A Phase-III Random Assignment Trial Comparing Percutaneous Hepatic Perfusion with Melphalan (PHP-mel) to Standard of Care for Patients with Hepatic Metastases from Metastatic Ocular or Cutaneous Melanoma. (LBA #8512)

James F. Pingpank, Jr, FACS

Associate Professor of Surgery, Division of Surgical Oncology

Department of Surgery, University of Pittsburgh, Pittsburgh, PA

Authors: JF Pingpank, MS Hughes, HR Alexander, MB Faries, JS Zager, RE Royal, ED Whitman, CW Nutting, GP Siskin, SS Agarwala

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Disclosures

James F. Pingpank, Jr., MD
- Scientific Advisory Board (Delcath Systems, Inc; New York, NY)
- Research Support (Delcath Systems, Inc; New York, NY)

Jonathan Zager, MD:
- Scientific Advisory Board (Delcath Systems, Inc; New York, NY)

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Intra-arterial melphalan and Delcath double balloon catheter under IND (FDA)

Treatment of Patients with Hepatic Metastases from Ocular Melanoma

Incidence of ocular melanoma is 3,500-4,000/year

- 50 to 60% of patients with ocular melanoma will recur
- Liver is the sole or dominant site of disease in over 80%
  - 1,500 to 2,000/year
  - median survival ~ 2 to 7 months
  - 1-year survival ~ 10%

Systemic chemotherapy or immunotherapy do not appear to alter the natural history of the disease

Regional/hepatic directed treatment strategies are justified to control tumor progression in liver

- HAI
- CE
- IHP

Rationale for Regional Therapy

Regional therapy allows **dose escalation** to the cancer-bearing region or organ of the body while minimizing systemic exposure and toxicity, via complete separation of the regional and systemic circulation

Eliminates or significantly **reduces systemic toxicity**, and dose escalation of therapeutic agents is limited largely by the tissue tolerance of the perfused organ/limb

- Improved efficacy/tumor response

Based on its unique **vascular anatomy** the liver is a favorable site for delivery of regional therapy

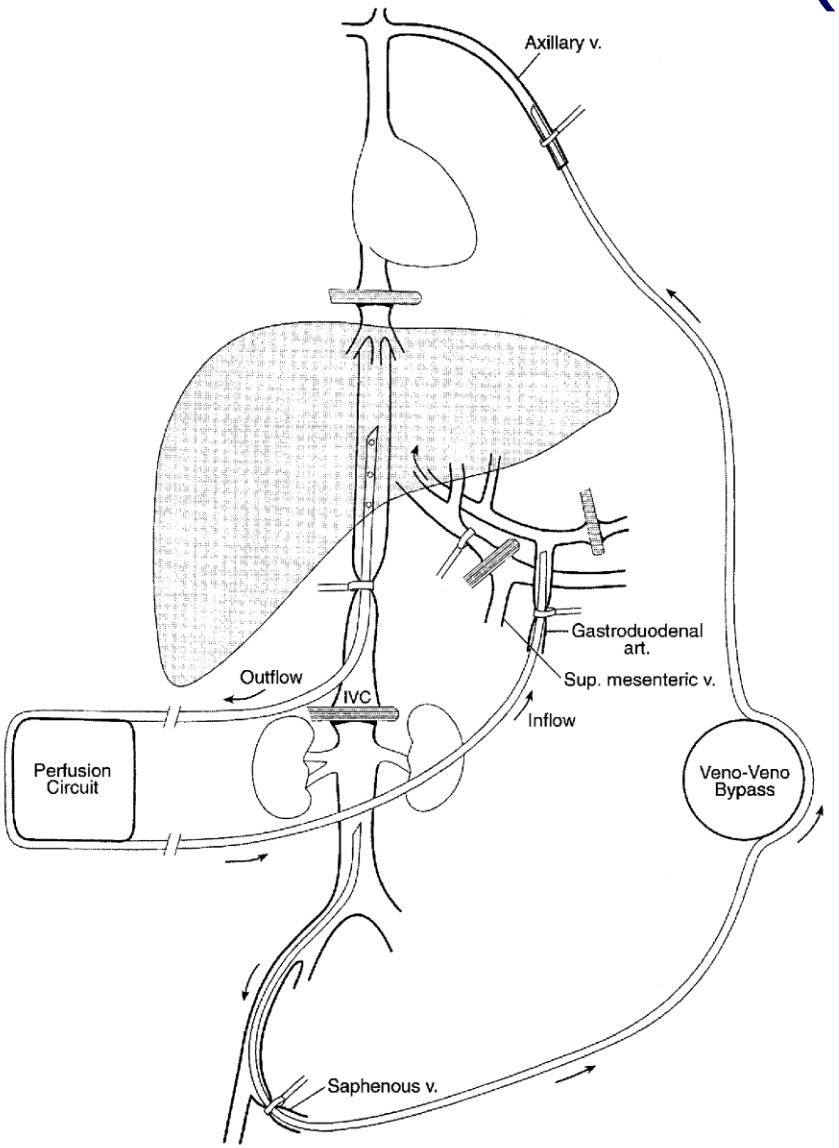
- Established tumors in liver derive the majority of blood flow from the arterial tree (tumors: 100% versus normal liver: 25%)

Potential for delivery of clinically relevant levels of **hyperthermia** or **biologic agents**

Allows treatment of the **entire tumor burdened organ**

- Versus local ablative or embolization procedures

Schematic of IHP Circuit and Operative Dissection (290 procedures)

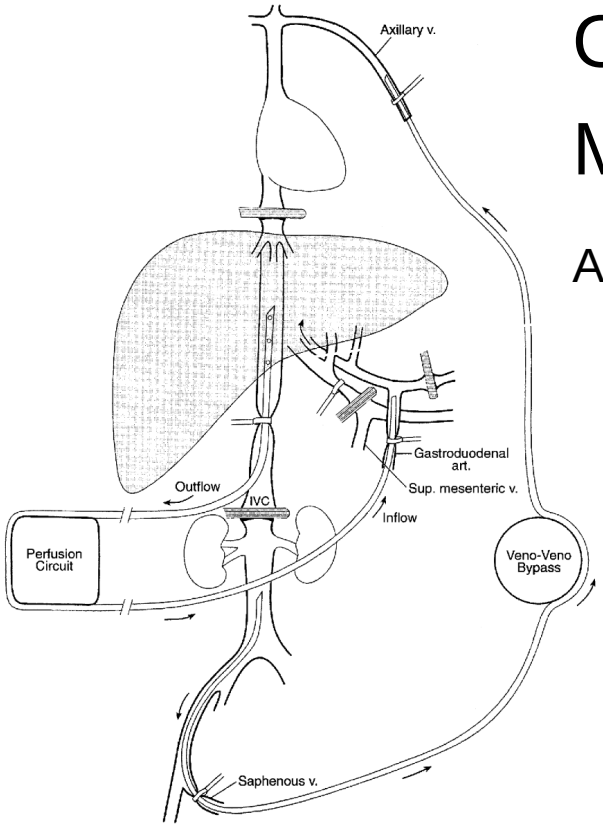


Supra-Hepatic IVC

Retro-Hepatic IVC

Porta Hepatis Dissection

Isolated Hepatic Perfusion (Melphalan) -Ocular Melanoma-



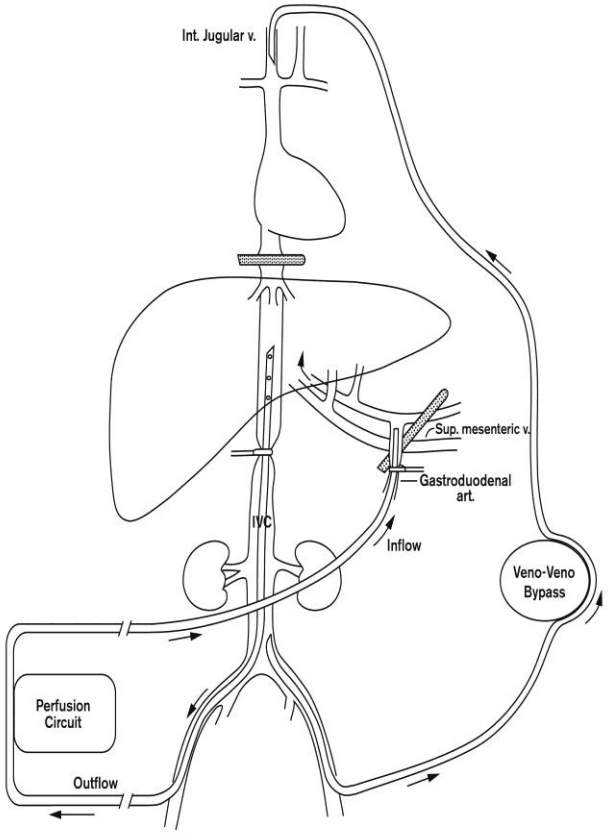
Patients: n=29 pts

Overall Response Rate: 62%

Median OS: 12.1 m

Alexander HR: Clin Cancer Res 2003 15;9(17):6343-9.

Updated IHP Dissection and Circuit
(Combined percutaneous and operative technique)



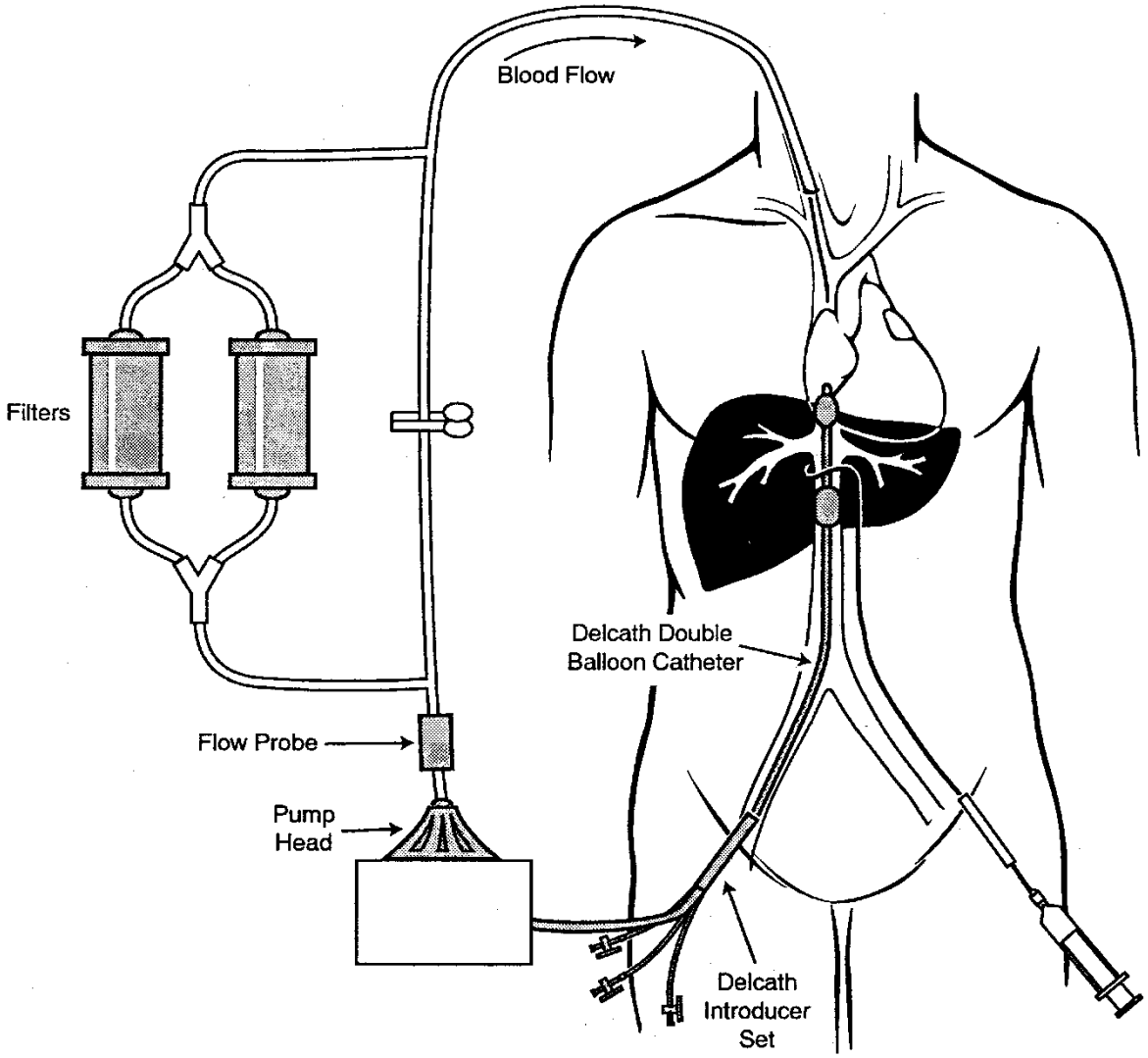
Supra-Hepatic IVC

Retro-Hepatic IVC

Zeh HJ, Bartlett DL. Ann Surg Oncol 2009; 16:385-94.

Porta Hepatis Dissection

Percutaneous Hepatic Perfusion



Melphalan Phase I MTD: 3.0 mg/kg (based upon IBW)

Phase I Trial Design

12 Patient “Feasibility”

Dose Escalation Schedule

Dose Level	Melphalan (mg/kg)	No. of Patients
1	2.0	12
2	2.5	3
3	3.0	7
4	3.5	6

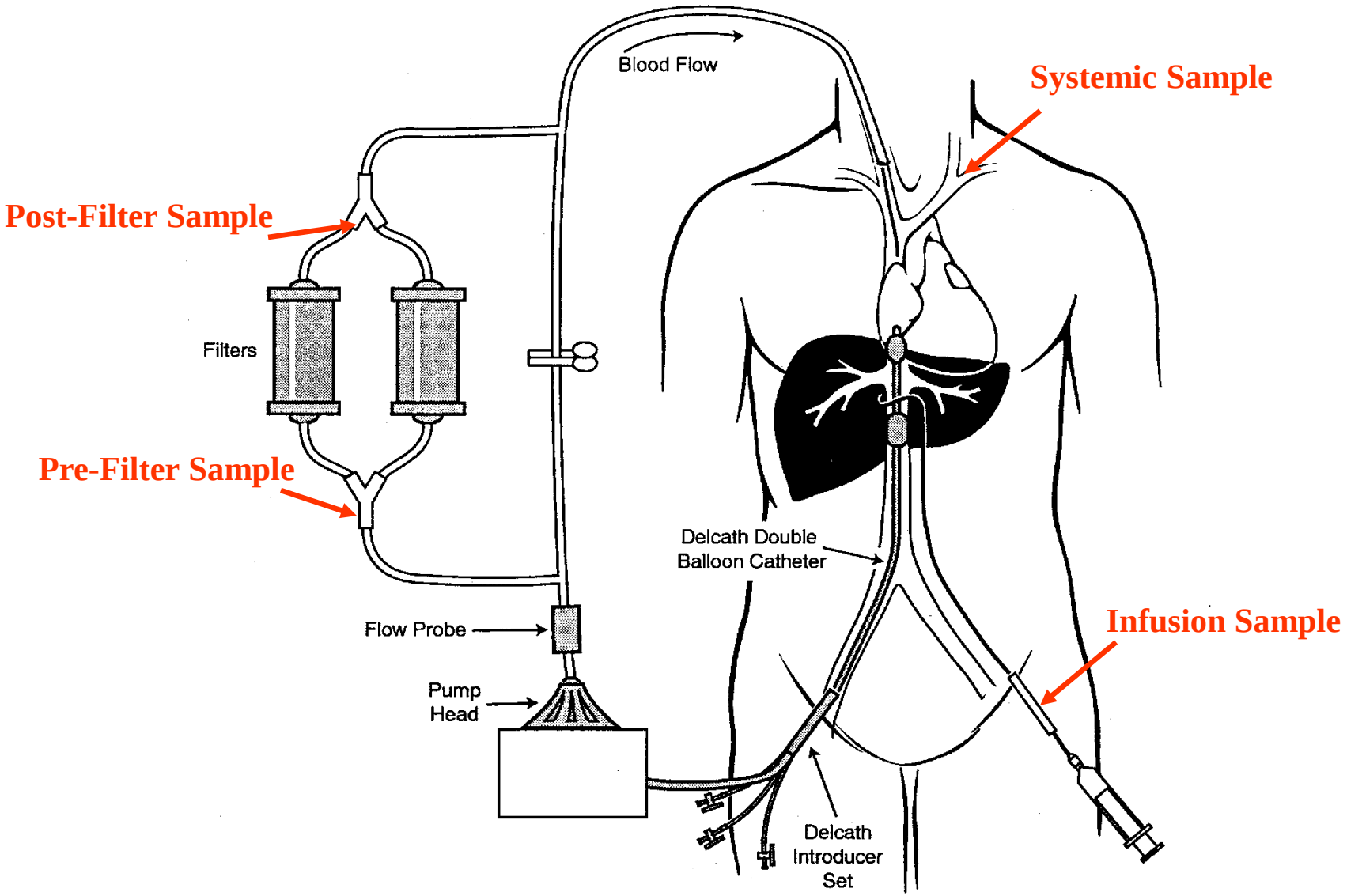
Dose Limiting Toxicity

1. Grade IV neutropenia > 72 hours or with fevers
2. Grade III thrombocytopenia > 72 hours/bleeding
3. Grade IV hemoglobin > 7 days
4. Grade III/IV non-hematologic organ toxicity > 24h

No planned modifications in perfusion/filter circuit

Pingpank JF. J Clin Oncol 2005; 23, 3465-3474

Percutaneous Hepatic Perfusion

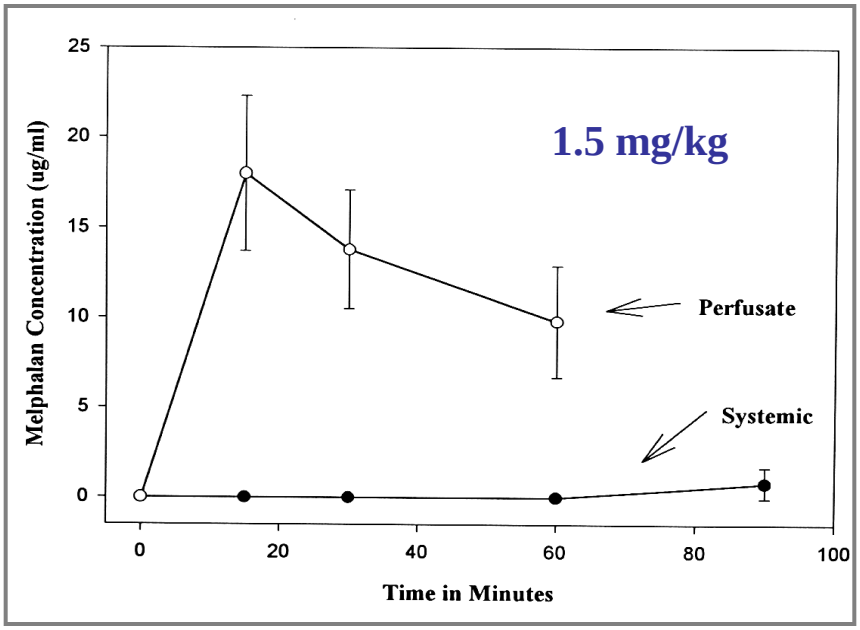


Pingpank JF. J Clin Oncol 2005; 23, 3465-3474

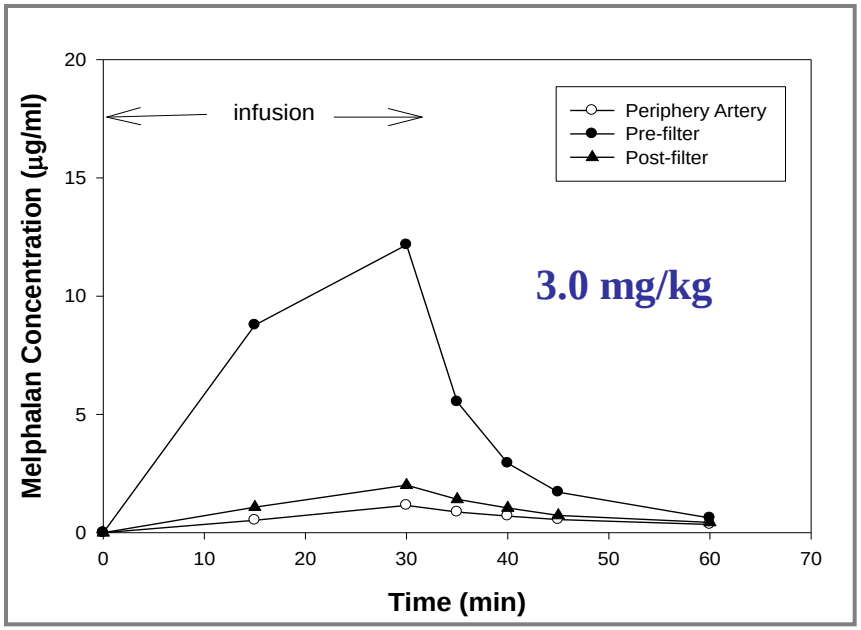
Chemotherapy Levels During Therapy

IHP vs PHP

Isolated Hepatic Perfusion



Percutaneous Hepatic Perfusion



Phase I PHP: Metastatic Melanoma

Radiographic Treatment Response (n=16)

Response	n	%	Duration
Overall	8	50	
Complete	2	13	10, 15
Partial	6	37.5	2+,8, 8, 12, 15, 16
Stable Disease	4	25	7, 7, 8, 8+
Progressive Disease	4	25	
Not Evaluable	2	13	(vascular anomaly)
Follow-up Status			
DOD (Dead of disease)	16	100	
Site of Disease Recurrence/Progression (n=12 responders)			
Hepatic	6	50	
Systemic	4	33	
Both	2	17	

+ censored with stable or responding hepatic disease with systemic progression

Finalized June 2007

Phase III Random-Assignment PHP vs. Best Available Care (FDA SPA)

Accrual goal: 92 patients (Cross-over at Hepatic progression)

10 Institutions

Melphalan dose: 3.0 mg/kg

Stratification: Cutaneous vs. Ocular

Primary endpoint: Hepatic PFS

Secondary endpoints:

1. Response rates, DFS with best available therapy
2. Response rates for patients treated with PHP

Initiated as a single institution study (Surgery Branch, NCI) and transitioned (planned) into a multicenter trial, under external DSMB monitoring.

Phase III Random-Assignment PHP vs. Best Available Care

Sample size: 46 patients per arm

Alpha: $p \leq 0.05$ (2-sided)

Power: 80% to detect a difference of 4 months Hepatic PFS

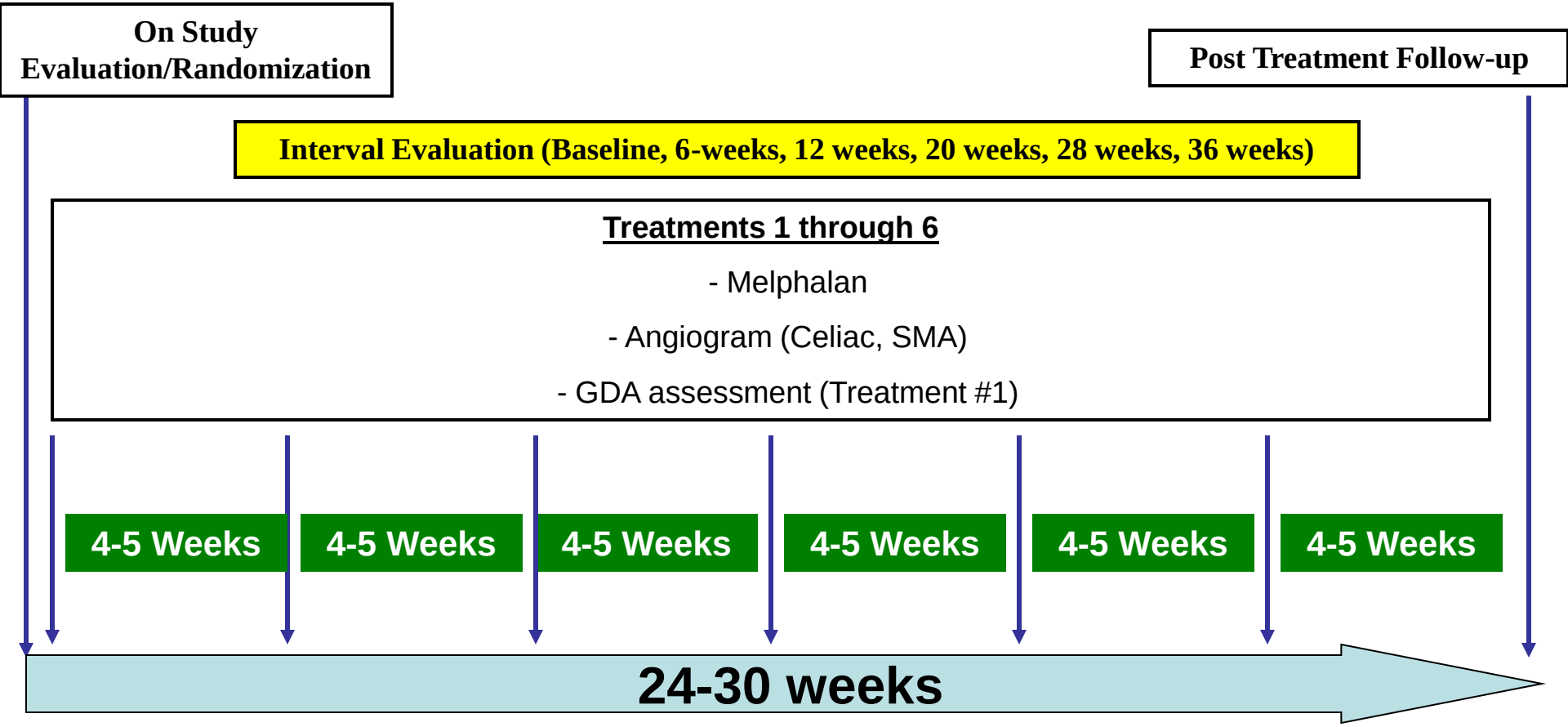
Expected Hepatic PFS

- PHP: 7.73 months
- Best Alternative Care (Control): 4 months

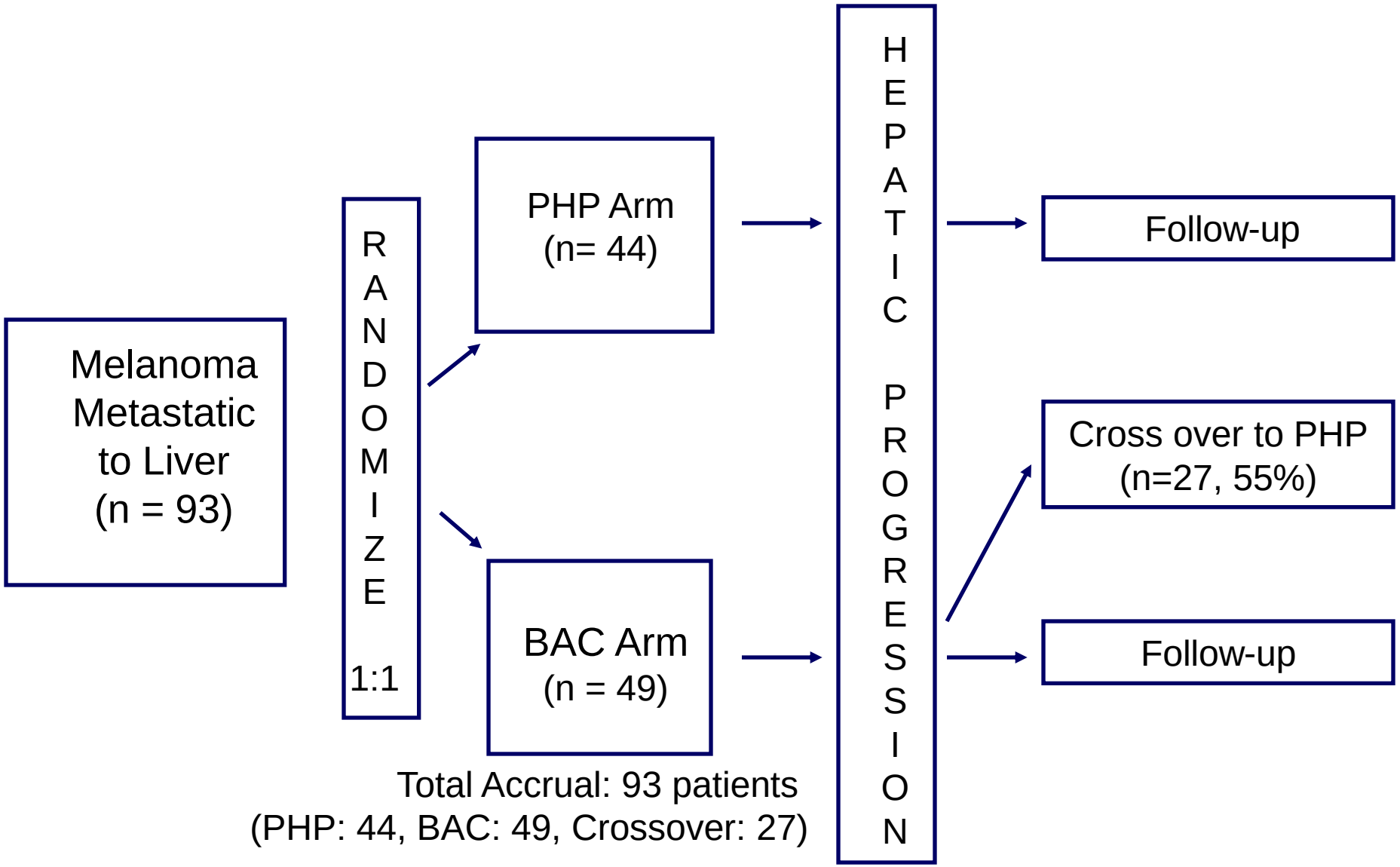
Staging Scans: Baseline, 6 weeks, 12 weeks, then q2 months

Response Rate (CR+PR) Detection: 88% power to detect a difference between 40% (Treatment) and 10% (BAC)

PHP Arm Treatment Schema



Results: Randomization and Treatment Schema -93 Patients at 10 Institutions-



Total Accrual: 93 patients
(PHP: 44, BAC: 49, Crossover: 27)

Results: Patient Demographics

Baseline Characteristic	Category	PHP (N=44)	BAC (N=49)	P value*
Age (years)	Mean	54.8	54.8	0.9866
Gender	Male Female	23 (52.3%) 21 (47.7)	22 (44.9%) 27 (55.1)	0.5362
Race	White Non-White	44 (100.0) 0 (0.0)	48 (98) 1 (2.0)	1.0000
ECOG	Missing 0 1	3 (6.8) 37 (84.1) 4 (9.1)	4 (8.2) 42 (85.7) 3 (6.1)	0.7044
Primary Tumor	Ocular Cutaneous	39 (88.6) 5 (11.4)	43 (87.8) 6 (12.2)	1.0000

*Fisher's Exact Test. Two-sided PR <= P

Results: Patient Demographics

-Prior Therapy-

Therapy	PHP (N=44)	BAC (N=49)	All (N=93)	P Value*
Radiation Therapy (primary tumor)	23 (52.3%)	24 (49.0%)	47 (50.5%)	0.8364
Chemotherapy	7 (15.9%)	6 (12.2%)	13 (14.0%)	0.7664
Immunotherapy	6 (13.6%)	7 (14.3%)	13 (14.0%)	1.0000
Image Directed Local Therapy	2 (4.5%)	3 (6.1%)	5 (5.4%)	1.0000
Unknown	0 (0.0%)	1 (2.0%)	1 (1.1%)	1.0000

*Fisher's Exact Test. Two-sided PR <= P

Results: Treatment Related Toxicities

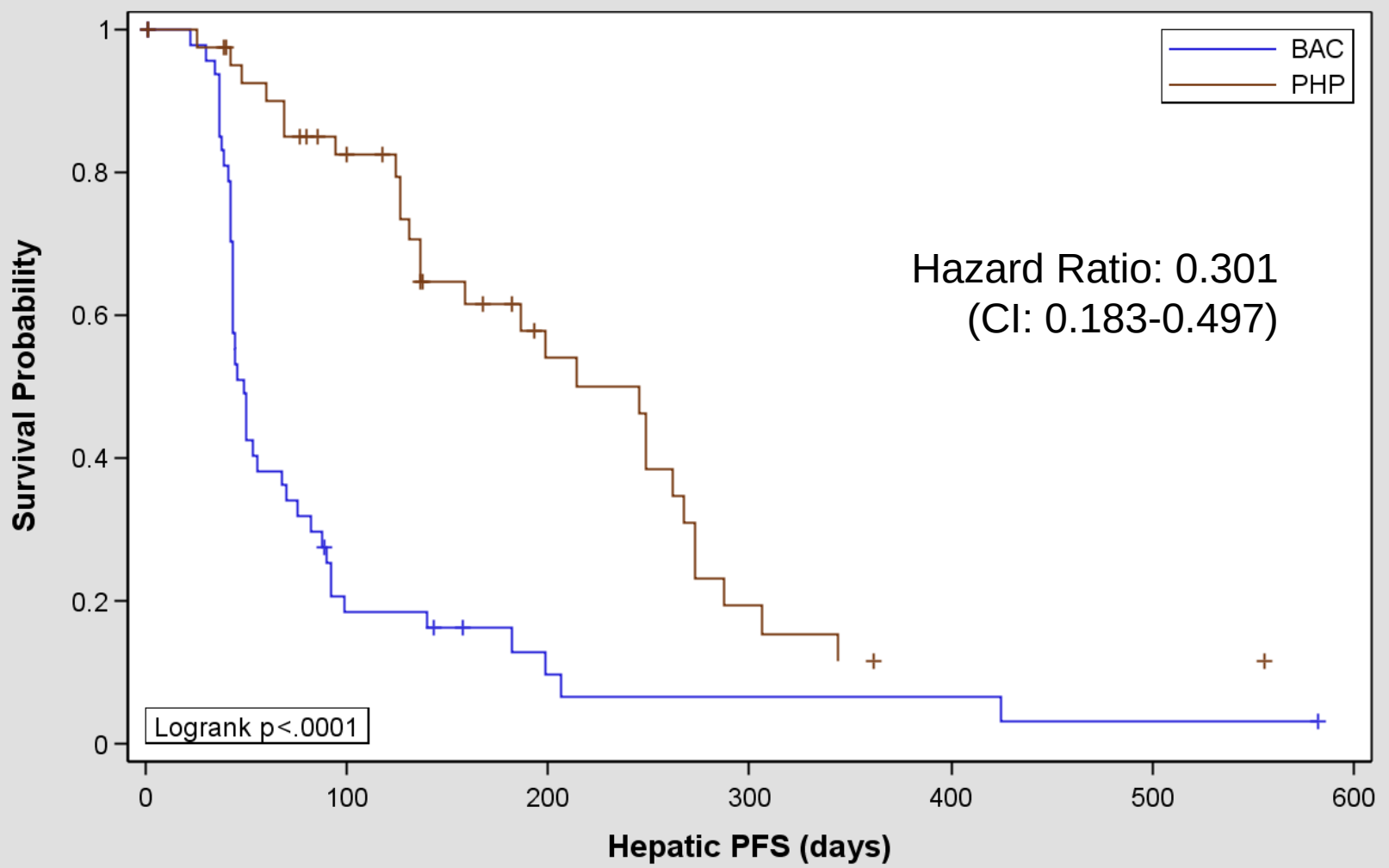
(40 Patients, 116 Treatments)

Treatment Related Toxicity, Grade 3-4 and Grade 5 (n=116 treatments)

	Grade 3-4 (n,%)	Grade 5 (n,%)
Hematologic		
Neutropenia	71 (61.2%)	2 (1.7%)
Thrombocytopenia	86 (74.1%)	
Anemia	54 (46.6%)	
Hepatic		
Elevated AST	14 (12.1%)	
Elevated ALT	6 (5.2%)	
Hyperbilirubinemia	8 (6.9%)	1 (0.86%)
Increase Alkaline Phosphatase	6 (5.2%)	
Other GI		
Acute Cholecystitis (Grade 3)	1	
Gastric Ulcer/perforation	1/1	
Vascular		
Arterial Pseudoaneurysm with A-V fistula	1 (0.86%)	

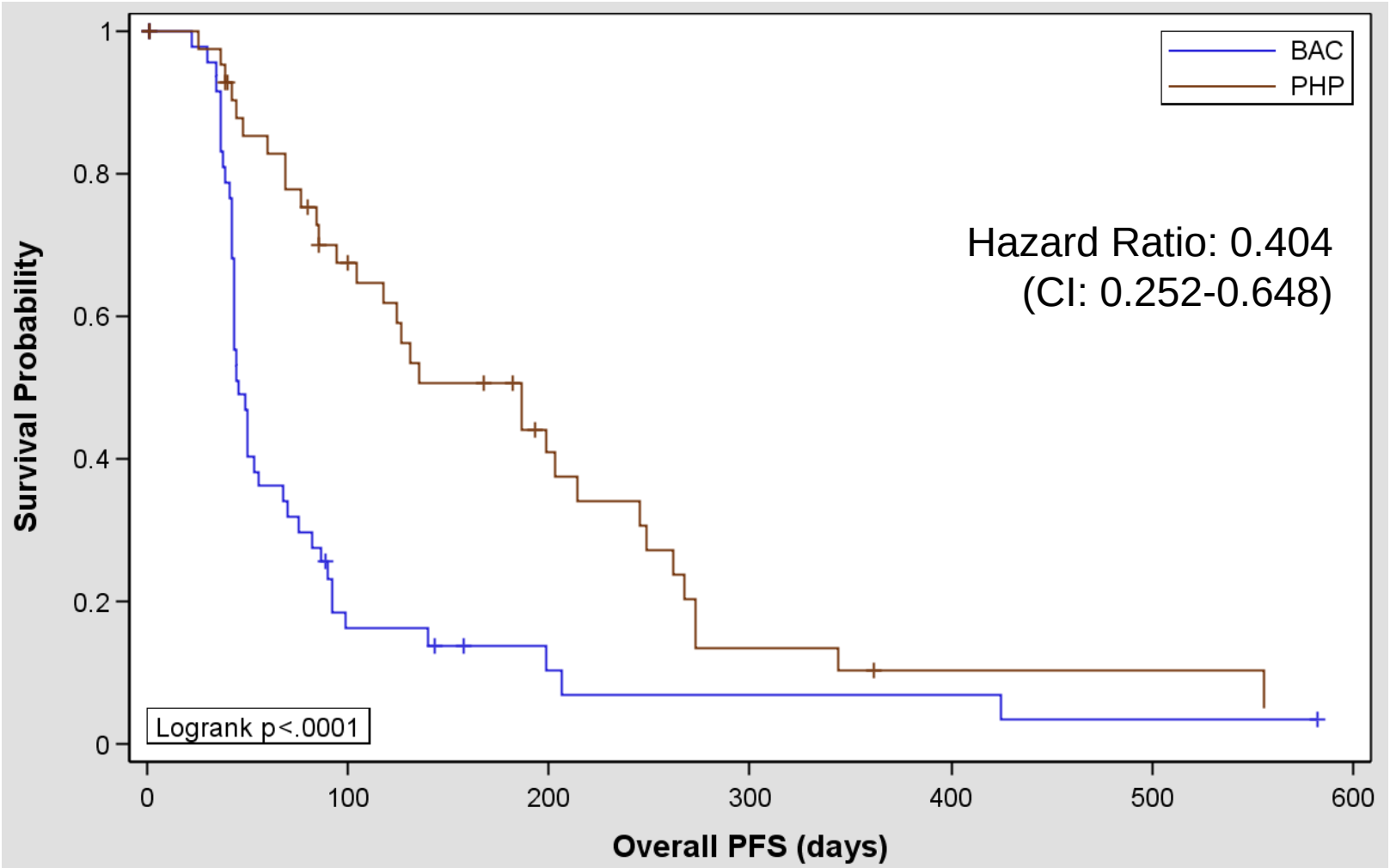
Mortality Rate:
3/40 patients (7.5%), 3/116 procedures (2.6%)
Treatment Related Deaths:
Neutropenic Sepsis (n=2), Hepatic Failure (n=1)

Results: Primary Endpoint
-Hepatic Progression Free Survival (ITT) -



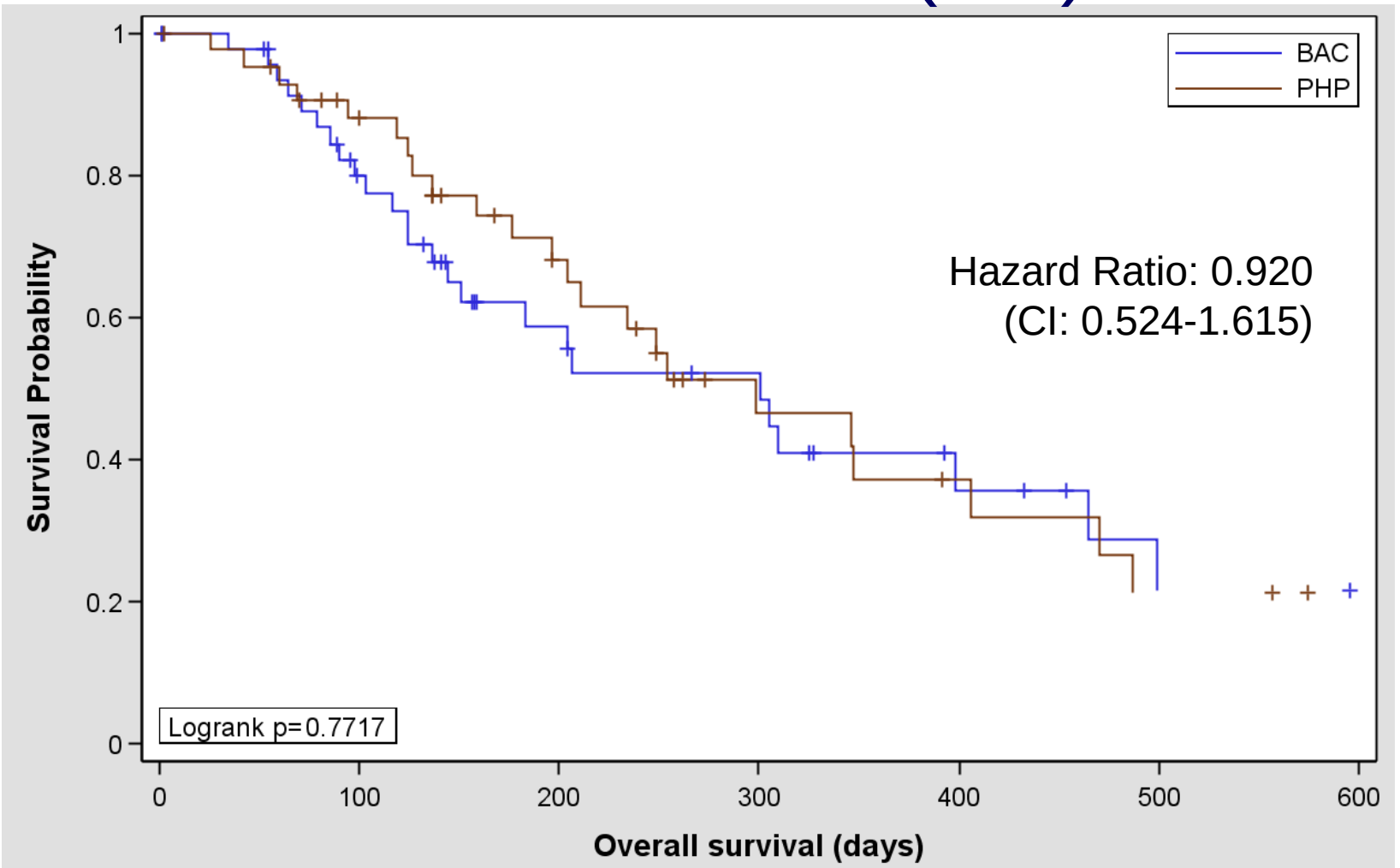
	No. of Subjects	Event	Censored	Median Survival (95% CL)
BAC	49	88% (43)	12% (6)	49.0 (43.0 68.0)
PHP	44	61% (27)	39% (17)	245.0 (136.0 267.0)

Results: Secondary Endpoint
-Overall Progression Free Survival (ITT)-



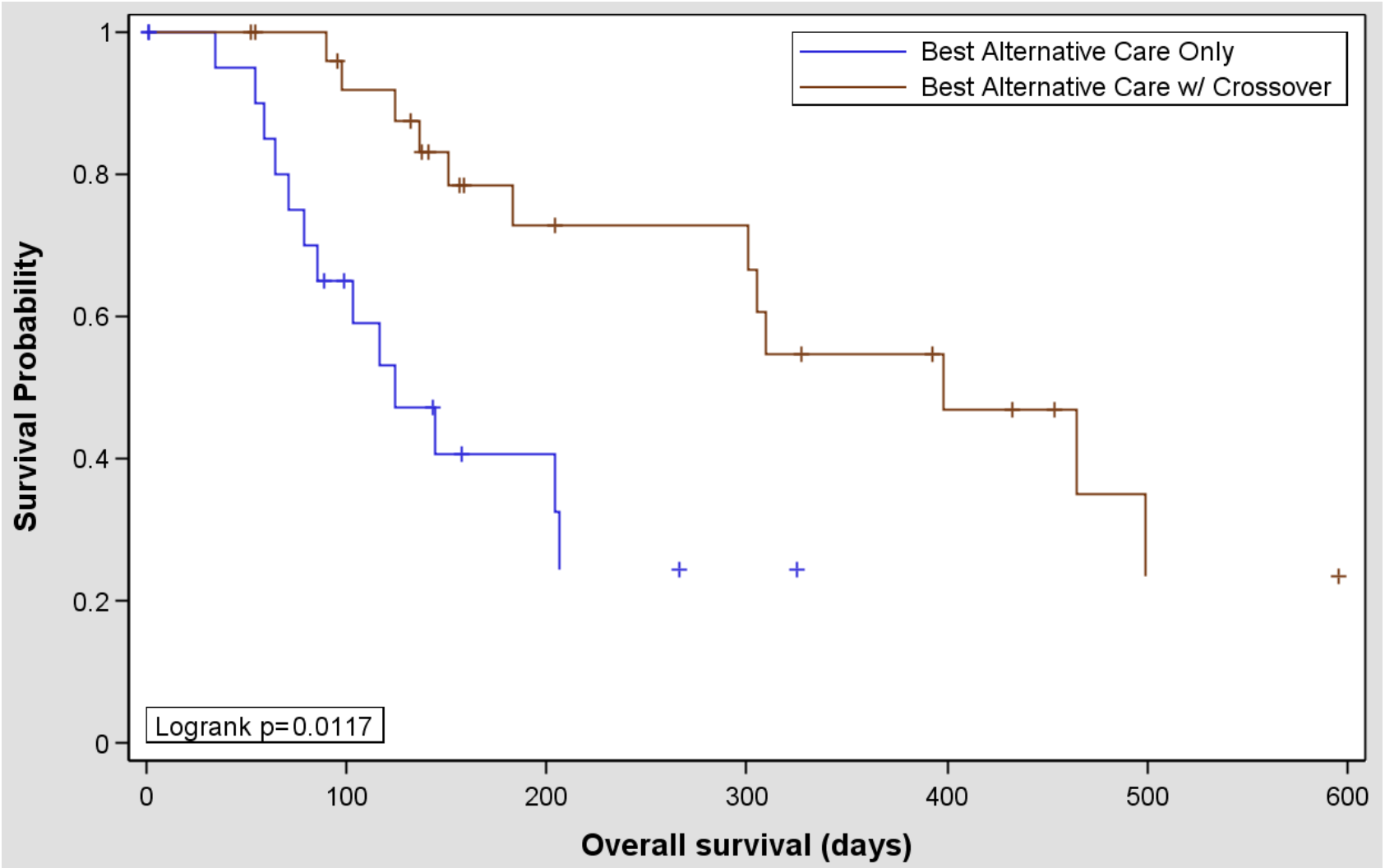
	No. of Subjects	Event	Censored	Median Survival (95% CL)
BAC	49	88% (43)	12% (6)	46.0 (43.0 56.0)
PHP	44	73% (32)	27% (12)	186.0 (104.0 245.0)

Results: Secondary Endpoint -Overall Survival (ITT)-



	No. of Subjects	Event	Censored	Median Survival (95% CL)
BAC	49	51% (25)	49% (24)	301.0 (151.0 465.0)
PHP	44	55% (24)	45% (20)	298.0 (204.0 470.0)

Results: Secondary Endpoint
-Overall Survival BAC Patients-



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Best Alternative Care Only	22	59% (13)	41% (9)	124.0 (79.0 206.0)
Best Alternative Care w/ Crossover	27	44% (12)	56% (15)	398.0 (301.0 499.0)

Results: Analysis of Factors Associated with Survival

Variable	Hazard Ratio	Confidence Interval
Melphalan	0.301	0.18 – 0.50
Gender	1.1	0.70 – 1.81
>65 years old	1.3	0.66 – 2.56
Ocular/Cutaneous	0.7	0.32 – 1.71
>1 year of disease	0.8	0.45 – 1.46
Melphalan, controlling for all of the above	0.283	0.17 – 0.47

Results: Secondary Endpoint -Response (ITT)-

		Best Alternative Care		
Overall Response: n (%)	**PHP (N= 44)**	**All (n=49)**	**Crossover (N= 27)**	**Non-Cross (N= 22)**
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	15 (34.1)	1 (2.0)	6 (22.2)	1 (4.5)
SD	23 (52.3)	13 (26.5)	11 (40.7)	6 (27.3)
PD	2 (4.5)	31 (63.3)	1 (3.7)	12 (54.5)
NE	4 (9.1)	4 (8.2)	9 (33.3)	3 (13.6)
Objective Response Rate (CR+PR)	15 (34.1)	1 (2.0)	6 (22.2)	1 (4.5)

Results: Secondary Endpoint -Response (ITT)-

		Best Alternative Care		
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p<0.001

Results: Secondary Endpoint -Response (ITT)-

		Best Alternative Care		
Overall Response: n (%)	**PHP (N= 44)**	**All (n=49)**	**Crossover (N= 27)**	**Non-Cross (N= 22)**
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	15 (34.1)	1 (2.0)	6 (22.2)	1 (4.5)
SD (median 259 days)	23 (52.3)	13 (26.5)	11 (40.7)	6 (27.3)
PD	**2 (4.5)**	31 (63.3)	1 (3.7)	12 (54.5)
NE	**4 (9.1)**	4 (8.2)	9 (33.3)	3 (13.6)
Objective Response Rate (CR+PR)	15 (34.1)	1 (2.0)	6 (22.2)	1 (4.5)

Patients without Clinical Benefit from Experimental Treatment

Progressive Disease on Therapy (n=2): No treatment (symptomatic PD, vascular anomaly)

Not Evaluable (n=4): Hepatic progression prior to therapy (n=2), Mortality from Hepatic insufficiency (n=1), patient withdrew secondary to toxicity (n=1).

Conclusions

Increased drug delivery achieved through novel regional therapeutic approaches may increase efficacy of a given agent (vs. systemic administration) by overcoming a low therapeutic index.

High-dose Melphalan, delivered via intra-arterial administration with subsequent hepatic venous hemofiltration is effective against hepatic metastases from ocular and cutaneous melanoma, and provides improved disease control when compared with standard treatment regimens.

Expansion to multiple clinical centers proved safe and effective

FDA IND Submission has been initiated

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