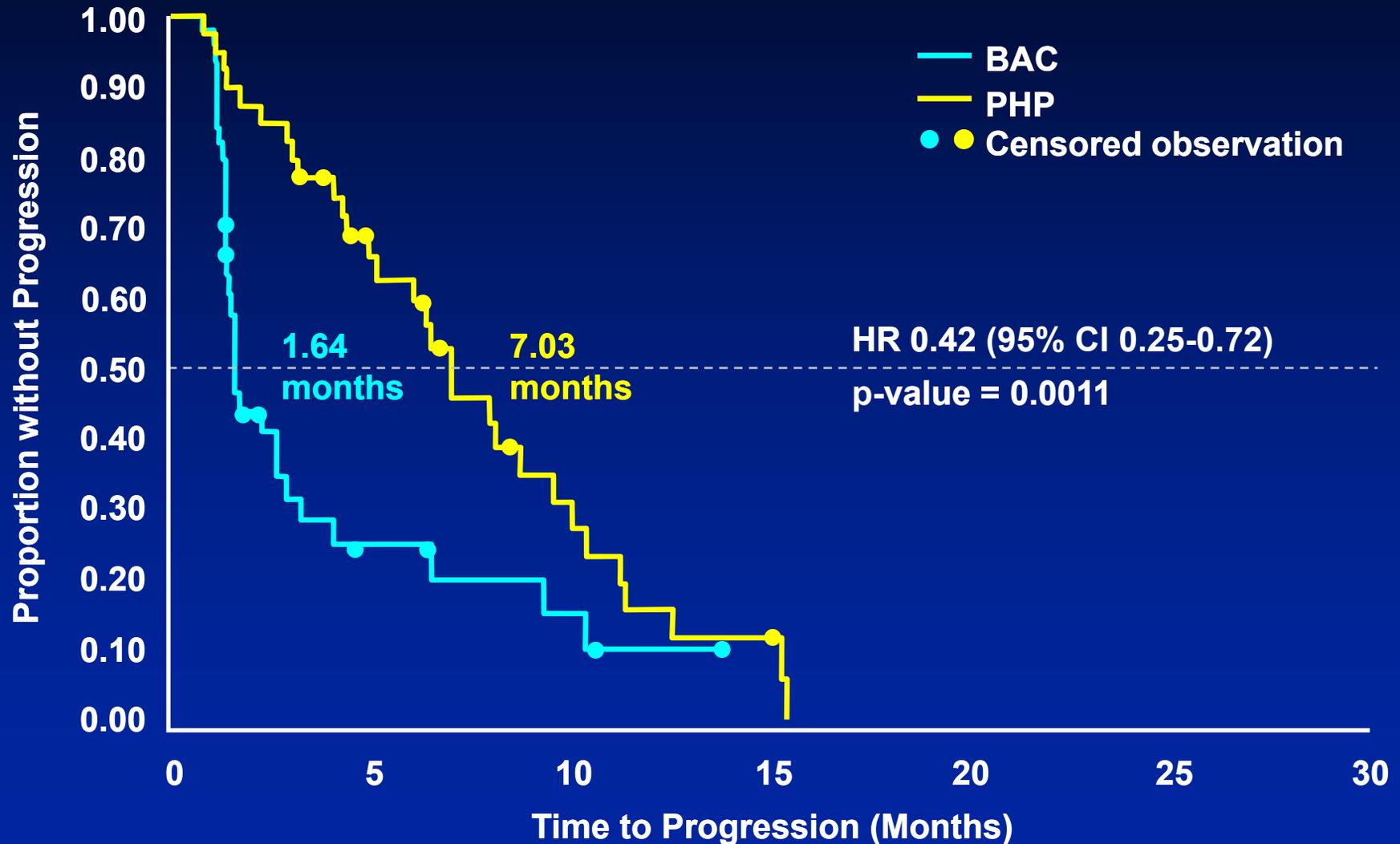
Kaplan Meier Curve of hPFS by IRC

ITT population

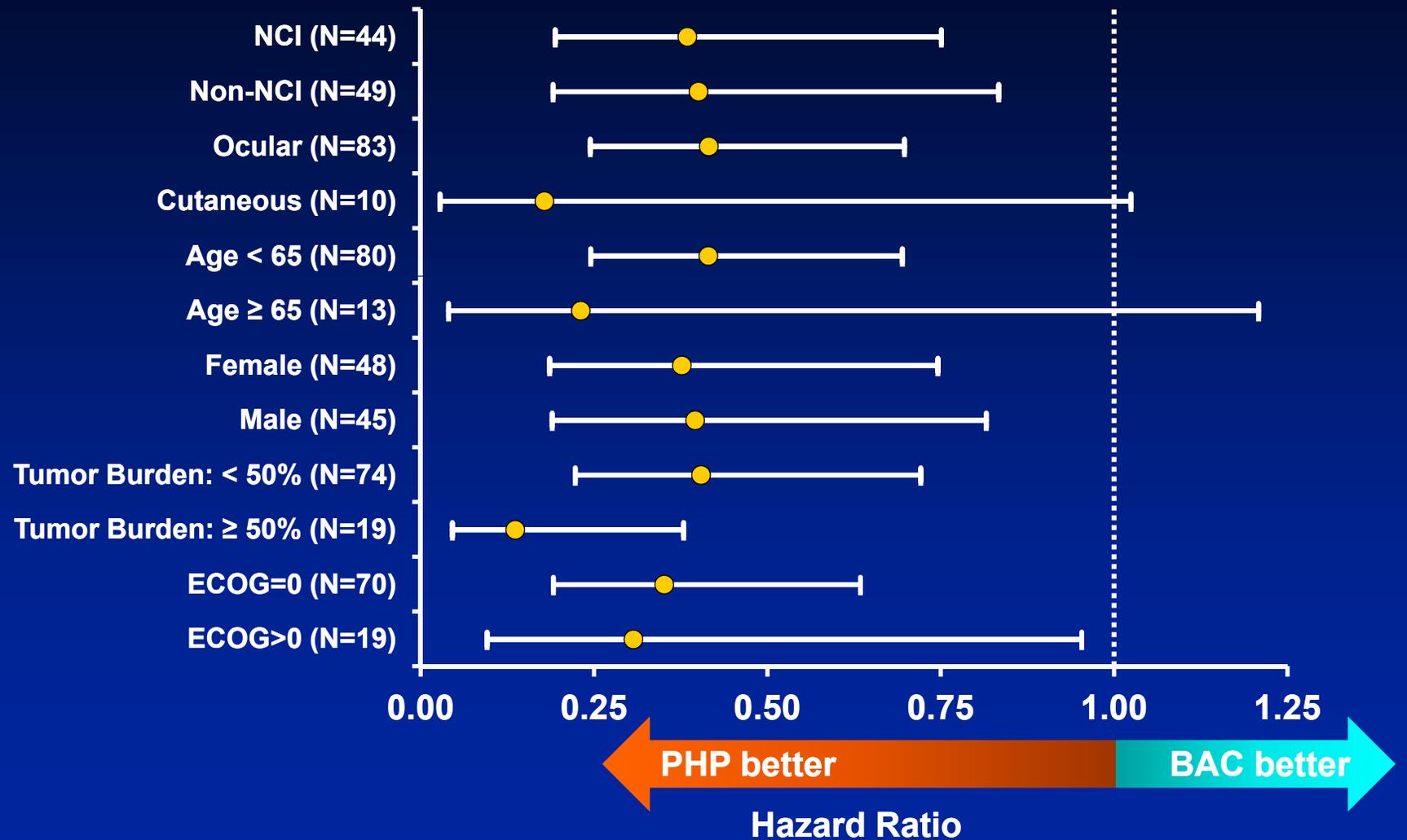


Kaplan Meier Curve of hPFS by IRC

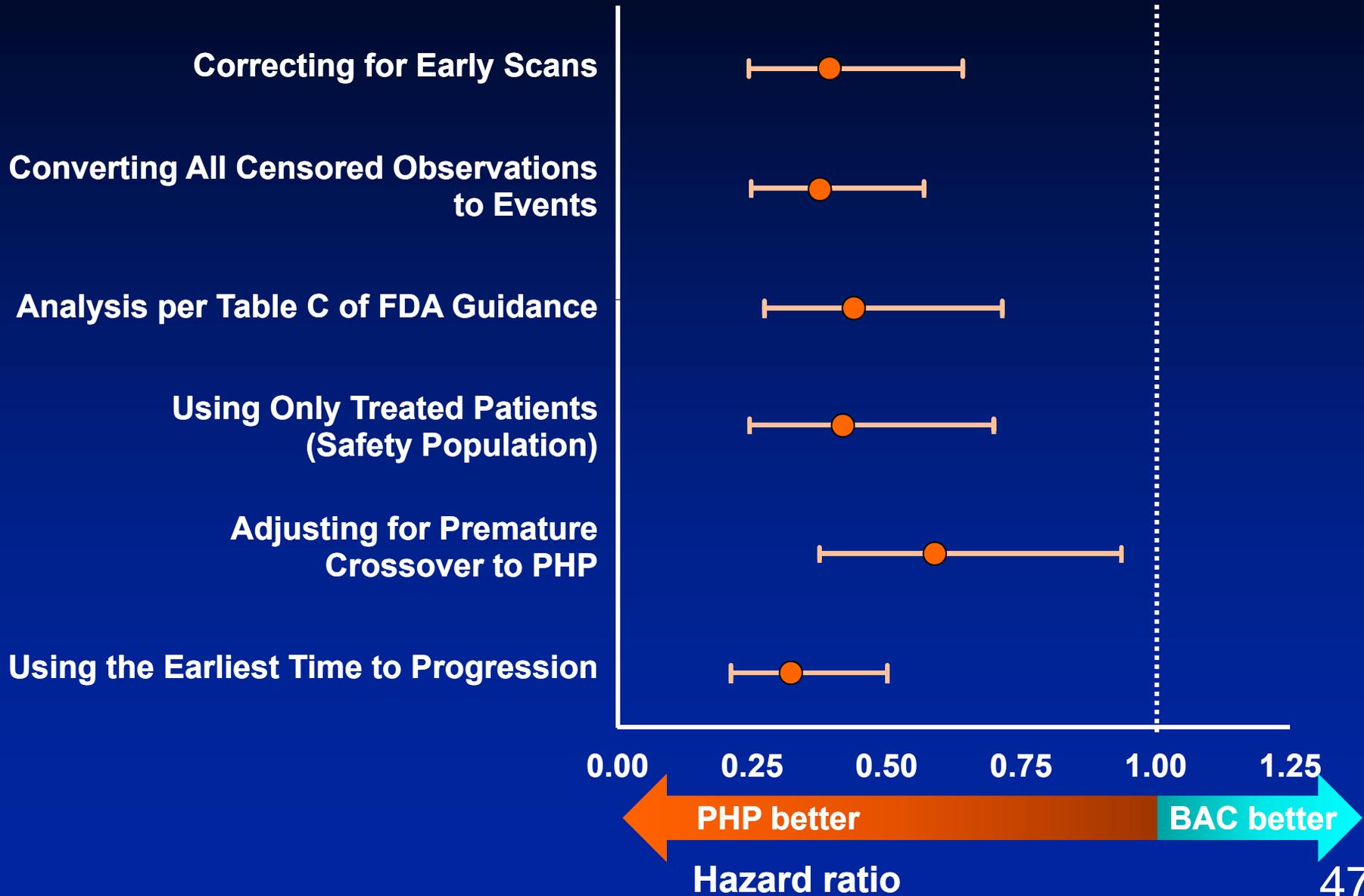
Ocular ITT population



hPFS in Subgroups



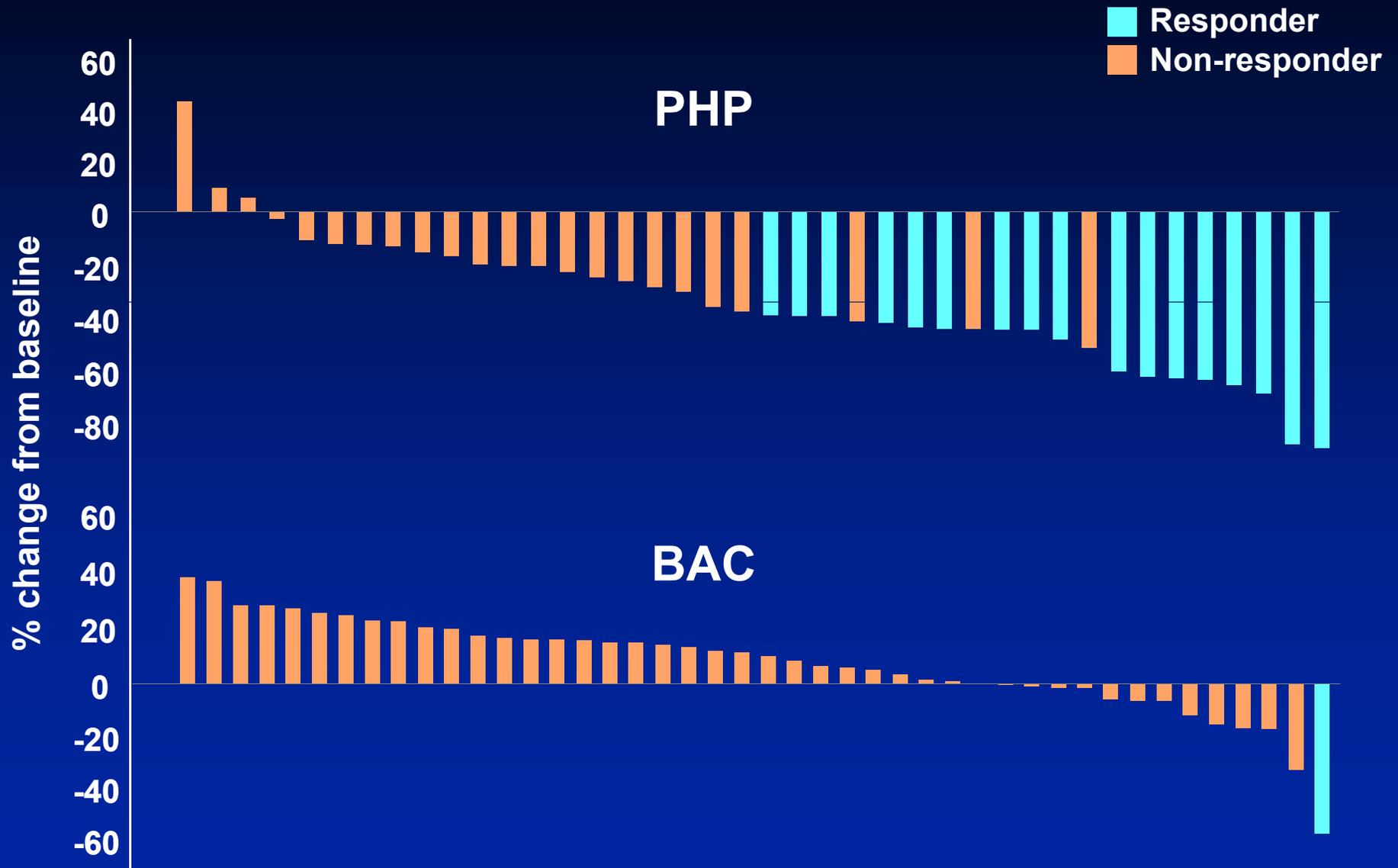
Sensitivity Analyses of hPFS



Efficacy Results: Key Secondary Endpoints

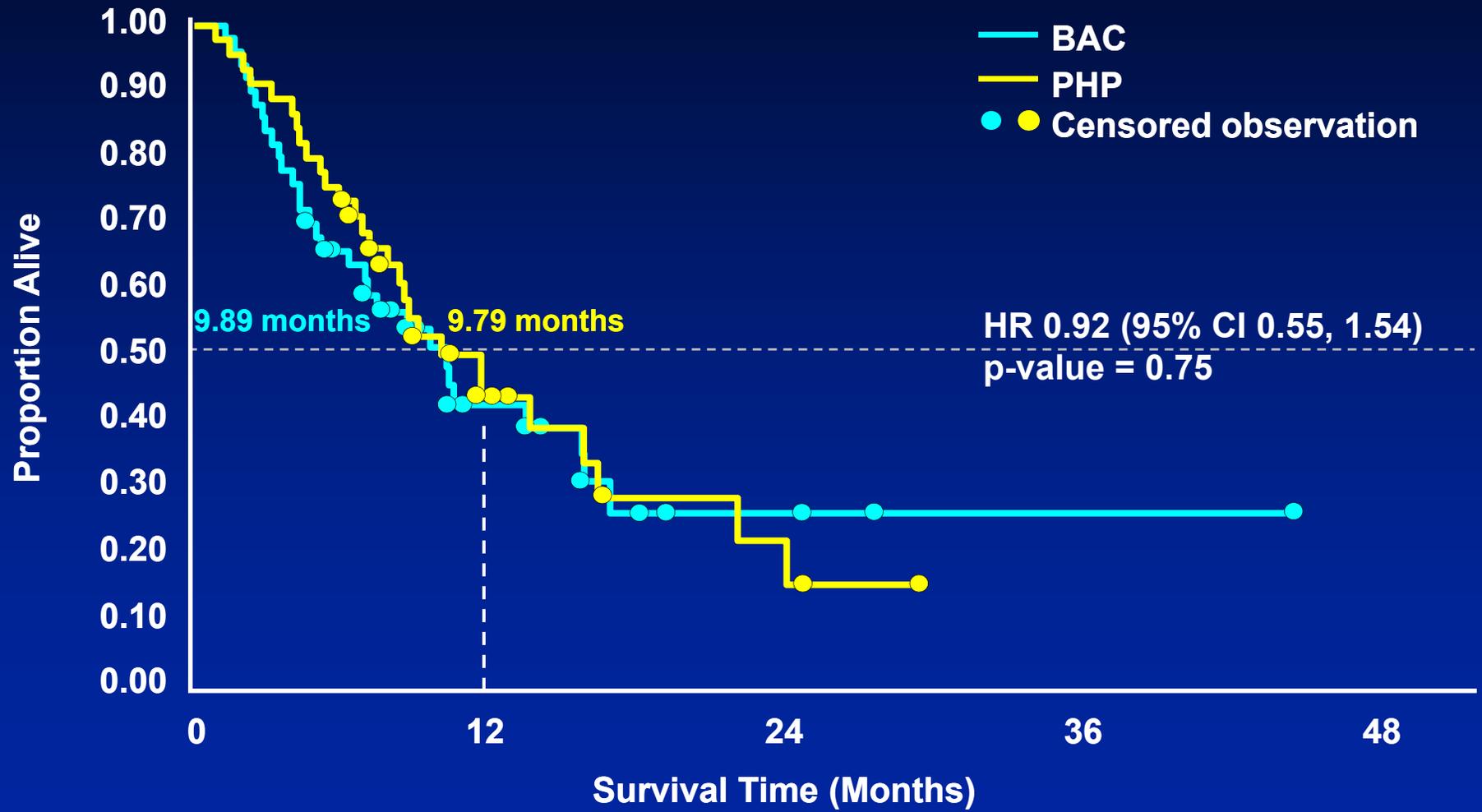
	PHP N=44	BAC N=49	p-value
hPFS (Investigator), months	8.05	1.64	0.0001
hPFS (Investigator), HR		0.28	<0.0001
hOR (IRC), %	36.4	2	<0.0001
hOR (Investigator), %	38.6	2	<0.0001
PFS (Investigator), months	4.76	1.64	<0.0001
OS, months	9.79	9.89	0.75

Waterfall Plots of Hepatic Response (IRC)



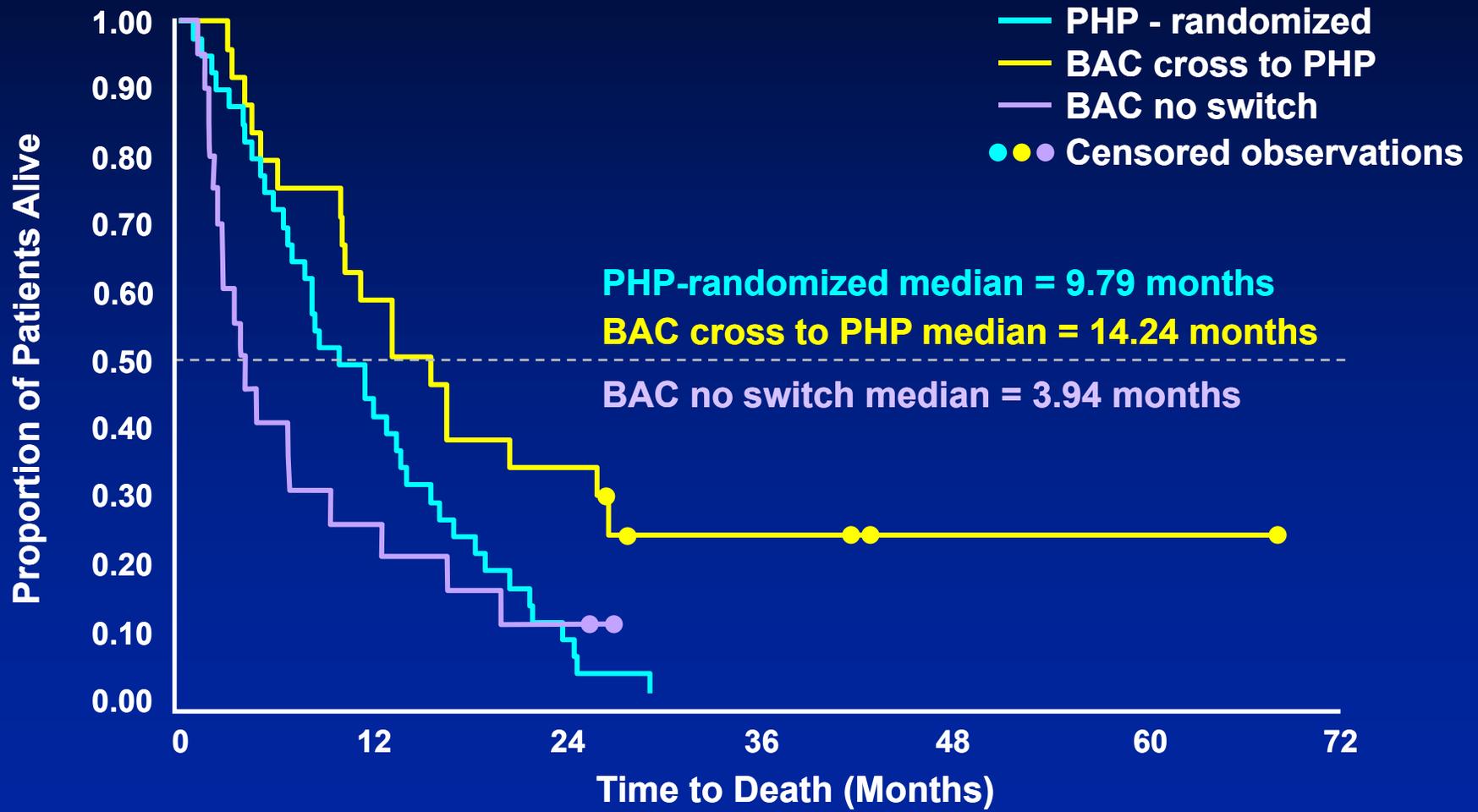
Kaplan-Meier Curve of Overall Survival

ITT population



Exploratory Analysis of Overall Survival

ITT population June 2012



Efficacy Results: Cross-Over Group

	Overall	
	Cross-Over N=28	PHP N=44
hPFS (IRC), months 95% CI	8.44 3.06-11.17	7.03 5.22-9.66
hPFS (investigator), months 95% CI	6.70 3.88-9.72	8.05 5.78-8.90
hOR (IRC), %	28.6	36.4
hOR (investigator), %	35.7	38.6
OS, months 95% CI	15.2 9.89 -	9.79 6.93-15.44

Phase III Efficacy Conclusions

- **PHP had a clinically meaningful effect on hPFS**
 - 5.5 month improvement in the overall study population
 - Statistically significant
- **OS confounded by significant cross-over**
- **Consistent PHP treatment effect in**
 - Investigator and IRC assessments
 - Patient subgroups
 - Hepatic response by investigator and IRC
 - Cross over group
 - Ocular melanoma patients

SAFETY

Pooled Safety Population

Study	N
Phase 3 PHP Randomized	42
Phase 3 Cross-over to PHP	28
Phase 2	52
Pooled Safety Population[†]	121

[†] Combines enrollments of 1 patient who was included in phase 3 then phase 2

Definition of Peri- and Post-Procedure Safety

- **Peri-procedure**

- Starting within 72 hrs (3 days) of initiation of PHP
- Likely due to device, procedure or direct effect of melphalan infusion

- **Post-procedure**

- Starting > 72 hrs (3 days) after initiation of PHP
- Until next PHP or 30 days post previous PHP
- Likely due to melphalan or delayed effects of PHP procedure

Treatment Exposure

Variable	Pooled N=121
Number of Completed Cycles	
n	116
Median	3.0
Range	1-7
Cumulative Dose	
n	116
Median	449.5
Range	81-1430

Overview of Adverse Events

n (%)	Phase 3					
	Pooled N=121		PHP N=42		BAC N=49	
	All	Grade 4	All	Grade 4	All	Grade 4
AE	115 (95.0)	110 (90.9)	40 (95.2)	40 (95.2)	31 (63.3)	6 (12.2)
Serious AE	101 (83.5)	88 (72.7)	33 (78.6)	28 (66.7)	8 (16.3)	1 (2.0)
AE Resulting in Death	5* (4.1)	—	3 (7.1)	—	—	—
AE Leading to Drug Discontinuation	46 (38.0)	24 (19.8)	17 (40.5)	10 (23.8)	4 (8.2)	2 (4.1)

* 1 phase 2 patient; 1 cross-over patient

Most Common Adverse Events (>15%) Peri- and Post-procedure

Event, n (%)	Pooled N=121	
	All	Grade 4
Thrombocytopenia	111 (91.7)	95 (78.5)
Neutropenia	106 (87.6)	87 (71.9)
Febrile neutropenia	22 (18.2)	9 (7.4)
Anemia	98 (81.0)	16 (13.2)
Hypoalbuminemia	46 (38.0)	0
AST increased	40 (33.1)	11 (9.1)
Leukopenia	34 (28.1)	21 (17.4)
Hyperbilirubinemia	26 (21.5)	10 (8.3)
ALT increased	25 (20.7)	2 (1.7)

AEs Leading to Death in PHP Development Program (Phase I, II and III)

Tx Group	Age	Sex	Cause of Death	Study Day	Cycle	Cycle Day	Comment
Ph2 001-038	67	M	GI hemorrhage/ ruptured R hepatic artery	74	1	74	<p>Prior Whipple's procedure</p> <ul style="list-style-type: none"> • Liver abscess, liver dysfunction • Renal insufficiency • Aspiration, ARDS
Ph3 001-006	56	M	Hepatic failure	42	1	29	<p>Disease burden (>90%)</p> <ul style="list-style-type: none"> • Hepatorenal syndrome • Myelosuppression
Ph3 001-010	62	M	Gastric perforation	151	2	18	<p>Melphalan infused during hepatic artery spasm, reflux</p> <ul style="list-style-type: none"> • With bleeding
Ph3 009-650	54	F	Streptococcal sepsis	60	2	13	<p>G4 hypoxia, G3 anemia, G4 thrombocytopenia, G4 neutropenia</p>
Ph3 012-360	66	M	Neutrophil count decreased	94	2	40	<ul style="list-style-type: none"> • Mouth infection herpes simplex • Pulmonary edema

Review Additional Treatment-related Deaths from FDA Analysis

Tx Group	Age	Sex	Cause of Death	Study Day	Cycle	Cycle Day	Comment
Ph3 001-024	31	M	Cerebral PD FDA hemorrhagic brain lesions + thrombocyto- penia	499	2	38	<ul style="list-style-type: none"> • PD D30 brain and liver • G4 thrombocytopenia • Bleeding in brain met
Ph2 001-023	66	M	Hepatic PD FDA Hepatic failure	52	1	52	<ul style="list-style-type: none"> • Prior oxaliplatin, irinotecan • 20+ liver mets at baseline and encephalopathy • hPD D52 with G4 bilirubin
Ph3 001-005	44	F	Hepatic PD FDA Hepatic failure	124	2	52	<ul style="list-style-type: none"> • 60% liver involved at BL • Massive hPD D41, ascites • Died with G3 bilirubin

Timeline of Treatment Related Deaths

Patient ID:

Hepatic failure
A/001-023

Hepatic failure
B/001-006

Hepatic failure
C/001-005

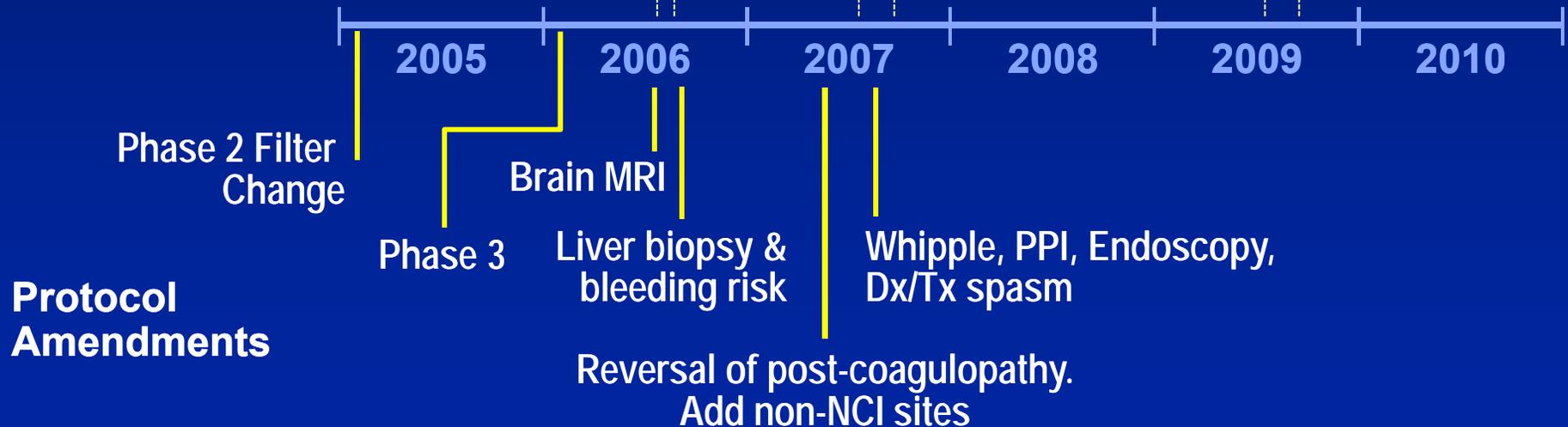
RHA hemorrhage
D/001-038

GI perforation
E/001-010

Streptococcal sepsis
F/009-650

Hemorrhage/bone marrow failure
G/001-024

Neutropenia/thrombocytopenia
H/012-360



Most Common SAEs ($\geq 5\%$)

n (%)	Pooled N=121	Peri N=121	Post N=121
Neutropenia	71 (58.7)	0	71 (58.7)
Thrombocytopenia	62 (51.2)	9 (7.4)	60 (49.6)
Febrile neutropenia	20 (16.5)	0	20 (16.5)
Anemia	13 (10.7)	2 (1.7)	12 (9.9)
Hyperbilirubinemia	7 (5.8)	1 (0.8)	6 (5.0)

Hospitalization

Reason	Pooled N=121	
	% Patients	Median Duration (Days)
For procedure	100	4
Total duration of prolongation due to AE	29.8	5.5
Re-hospitalization for AE	51.2	5

Most Common AEs Leading to Treatment Discontinuation

n (%)	Pooled N=121
Any AE resulting in drug discontinuation	46 (38.0)
Thrombocytopenia	19 (15.7)
Neutropenia	9 (7.4)
Hyperbilirubinemia	5 (4.1)

Cycle Delays and Dose Reductions

Patients with >1 cycle PHP	Pooled N=92
Any cycle delayed, % patients	57.6
Median, days	6

- **Dose reductions in 23.1% (28/121)**
- **Reasons: thrombocytopenia, neutropenia**

Most Common Adverse Events (>15%) Peri- and Post-procedure

n (%)	Peri Pooled N=121		Post Pooled N=121	
	All	Grade 4	All	Grade 4
Thrombocytopenia	89 (73.6)	53 (43.8)	97 (80.2)	81 (66.9)
Neutropenia	5 (4.1)	0	105 (86.8)	87 (71.9)
Febrile neutropenia	0	0	22 (18.2)	9 (7.4)
Anemia	75 (62.0)	8 (6.6)	71 (58.7)	6 (5.0)
Hypoalbuminemia	43 (35.5)	0	7 (5.8)	0
AST increased	30 (24.8)	8 (6.6)	16 (13.2)	2 (1.7)
Leukopenia	3 (2.5)	0	34 (28.1)	20 (16.5)
Hyperbilirubinemia	17 (14.0)	2 (1.7)	18 (14.9)	10 (8.3)
ALT increased	12 (9.9)	1 (0.8)	14 (11.6)	1 (0.8%)

Adverse Events of Special Interest

- **Cardiovascular toxicity**
- **CNS**
- **Nephrotoxicity**
- **Hepatotoxicity**
- **GI toxicity**
- **Bleeding**

Cardiovascular Safety

- **6 arrhythmias in pooled database**
 - 3 were transient sinus tachycardias
 - There were 2 AF, 1 VT, all transient and resolved
 - 2 at filter opening
 - all cardioverted
 - VT led to patient withdrawal
 - No long term consequences
- **7 ischemic-type events included troponin elevations**
 - 1 acute non-T-wave MI (cycle 1) + grade 4 troponin
 - 4 cycles, withdrawn for Vtach see above
 - 2 cases of troponin elevations with EKG changes - all resolved
 - 4 cases of troponin elevations with no EKG changes - all resolved
- **Cardiac events did not lead to cumulative or clinically relevant myocardial damage**
 - Patients received multiple subsequent cycles after the event

CNS Ischemic Events

- **There were 4 cerebral infarct events**
 - 3 infarcts leading to withdrawal
 - 1 associated with brain metastases, occurring late, after PD
- **There were 3 TIA-type events, all resolved, with no withdrawals**
- **Timing can be on D1 or post-procedure**

Nephrotoxicity

- **No evidence that hypotension led to severe renal toxicity in any patient**
- **3 patients with renal failure AEs**
 - Temporally dissociated from procedure
 - Patients Ph3 001-006 and 001-024, Ph2 001-038
 - Late events during multi-organ failure, death due to other causes
- **No evidence of worsening renal function with repeated courses**

Hepatotoxicity

- **All intra-arterial liver-directed therapies have liver toxicity**
- **High dose melphalan for myeloablation and IHP is associated with liver toxicity**
- **All liver-related deaths had >50% tumor burden at baseline and hPD prior to death**
- **Careful patient selection, laparoscopy & biopsy if tumor burden >50% has prevented further deaths**
- **No evidence of cumulative liver damage**

Overview of Hepatic Adverse Events

n (%)	Pooled N=121
Hepatic AE	53 (43.8)
Grade 4	18 (14.9)
SAE	11 (9.1)
Leading to treatment discontinuation	7 (5.8)
Resulting in death	1 (0.8)

Gastrointestinal Toxicity

Category, n (%)	Pooled N=121	Peri N=121	Post N=121
Any gastrointestinal event	31 (25.6)	9 (7.4)	28 (23.1)
Ulcers, gastritis, perforations, bleeds	13 (10.7)	2 (1.7)	11 (9.1)
Pancreatitis, cholecystitis	6 (5.0)	2 (1.7)	5 (4.1)

Bleeding

- **There is risk of bleeding during the procedure due to**
 - Anticoagulation
 - Filter sequestration of platelets
- **There is an additional risk due to thrombocytopenia from melphalan-induced bone marrow toxicity**
- **PHP requires diligent reversal of anticoagulation, close monitoring and transfusion as required**

Overview of Bleeding Events

Event, n (%)	Pooled N=121
Bleeding AE*	16 (13.2)
Grade 4	3 (2.5)
Serious	10 (8.3)
Leading to hospitalization	9 (7.4)
Leading to treatment discontinuation	4 (3.3)
Resulting in death**	1 (0.8)

* omits 3 patients: Ph2 001-006 urethral hemorrhage pre-PHP; Ph3 001-013 subcapsular hepatic bleed and 009-650 vaginal hemorrhage in PV database only

**Ph2 patient 001-038 R hepatic artery hemorrhage (prior Whipple's) no thrombocytopenia

REMS

Learnings Incorporated into Training

- **Risk of hepatic failure**
 - Added diagnostic laparoscopy for patients with 50% of their liver replaced by tumor
- **Risk of gastrointestinal toxicity**
 - Exclude patients with prior surgeries that could potentially affect normal hepatic biliary/vascular anatomy
 - e.g., Whipple's procedure
 - Endoscopy of patients with history of peptic ulcer disease
 - Added procedures for diagnosing and treating hepatic artery spasm before melphalan infusion
 - Use of IA NTG to prevent melphalan reflux
 - Caution for placement of catheters and infusing melphalan due to inflammation or injury to nearby tissues and organs

Learnings Incorporated into Training (con't)

- **Risk of hemorrhage**
 - Added brain MRI to detect active intracranial metastases or brain lesions
 - Hormonal suppression in premenopausal women
- **Risk of thrombocytopenia**
 - Can lead to bleeding
 - Managed with transfusions
- **Risk of anemia**
 - Managed by RBC transfusion, erythropoietin

Mitigating Consequences of Neutropenia

- **Neutropenia and febrile neutropenia**
 - **Requires prophylactic growth factor support**
 - **New recommendation based on 20% risk of complicated neutropenia**

Mitigating Risks of CV Complications

- **Patient selection**
 - NYHA classification 1 only
 - Normal baseline ECG, echo and troponins
- **Pre-procedural monitoring and management**
 - Adequate fluid pre-load prior to balloon inflation
 - 12-lead ECG prior to hydration, morning of procedure
 - Continuous BP monitoring, vasopressor response test
 - Vasopressors to keep MAP >65 mmHg
- **Post-procedural monitoring and management**
 - ECG within 2 hours and daily until hospital discharge
 - Echos prior to each PHP cycle and 30 days after last PHP
 - Troponins at end of PHP, q6h for 24 hours, daily until discharge

Elements of the ETASU Melblez Kit REMS

- Medication guide, communication plan
- Hospital qualification and certification
 - Appropriate equipment
 - Qualified procedure team
- Prescriber certification
 - Interventional radiologist, surgical oncologist, anesthesiologist, perfusionist
- Restricted distribution to certified hospitals

Elements of the ETASU Melblez Kit REMS – Training Program

- **Mandatory training of entire procedural team**
- **Based on experience gained in the development program**
- **Education about risks, causes and management due to procedure and myelosuppression**
- **Three-stage process:**
 - **Didactic classroom training with experienced team**
 - **Video of procedure, emphasis on team coordination and communication**
 - **Hands on experiential training for initial cases**

Benefit/Risk Summary

- **Key Benefits**

- **Compelling disease control in a rare, rapidly fatal disease with limited treatment options and no approved therapies**
- **Consistent efficacy across subgroups**
- **Primary efficacy supported by secondary endpoints**
- **Overall survival analysis confounded by substantial efficacy of PHP in cross over patients**

- **Key Risks**

- **Complex procedure with significant but manageable procedure related toxicity**
- **Significant myelosuppression due to high dose melphalan**
- **Treatment related mortality is consistent with other aggressive treatments for rapidly fatal cancers**
- **Careful patient selection, close monitoring and aggressive intervention for toxicity necessary to mitigate risk**

Clinical Perspective

Melblez Kit for Ocular Melanoma

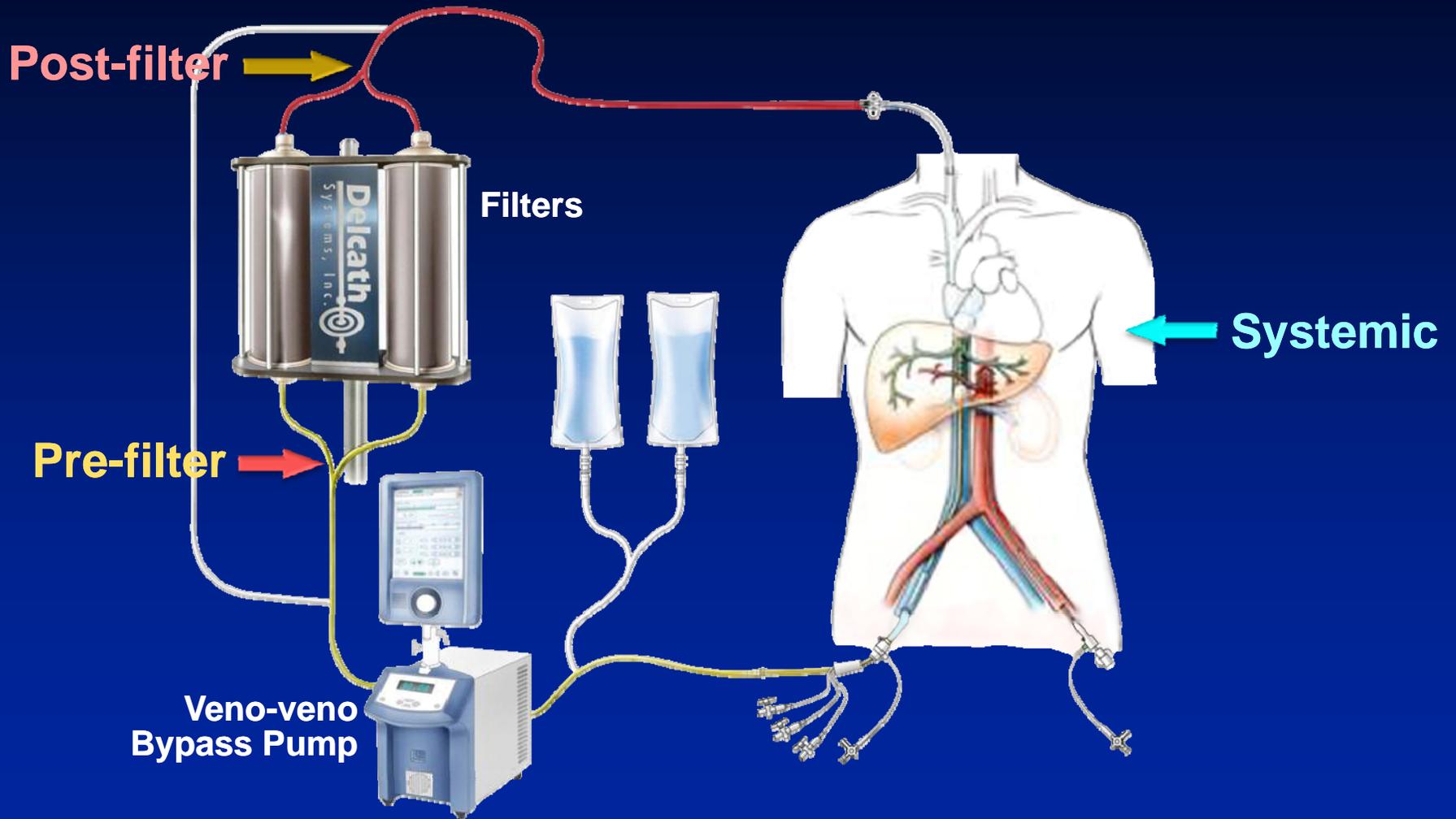
**FDA Oncologic Drugs
Advisory Committee Meeting**

Delcath Systems, Inc.

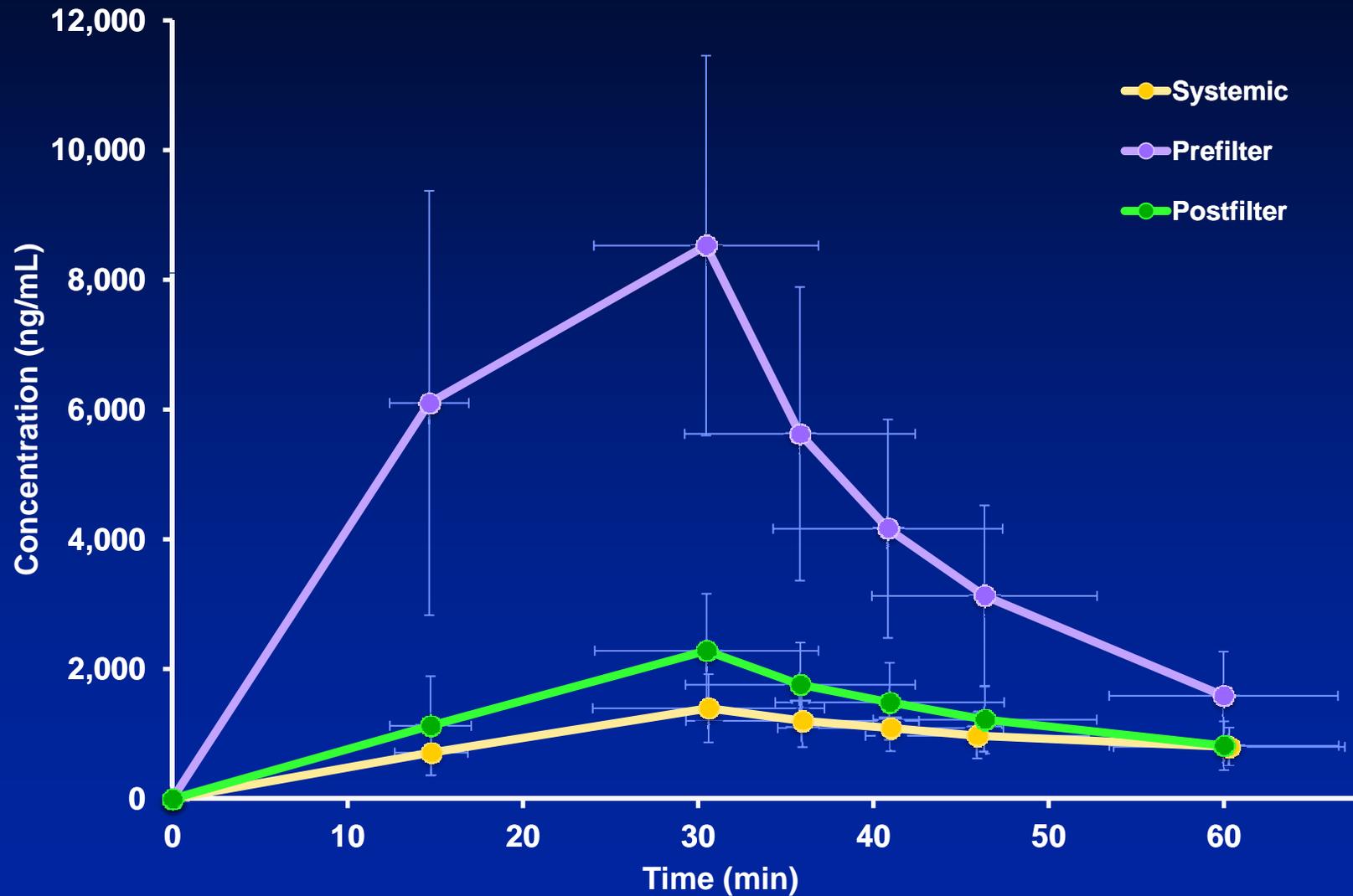
Overall PFS by Baseline Extra-Hepatic Lesion Status ITT (April 2010)

Extra-hepatic lesions	Randomized to PHP N=44	Randomized to BAC N=49	Hazard Ratio		Interaction p-value
			Estimate	(95% CI)	
% patients with PFS event	88.2	95.2	0.34	(0.17, 0.68)	0.8821
Median PFS, months (95% CI)	6.54 (2.27, 7.16)	1.71 (1.41, 2.69)			
Liver lesions only					
% patients with PFS event	85.2	100	0.36	(0.21, 0.64)	
Median PFS, months (95% CI)	4.67 (3.22, 8.61)	1.64 (1.41, 2.33)			

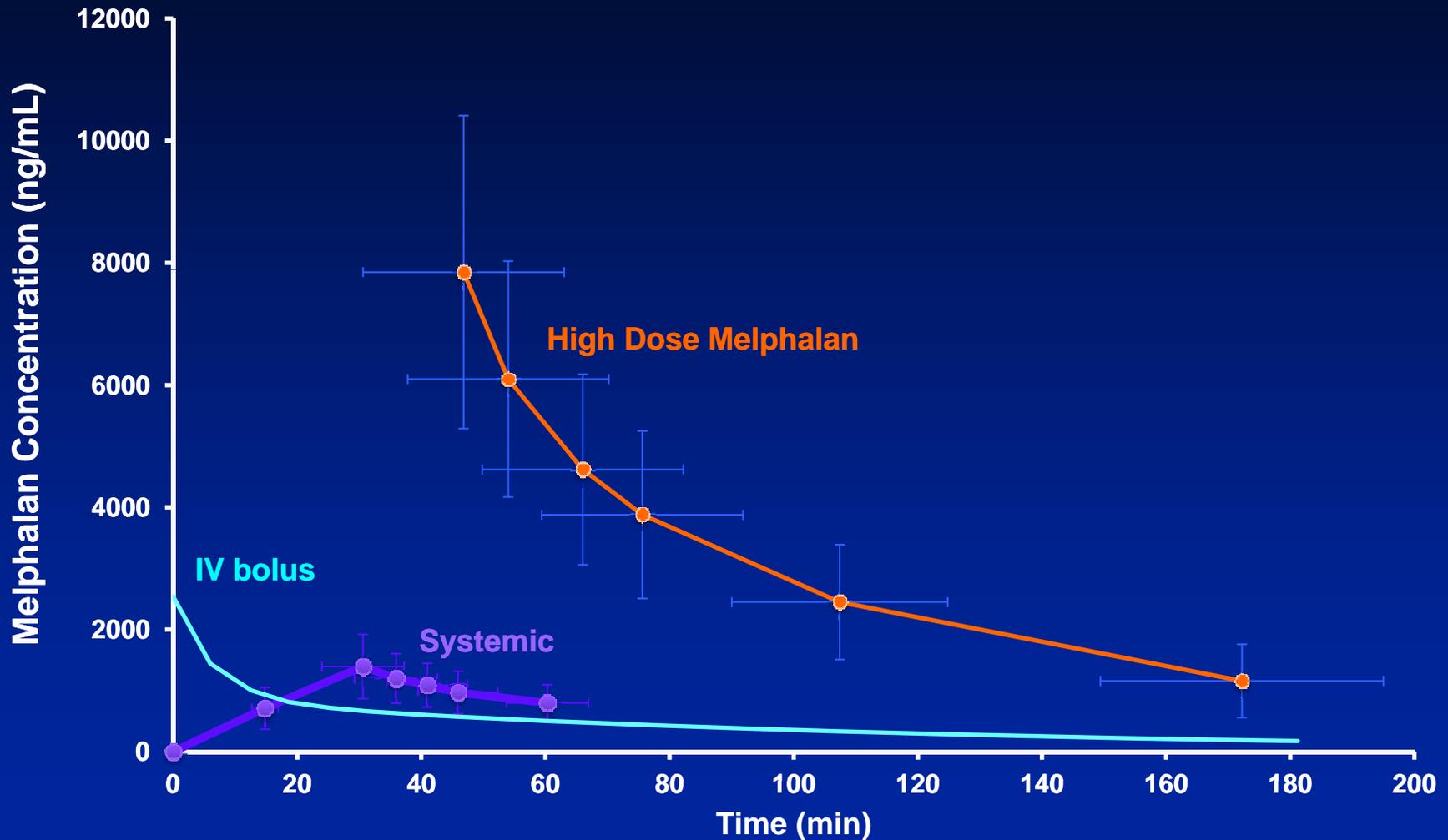
PK Sampling Sites



Phase III – Mean Concentration – Time Profiles

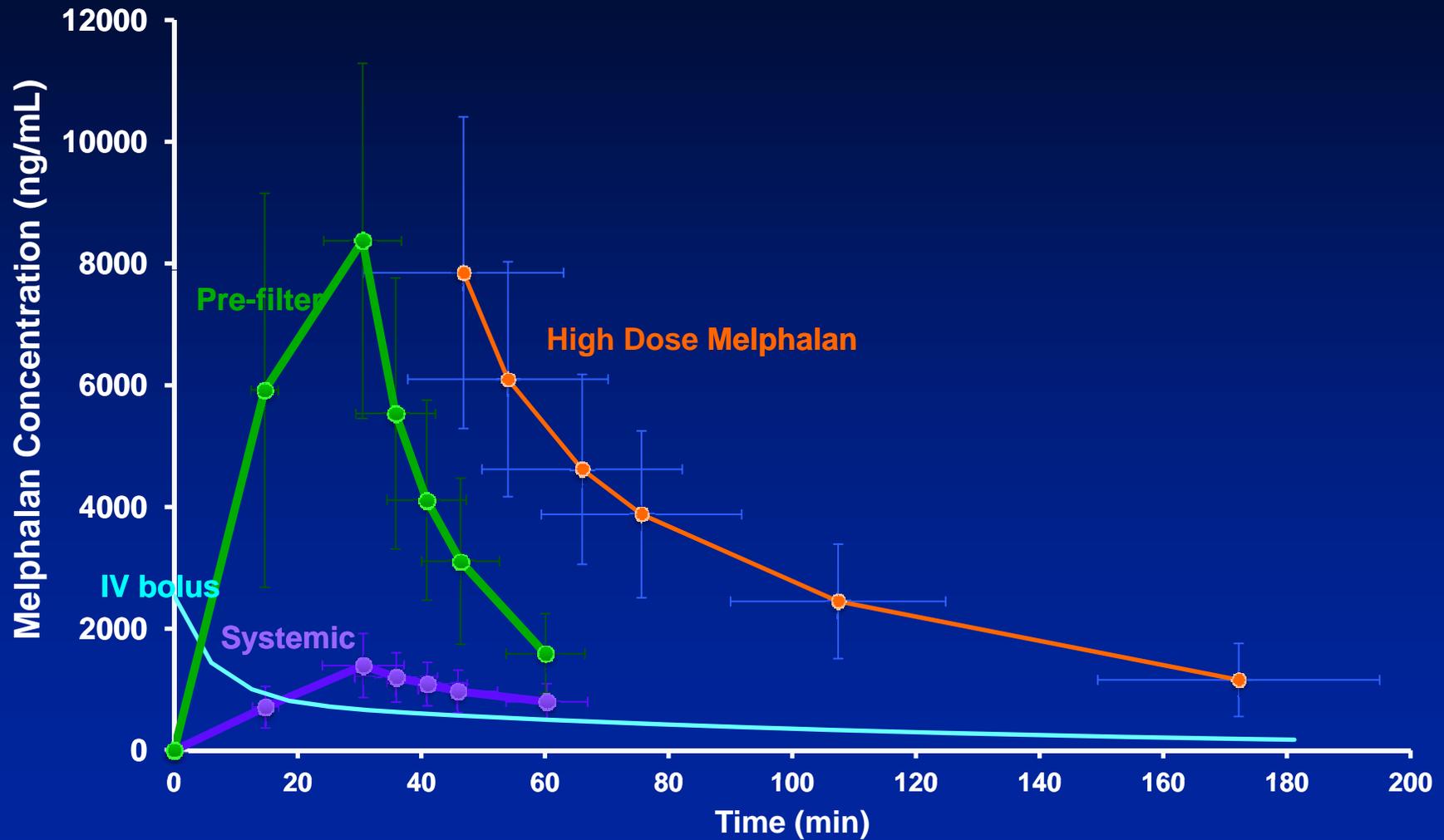


Systemic Exposure: Comparison with Published Data



*192 mg/m² over ~34 min inf, Nath 2010. ^IV bolus, Alberts, 1979. 0.6 mg/kg.

Exposure: Comparison with Published Data



*192 mg/m² over ~34 min inf, Nath 2010. ^IV bolus, Alberts, 1979. 0.6 mg/kg.

OS by Baseline Extra-Hepatic Lesion Status

ITT Ocular (June 2012)

Extra-hepatic lesions	Randomized to PHP N=39	Randomized to BAC N=44	Hazard Ratio		Interaction p-value
			Estimate	(95% CI)	
					0.6040
Baseline extra-hepatic lesions					
Patients who died n/m (%)	16/16 (100.0)	15/18 (83.3)	1.15	(0.57, 2.35)	
Median (95% CI) time to death (months)	10.25 (6.44, 16.00)	9.59 (4.07, 13.04)			
Minimum time to death (months)	0.9	1.8			
Maximum time to death (months)	24.4	42.3+			
Baseline hepatic lesions only					
Patients who died n/m (%)	23/23 (100.0)	21/26 (80.8)	1.47	(0.81, 2.68)	
Median (95% CI) time to death (months)	9.79 (5.22, 13.60)	10.64 (3.81, 16.53)			
Minimum time to death (months)	2.0	1.1			
Maximum time to death (months)	28.8	67.3+			

BAC hPFS: Liver-directed Therapies vs. Systemic vs. No Therapy

	TACE/SIRT BAC N=15	Systemic BAC N=24	No therapy BAC N=10
Median hPFS, months	2.69	1.64	1.61
95% CI	1.38-9.30	1.28-2.92	1.35-2.30
P-value from log-rank test			0.46
Hazard ratio vs. no therapy	0.56	0.82	
95% CI	0.21-1.53	0.33-2.01	

Troponin Perspective

- **Cardiovascular sequelae have been minimal**
- **There have been some cardiovascular events and, given the benefit of PHP, they are not disproportionately high**
- **Troponins are not a specific marker for infarction**
 - **Elevated in marathon runners**
- **Troponin elevations appeared commonly but clinically meaningful sequelae are uncommon**
- **There is little if anything to be gained from considering troponins in isolation**

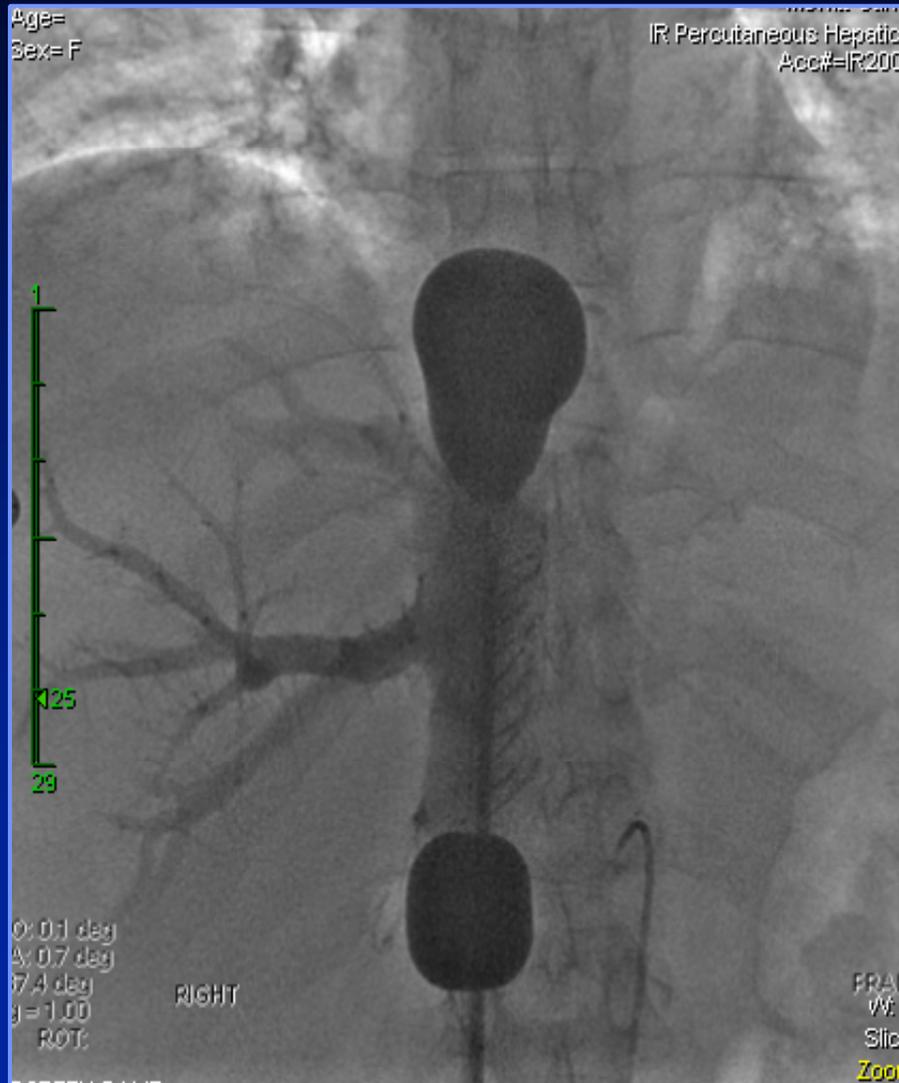
Hypotension and Cardiac Events

- **EXAMPLE: Patient 600—73 year-old male**
 - History of hyperlipidemia
 - No history of coronary artery disease
 - Hypertension
 - Dysrhythmia
 - Ocular melanoma
 - Perfusion #1 Dec. 17, 2008
 - ECGs
 - Dec 16, '08: (Pre Rx) Inverted “T” waves in lead III
 - Dec 17, after low perfusion: rate 104, inferior “T” waves more inverted
 - Dec 18-20: similar to Dec. 16 (fluctuations of “T” wave in a single lead (lead III)—read as “normal”
 - Echo Dec 18: EF 55-60% (normal)
- **Diagnosis of MI only on the basis of troponin**

Hypotension and Cardiac Events

- **EXAMPLE: Patient 600—73 year-old male**
 - **Diagnosis of MI on the basis of troponin!**
 - **ECG/Echo changes do not meet criteria for MI**
 - **Cycle 1 Dec 17, 2008; troponin elevated**
 - **Cycle 2 Jan 27, 2009; Fluid overload**
 - **Cycle 3 Mar 17, 2009; Fluid overload**
 - **Cycle 4 May 6, 2009; Wide-complex tachycardia reported on anesthesia strips, but tracings not available for review; PHP aborted**
 - **Patient expired on Dec. 23, 2010 (21 months after last PHP)**
 - **There were no other known cardiac concerns**

IVC Venogram



- Turn off pump
- Shoot IVC venogram
- Back filling of hepatic veins
 - Left usually does not fill
- No leak around cranial balloon into right atrium
- Shows isolation of hepatic venous return

Reasons for Discontinuation by Cycle

Reason, n (%)	Cycle	Pooled, N=121					
		1 N=116	2 N=92	3 N=60	4 N=26	5 N=6	6 N=3
All		24 (20.7)	32 (34.8)	34 (56.7)	20 (76.9)	3 (50.0)	2 (66.7)
Death		0	0	0	0	0	0
PD		7 (6.0)	22 (23.9)	8 (13.3)	2 (7.7)	0	0
Hepatic		3 (2.6)	12 (13.0)	3 (5.0)	1 (3.8)	0	0
Extra-Hepatic		4 (3.4)	10 (10.9)	5 (8.3)	1 (3.8)	0	0
AE		11 (9.5)	7 (7.6)	17 (28.3)	2 (7.7)	0	0
Investigator opinion		0	0	5 (8.3)	1 (3.8)	2 (33.3)	0
Lost to follow-up		0	0	0	0	0	0
Completed 4 Cycles		0	0	0	15 (57.7)	0	0
Completed 6 Cycles		0	0	0	0	0	2 (66.7)
Withdrew Consent		1 (0.9)	0	1 (1.7)	0	0	0
Other		3 (2.6)	1 (1.1)	3 (5.0)	0	1 (16.7)	0
Unknown		2 (1.7)	2 (2.2)	0	0	0	0

Median hPFS (IRC) by # of Cycles Received

(April 2010)

Median hPFS, Months (95% CI)	Randomized to PHP N=44	Crossover to PHP N=28	Total PHP N=72
Overall	7.03 (5.22, 9.66)	8.44 (3.06, 11.17)	8.05 (5.22, 9.72)
0	2.63 (0.89, 6.44)	1.45 (,)	1.86 (0.89, 6.44)
1	5.72 (1.22, 10.05)	12.12 (1.38, 12.12)	10.05 (1.22, 12.12)
2	3.22 (1.41, 5.22)	4.27 (2.07, 10.15)	3.22 (2.07, 4.99)
3	8.15 (6.11, 12.58)	11.17 (8.34,)	8.34 (6.54, 12.58)
4	8.05 (6.34, 15.28)	- (8.44,)	15.28 (6.34,)
5	9.61 (8.77, 10.45)	-	9.61 (8.77, 10.45)
6	11.30 (,)	9.72 (,)	10.51 (9.72, 11.30)