ONCOLOGY DRUGS ADVISORY COMMITTEE MEETING

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DELCATH SYSTEMS, INC

BRIEFING DOCUMENT

MELBLEZ KIT

Treatment of patients with unresectable, metastatic ocular melanoma in the liver

ADVISORY COMMITTEE BRIEFING MATERIALS:

AVAILABLE FOR PUBLIC RELEASE

List of Abbreviations

ACC	Adenocarcinoma
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC_{last}	Area under the curve from time zero to the time of last measured concentration
BAC	Best alternative care
C_{max}	Maximum concentration
CI	Confidence interval
CR	Complete response
CRF	Case Report Form
CT	Computed tomography
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
HCC	Hepatocellular carcinoma
hOR	Hepatic objective response
hPFS	Hepatic progression free survival
HR	Hazard ratio
IBW	Ideal body weight
ICU	Intensive Care Unit
IHP	Isolated hepatic perfusion
IND	Investigational New Drug
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Affairs

MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NDA	New Drug Application
NET	Neuroendocrine tumor
NYHA	New York Heart Association
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PHP	Percutaneous hepatic perfusion
PR	Partial response
PT	Preferred term
PT	Prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System organ class
SPA	Special protocol assessment
TACE	Transcatheter arterial chemoembolization
ULN	Upper limit of normal
U.S.	United States

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1. EXECUTIVE SUMMARY

The MELBLEZ KIT is a drug/device combination product containing melphalan hydrochloride and a Hepatic Delivery System that is used to perform an intensive local hepatic chemotherapy known as percutaneous hepatic perfusion (PHP). Delcath Systems, Inc is seeking United States (U.S.) Food and Drug Administration (FDA) approval for the MELBLEZ KIT for the treatment of patients with unresectable, metastatic ocular melanoma in the liver.

Treatment with the MELBLEZ KIT is referred to in this document as melphalan/PHP treatment.

The melphalan/PHP system to be used in the treatment of malignant melanoma received Fast Track designation in 2005 in recognition of its potential to address an unmet medical need or to treat a serious or life-threatening condition. A special protocol assessment (SPA) for the pivotal Phase 3 study was accepted in 2006. Orphan drug designation for the melphalan/PHP system for treatment of ocular and cutaneous melanoma was granted in 2008.

Delcath's New Drug Application (NDA) was filed as a 505(B)(2) application in December 2010 with Alkeran® (melphalan hydrochloride) for Injection (approved in the U.S. in 1992) as the reference listed product. In order to provide patient access to melphalan/PHP treatment in the U.S., compassionate use and an expanded access protocol are ongoing.

The PHP delivery system was approved under device regulations in the European Union (EU) in April 2011 and in Australia in February 2012.

Ocular Melanoma and Unmet Medical Need

Ocular melanoma affects up to 2,800 adults annually in the U.S., according to the American Cancer Society. It is estimated that up to 70% of patients with ocular melanoma will develop metastases within 2 to 5 years of the initial diagnosis with the liver involved in up to 90% of these individuals. Most patients die of liver metastases within 2-6 months of diagnosis.

Complete surgical resection of liver metastases is the only potentially curative option for ocular melanoma patients with liver metastases. However, less than 10% of ocular melanoma patients with liver metastases are suitable for surgical resection because of the multifocal and miliary distribution of their disease. Systemic chemotherapy has failed to show clinical efficacy against metastatic ocular melanoma. Various regional treatments (ie, transcatheter arterial chemoembolization [TACE], immunoembolization) have been developed for the treatment of unresectable liver metastases, however, these treatments are limited to patients with isolated metastases and therefore are not an option for the majority of ocular melanoma patients. In addition, there are no prospective, randomized, controlled data to support the efficacy of any of these regional treatments.

There is a critical unmet medical need for effective treatments for patients with hepatic metastases from ocular melanoma since there are no approved therapies. To fulfill this unmet need, the efficacy and safety of melphalan/PHP treatment was investigated in this setting.

Melphalan/PHP Treatment

The melphalan/PHP System is a drug-device combination product that is composed of the chemotherapeutic agent, melphalan hydrochloride, and a number of sterile, single-use, medical device components, including catheters and an extracorporeal circuit with hemofiltration

cartridges. The system is used in a procedure known as PHP. In the PHP procedure, one catheter is used to infuse high-dose melphalan to the liver via the hepatic artery and another catheter is used to collect the hepatic venous effluent, which is sent through extracorporeal hemofiltration cartridges to lower the concentration of melphalan from the blood before it is returned to the systemic circulation via the jugular vein. Following catheter placement, the PHP procedure requires the administration of heparin for anticoagulation to assure free blood flow. Hypotension will occur during the PHP procedure at balloon inflation and when the filter cartridges of the extracorporeal circuit come on line. Hypotension is managed by administration of vasopressors.

Patients are typically hospitalized for 4 days for melphalan/PHP treatment. The PHP procedure is conducted in an interventional radiology suite under general anesthesia and takes approximately 3 hours to complete. The procedure requires a multi-disciplinary team, including an interventional radiologist, surgical or medical oncologist, anesthesiologist, perfusionist, certified healthcare provider for chemotherapy delivery, interventional radiology staff, and a pharmacist.

Clinical Development Program

The clinical development program for melphalan/PHP treatment consisted of the following studies:

- A Phase 1 study 01-C-0215 in 34 patients with unresectable hepatic metastases from solid tumors (ocular melanoma, 12 patients; cutaneous melanoma, 3 patients; other tumor types, 19 patients) that was conducted at the National Cancer Institute (NCI)
- A Phase 2 study 04-C-0273 in 56 patients with either unresectable primary hepatic tumors or unresectable hepatic metastases from solid tumors that was conducted at NCI
- A pivotal Phase 3 study DSI MEL 2005-001 in 93 patients with unresectable hepatic metastases from either ocular (n=83) or cutaneous (n=10) melanoma that was conducted at NCI and 9 additional sites

The Phase 1 study identified the maximum tolerated dose (MTD) of melphalan administered by PHP and provided evidence of antitumor activity in melanoma patients supporting the initiation of the pivotal Phase 3 study. The Phase 2 study was conducted in parallel with the pivotal Phase 3 study to examine the efficacy and safety of melphalan/PHP treatment in patients with unresectable hepatic metastases from non-melanoma tumors. Four patients with ocular melanoma, who were ineligible for the Phase 3 study, were enrolled in the Phase 2 study.

Efficacy of Melphalan/PHP Treatment in Patients with Unresectable Metastatic Ocular Melanoma in the Liver

Pivotal efficacy for melphalan/PHP in the treatment of unresectable, metastatic ocular melanoma in the liver is provided by the randomized Phase 3 study, DSI MEL 2005-001, which compared the efficacy of melphalan/PHP treatment to best alternative care (BAC), which was selected by the investigator. Patients in the BAC group were allowed to crossover to melphalan/PHP treatment at the time of hepatic progression. The primary efficacy endpoint was hepatic progression free survival (hPFS) by Independent Review Committee (IRC) assessment and secondary efficacy endpoints were hPFS by investigator assessment, the rate of hepatic objective response (hOR) by IRC and investigator assessment, and overall survival (OS).

All patients in the Phase 3 study had histologically- or cytologically-confirmed ocular or cutaneous melanoma and were treated with a melphalan dose of 3.0 mg/kg based on ideal body weight (IBW) in 4-week cycles for a maximum of 6 cycles. Treatment could be delayed for up to an additional 4 weeks to allow for resolution or reduction of toxicity to ≤grade 2. A melphalan dose reduction to 2.5 mg/kg IBW was allowed during treatment for patients based on toxicities.

A total of 93 patients were randomized in the pivotal Phase 3 study: 44 to the PHP and 49 to BAC. The majority of patients had ocular melanoma; 5 patients with cutaneous melanoma were enrolled in each group. Approximately half of the patients had no extrahepatic metastasis. When present, the most common site of extrahepatic metastasis was the lung. Demographics and baseline disease characteristics were well-balanced between the PHP and BAC groups. The median age for all patients was 56 years; 52% of patients were female and 48% were male. The median time since diagnosis of liver metastasis in both groups was approximately 2 months. Approximately 30% of patients in both groups received prior systemic therapy; chemotherapy and immunotherapy were the most frequent prior systemic therapies.

Twenty-eight patients in the BAC group experienced hepatic disease progression and crossed over to PHP treatment after fulfilling the study eligibility criteria.

Key efficacy data from the Phase 3 study (Table 1) are summarized as follows:

- The primary efficacy endpoint of hPFS by IRC assessment was met in the overall patient population. Melphalan/PHP treatment of patients specifically with unresectable, metastatic ocular melanoma in the liver resulted in a statistically significant and clinically meaningful increase in hPFS by IRC assessment compared to BAC treatment with a median 5-month difference in favor of melphalan/PHP treatment.
- hPFS results by investigator assessment were similar to the IRC's.
- The robustness of the hPFS benefit was evidenced by consistent results across prespecified sensitivity analyses and all subgroup analyses, including patients with ocular melanoma.
- Statistically significant higher rates of hOR were observed by both IRC and investigator assessment in the PHP group compared to the BAC group.
- Median survival was similar between the PHP and the BAC groups, but the survival data are confounded by the high percentage of BAC patients who experienced hepatic progression and crossed over to PHP treatment (57%).

The ocular melanoma subpopulation in the Phase 1 and Phase 2 studies showed similar median hPFS times and hOR rates as the Phase 3 study.

Table 1: Efficacy in the Pivotal Phase 3 Study DSI MEL 2005-001

Endpoint	PHP (N=44)	BAC (N=49)	HR (95% CI)	p-value
hPFS	Median (95% CI) in months			
Overall population				
IRC	7.03 (5.22, 9.66)	1.64 (1.48, 2.92)	0.39 (0.24, 0.64)	0.0001
Investigator	8.05 (5.78, 8.90)	1.64 (1.45, 2.27)	0.28 (0.18, 0.45)	<0.0001
Ocular melanoma patients				
IRC	7.03 (4.99, 9.66)	1.64 (1.41, 2.69)	0.42 (0.25, 0.72)	0.0011
Investigator	7.89 (5.22, 8.84)	1.64 (1.41, 2.27)	0.31 (0.19, 0.50)	<0.0001
Response rate, CR+PR	N, (%) [95% CI]			
Overall population				
IRC	36.4	2.0	-	<0.0001
Investigator	38.6	2.0	-	<0.0001
Ocular melanoma patients				
IRC	35.9	2.3	-	<0.0001
Investigator	41.0	2.3	-	<0.0001
OS	Median (95% CI) in months			
	9.79 (6.93, 15.44)	9.89 (6.01, 15.28)	0.92 (0.55, 1.54)	0.7500

[a]Primary analysis cut off of April 2010.

Safety

The safety profile for melphalan/PHP treatment is primarily derived from pooled data (N=121) for PHP-treated patients from the Phase 3 (including 28 crossover patients from BAC to PHP) and Phase 2 studies. Adverse events were analysed for the overall study period and by two time periods called peri-procedure (0 to 72 hours) and post-procedure (>72 hours) in order to characterize the risks associated with the procedure/device and the risks associated with melphalan post-procedurally.

An overview of adverse events is provided in Table 2.

Almost all patients in the PHP group had at least one adverse event. Most (80%) of these adverse events were serious adverse events, which included hospitalizations.

There were 5 deaths during the clinical development program that resulted from adverse events, including gastrointestinal (GI) hemorrhage, hepatic failure, gastric perforation, streptococcal sepsis, and neutropenia.

Approximately 40% of patients had one or more adverse events leading to treatment discontinuation.

Table 2: Overview of Adverse Events

	Pooled (N=121)	
Type of Event, n (%)	All	Grade 4
Adverse event	115 (95.0)	110 (90.9)
Serious adverse event	101 (83.5)	88 (72.7)
Adverse event resulting in death	5 (4.1)	-
Adverse event leading to treatment discontinuation	46 (38.0%)	24 (19.8%)

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

Melphalan-related bone marrow suppression, including neutropenia (87%), complicated neutropenia (21%), thrombocytopenia (80%), and anemia (59%) occurred. There were two deaths from complicated neutropenia (streptococcal sepsis and neutropenia) in the clinical development program. Thrombocytopenia (22%), febrile neutropenia (15%), and neutropenia (15%) were the most frequent events resulting in rehospitalization. Thrombocytopenia (15.7%) and neutropenia (7.4%) were the most frequent adverse events leading to treatment withdrawal. Most treatment withdrawals due to thrombocytopenia and neutropenia occurred after either the second or third melphalan/PHP treatment.

There is a risk of cardiovascular events with melphalan/PHP treatment because of intra-procedural hypotension. Cardiovascular events occurred in 24% of patients with 17% of patients with a Grade 3/4 cardiovascular event. Cardiovascular events seen during clinical development included arrhythmias, cerebral ischemia/infarct, cardiac ischemia/infarct, thromboembolism, and cerebral hemorrhages; each of these events was reported in a small number of patients. No patients died from a cardiovascular event. Ten patients (8%) were withdrawn from treatment because of a cardiovascular event.

There is a risk of GI events because of misperfusion of melphalan into GI vessels either because vessels were not embolized or there was reflux of melphalan into GI branches. GI events, including gastritis, ulceration, perforation, bleeding, and gall bladder-related events occurred in 25% of patients with 11% of patients with a grade 3/4 GI event. There were two deaths from GI events (ruptured right hepatic artery and gastric perforation) in the clinical development program. Six patients (5%) were withdrawn from treatment because of a GI event.

There is a risk of bleeding events because of the anticoagulation required for performance of the procedure, hemofiltration-related thrombocytopenia, and melphalan-related thrombocytopenia. Bleeding events occurred in 13% of patients with 7% of patients with a grade 3/4 bleeding event. One patient with brain metastases died from an intracranial hemorrhage. Four patients discontinued study treatment because of a bleeding event.

There is a risk of hepatic events as a consequence of underlying disease, liver-directed therapy, and melphalan treatment. Hepatic events occurred in 44% of patients with all of these patients having grade 3/4 events. Hepatic events were predominantly laboratory changes in liver function tests that were reported as adverse events, including elevated hepatic transaminases and hyperbilirubinemia. One patient died of hepatic failure related to underlying disease burden since his liver tissue was >90% tumor. Seven patients (5.8%) discontinued study treatment because of

a hepatic event, including increased blood bilirubin, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and hepatic failure.

Risk Management, Training, and Risk Evaluation and Mitigation Strategy

It is critical to have in-depth knowledge of the drug delivery system, the risks associated with the procedure and melphalan, and the coordination among the procedural team members during the preparation for and conduct of the procedure. In order to use the melphalan/PHP System, the Procedural Team must successfully complete a melphalan/PHP System Training Program, modeled after the training program used during clinical development and including additional lessons learned from the development program and EU marketing experience. This Training Module is part of the proposed Risk Evaluation and Mitigation Strategy (REMS), with elements to assure safe use, to ensure the benefits of melphalan/PHP treatment outweigh the aforementioned risks and procedural complications. In addition, both the hospital and specific members of the procedural team must be certified with the melphalan/PHP System REMS. The purpose of the melphalan/PHP System Training Program, as an important component of the melphalan/PHP System REMS, is to:

- Communicate the indications for use and patient selection criteria for the melphalan/PHP System
- Provide extensive and detailed procedural training so that each team member understands the PHP procedure and their role in each step, including:
  - Pre-procedural preparation
  - Procedural details
  - Post-procedural care
  - Expected complications and their management
- Communicate the requirements to receive and to ensure safe use of the melphalan/PHP System via hospital qualification, hospital certification, and healthcare provider training and certification requirements required for use of the melphalan/PHP System

An overview of the steps and training required for the use of the melphalan/PHP System are provided in Table 3.

Table 3: Overview of Requirements for Use of the Melphalan/PHP System

Hospital Requirements	Healthcare Provider Requirements
1. Qualified using the Hospital Qualification Criteria	1. Completion of didactic training
2. Hospital certification with the melphalan/PHP System REMS	2. Viewing of a video of a live case
	3. Completion of Knowledge Assessment
	4. Completion of experiential training
	5. Healthcare provider certification with the melphalan/PHP System REMS
Hospital authorized to receive the melphalan/PHP System	

Conclusions

There is no standard of care and no approved therapy for patients with unresectable, hepatic metastases from ocular melanoma. Thus, there is an unmet medical need for these patients. Treatment of this patient population with melphalan/PHP has been demonstrated to alter the disease course, as evidenced by the consistent, statistically significant, and clinically meaningful benefits seen with melphalan/PHP treatment across the tumor-related efficacy endpoints in the pivotal Phase 3 study. The toxicities associated with melphalan/PHP treatment need to be viewed within the context of the aggressive natural history of disease in these patients and the ability of melphalan/PHP treatment to alter the disease course. The REMS is designed to maintain a positive risk-benefit for melphalan/PHP treatment.

2. BACKGROUND

2.1. Melphalan/PHP System

The melphalan/PHP system is a drug/device combination product that is composed of the chemotherapeutic agent, melphalan hydrochloride, and a number of sterile, single-use medical device components, including catheters and hemofiltration cartridges. The device is used in a procedure known as percutaneous hepatic perfusion (PHP) to deliver melphalan directly to the liver via the hepatic artery using a catheter that is percutaneously inserted using standard interventional radiology techniques. Because liver metastases derive their blood supply primarily from the hepatic artery and normal hepatic parenchyma derive the majority of their blood supply from the portal system, hepatic arterial infusion delivers melphalan preferentially to hepatic tumors, including small undetected microscopic metastases. Intra-hepatic administration with subsequent hepatic venous effluent hemofiltration also allows the delivery of melphalan at a much higher concentration than what could be delivered intravenously.

Currently, hepatic artery infusions of chemotherapy are limited by either the dose or chemotherapy agent that can be infused. Isolated hepatic perfusion (IHP) has been used to administer high doses of melphalan to the liver in ocular melanoma patients. However, because IHP requires major surgical open-abdominal access, it cannot be repeated, limiting its therapeutic efficacy and utility. PHP was developed to replace IHP. PHP with melphalan reduces systemic melphalan exposure by isolating and filtering hepatic venous outflow and, since it uses percutaneous rather than open-surgical access to the vessels of liver, it can be repeated as many times as tolerated, allowing several cycles of therapy to be administered.

2.2. Choice of Melphalan

Melphalan was selected as the chemotherapeutic agent for PHP treatment because it binds melanin precursors, is an alkylating agent with a steep dose response [Teicher et al, 1988], and has been used successfully in an analogous regional procedure, IHP, for treating unresectable hepatic metastases from melanoma.

Melphalan is a bifunctional alkylating agent that is not cell-cycle-specific; its cytotoxic effects are related to its concentration and the duration of exposure of the cell to the agent. Melphalan has a short half-life (1.5 ±0.8 hours) and activity against a variety of tumors. Melphalan is currently approved at doses of 16 mg/m^2 or 0.43 mg/kg for a 60-kg patient for the palliative treatment of multiple myeloma.

2.3. Regulatory History

U.S. regulatory milestones and meetings with the FDA for the melphalan/PHP development program are summarized in Table 4.

Table 4: U.S. Regulatory History

Regulatory Milestone	Date
IND opened	June 2001
End-of-Phase 2 meeting and fast track designation	April 2005
SPA for Phase 3 study DSI MEL 2005-001	February 2006
Orphan drug designation for cutaneous and ocular melanoma	November 2008
Pre-NDA meeting with FDA	March 2010
Rolling NDA submission completed	December 2010
FDA refusal to file	February 2011
Refusal to file Type A FDA meeting to clarify issues in refusal to file	April 2011
Submission of remonitoring plan, updated CRF, and SAPs	September 2011
Pre-NDA meeting	January 2012
NDA resubmission to FDA	August 2012

IND: Investigational New Drug; CRF: Case Report Form; NDA: New Drug Application; SAP: Statistical Analysis Plan; SPA: special protocol assessment

The melphalan/PHP system to be used in the treatment of malignant melanoma received Fast Track designation in 2005 in recognition of its potential to address an unmet medical need or to treat a serious or life-threatening condition. A SPA for the pivotal Phase 3 study was accepted in 2006. Orphan drug designation for the melphalan/PHP system for treatment of ocular and cutaneous melanoma was granted in 2008.

Delcath's NDA was filed as a 505(B)(2) application in December 2010 with Alkeran® (melphalan hydrochloride) for Injection (approved in Europe and the U.S. in 1992) as the reference listed product. FDA issued a refusal-to-file in February 2011, citing insufficient safety information that did not allow the Agency to adequately assess the benefit-risk profile, including a lack of hospitalization data (reason for hospitalization, duration, and outcome). In response to the refusal-to-file, a Type A meeting was held with FDA in April 2011 to discuss the items needed to be included in an NDA resubmission to allow FDA to complete its clinical review.

Delcath developed a safety data remonitoring plan, an updated Case Report Form to collect additional safety data, and updated Statistical Analysis Plans for safety that were submitted to FDA in September 2011. Based on the completion of the remonitoring and data collection, an updated NDA was filed with FDA in August 2012.

In order to provide patient access to melphalan/PHP treatment in the U.S., compassionate use and expanded access programs have been put in place until a final decision on marketing authorization is reached.

The regulatory pathway in the rest of the world followed device regulations. The PHP delivery system was approved with a CE mark in April 2011 in the EU and February 2012 in Australia. In both regions, Delcath has implemented an extensive training program for the procedure and device based on the training and lessons learned from the clinical trials; a similar training program for the procedure, device, and melphalan is proposed for the U.S. (see Section 10.3.3).

2.4. Proposed Indication, Dose, and Dosing Regimen

The proposed indication for the melphalan/PHP system is for the treatment of patients with unresectable, metastatic ocular melanoma in the liver.

Melphalan is administered by infusion into the hepatic artery via a chemotherapy delivery catheter, which is a component of the PHP Delivery System. The recommended dose is 3.0 mg/kg based on IBW, infused over 30 minutes, with a maximum absolute dose of 220 mg during a single treatment. Treatments are recommended to be administered every 4 weeks. Both delays in treatment, for up to an additional 4 weeks until recovery from toxicities, and a dosage reduction, to 2.5 mg/kg IBW, are allowed.

Toxicities should have resolved to grade 2 or less, with the exception of hepatic toxicity due to underlying disease which should resolve to baseline, before additional treatments are considered.

A dosage reduction to 2.5 mg/kg IBW should be considered for subsequent treatments for the following reasons:

- Grade 4 neutropenia of >5 days duration despite growth factor support or associated with neutropenic fever
- Grade 4 thrombocytopenia of >5 days duration or associated with a hemorrhage that required a transfusion
- Grade 4 hemoglobin of >48 hours duration
- Grade 3 or 4 major non-hematologic organ toxicity not corrected within 24 hours of the procedure (excluding fever, nausea, and weight gain); for hepatic toxicity, grade 4 bilirubin of any duration, and doubling of liver function test values (AST, ALT, and total bilirubin) above the baseline value

Melphalan/PHP treatment should be permanently discontinued if patients have persistent toxicity that has not resolved to grade 2 or less by 8 weeks following treatment.

3. MEDICAL NEED

3.1. Ocular Melanoma

Ocular melanoma is a rare disease, affecting up to 2,800 adults annually in the U.S. according to the American Cancer Society. It is estimated that up to 70% of patients with ocular melanoma will develop metastases within 2 to 5 years of the initial diagnosis. The overwhelming clinical presentation of metastatic disease is liver only or liver-dominant disease, with the liver involved in up to 90% of individuals. Liver metastases in ocular melanoma are characteristically multifocal and multilobular and progress rapidly, leading to death from liver progression within 2 to 6 months of diagnosis [Miller and Mihm, 2006; Bedikian et al, 1995; Kujala et al, 2003]. Survivors beyond 2 years are rare. To date, metastatic ocular disease has been particularly resistant to systemic treatments, including chemotherapy and immunotherapy. There is currently no standard of care and no approved therapy. No randomized clinical trials have been published in metastatic ocular melanoma. Best supportive care, including symptom management and hospice support, are not uncommon first approaches for patients who present with liver metastases and this is reasonable given the lack of proven efficacy for any treatment.

Ocular melanoma, also known as choroidal or uveal melanoma, develops from the uveal pigmented cells located in the choroid, iris, and ciliary body. Ocular melanoma differs strikingly

from cutaneous melanoma in incidence, tumor genetics, chemosensitivity, metastatic pattern, overall survival, and cause of death (Table 5).

Table 5: Ocular Melanoma versus Cutaneous Melanoma

Characteristic	Ocular	Cutaneous
Genetic alterations	NBS1, MYC, DDEF1, GNAQ, CCND1, HDM2, BCL-2	NRAS, AKT3, BRAF, BCL-2, CDKN2A, PTEN
Metastatic spread	Liver, lung	Local lymph nodes, lung, brain, other organs
Distribution of metastases	Extensive liver micrometastases and miliary disease	Diffuse, involving multiple organs
Systemic treatment	No proven standard	Therapies available
Cause of death	Liver failure	Brain metastases, other

The somatic genetic profile of cutaneous melanoma includes mutations in BRAF, NRAS, and C-KIT. This has led to significant progress in the treatment of cutaneous melanoma with highly-sensitive, targeted inhibitors for BRAF, MEK, and C-KIT. Unfortunately, ocular melanoma only rarely has mutations in these oncogenes and a different genetic profile is emerging (Table 5) [Griewank et al, 2011]. To date, the genetic mutations associated with ocular melanoma have been more difficult to effectively target for clinical benefit.

Both ocular melanoma and cutaneous melanoma are highly metastatic with approximately 50% of ocular melanoma patients developing distant metastases. However, the pattern of metastases is strikingly different between the two malignancies [Diener-West et al, 1992; Harbour, 2009; van den Bosch et al, 2010]. Cutaneous melanoma spreads from its primary site by lymphatic drainage to regional lymph nodes and hematogenously to distant organs; the liver, central nervous system, lung, skin, bowel, and bone are the most common sites for cutaneous melanoma metastasis. In cutaneous melanoma, the two sites that invariably lead to the vast majority of deaths are the central nervous system and the liver, with an approximately equal contribution from both sites. In contrast to cutaneous melanoma, ocular melanoma spreads exclusively by hematogenous pathways. The liver is the first and dominant site of hematogenous spread of metastases in approximately 90% of ocular melanoma patients and the central nervous system is rarely involved. Because of this, the overwhelming cause of death for ocular melanoma patients is liver failure from progressive malignant disease.

Survival in cutaneous and ocular melanoma is invariably poor after the onset of visceral metastases. Median OS is short and 5-year survival is rare in both diseases. However, there is more variability in the survival of cutaneous melanoma patients depending on the site of metastases. As demonstrated in large, randomized, controlled clinical trials, both median and long-term survival for cutaneous melanoma has changed dramatically in recent years with vemurafinib and ipilimumab, neither of which has been shown to have efficacy in ocular melanoma.

Because of its liver-dominant visceral presentation, ocular melanoma has a more narrow range of median OS compared to cutaneous melanoma with a median OS of 2-6 months; 5-year survivors are extremely rare [Miller and Mihm, 2006; Bedikian et al, 1995; Kujala et al, 2003]. To date, no randomized, controlled trials have demonstrated a clinical benefit for any treatment for ocular melanoma and no therapies have been approved for the treatment of metastatic disease. No

standard of care exists for ocular melanoma patients with metastatic disease and supportive care alone has been a reasonable and frequently chosen option.

3.2. Treatment Options for Metastatic Ocular Melanoma

A number of different treatment approaches have been pursued in an effort to control liver metastases, palliate symptoms, and extend survival in patients with metastatic ocular melanoma.

A small proportion, approximately 10% of patients, will present with limited disease that is amenable to complete surgical resection or, if in a location in the liver that is not surgically resectable, amenable to percutaneous or surgical ablation with radiofrequency or cryotherapy probes. However, the majority of these patients, including those with a successful complete surgical resection, will have progressive liver metastases in a relatively short interval. Long-term survival is rare. In addition, a significant proportion of patients who were thought to have limited, surgically-resectable disease by pre-operative imaging will be found to have more extensive liver involvement with tumor at the time of surgery. In these patients, surgery is either aborted or they undergo a subtotal resection or a combination of resection and ablation. These patients have poor outcomes in general. Thus, surgical resection of metastatic ocular melanoma has significant limitations and benefits few patients.

Systemic treatment with the available agents, including dacarbazine, temozolamide, taxanes, and platinum agents, has failed to show clinical efficacy against metastatic ocular melanoma [Gragoudas, 1991; Kath et al, 1993; Korn et al, 2008; Unger et al, 2001]. Vemurafenib is not a treatment option because ocular melanoma lacks the BRAF mutation. Ipilimumab, which prolongs survival in cutaneous melanoma patients, has shown a lack of response in ocular melanoma patients. No targeted agents for ocular melanoma have been identified to date, despite the identification of specific genetic mutations associated with ocular melanoma (Table 5).

Percutaneous or surgical ablation using radiofrequency or ultrasound techniques can be used for smaller liver lesions when resection is anatomically impossible and the number of lesions is limited. Targeted radiation is sometimes feasible. However, responses to these treatments are short-lived because of progression of microscopic disease in new areas of the liver.

The most promising approaches remain local regional therapy to the liver. A number of strategies have been attempted with varying degrees of success. Hepatic artery infusion with a variety of chemotherapy agents or immune agents (ie, granulocyte-macrophage colony-stimulating factor, IL-2) is a common approach to local regional treatment of ocular melanoma. This approach takes advantage of the dual blood supply of the liver (hepatic artery and portal vein) and the preferential hepatic artery flow to tumors. Percutaneous hepatic artery catheters or permanent implantable hepatic artery in-dwelling pumps can be placed to deliver chemotherapy to the liver. Higher doses of chemotherapy can be used if the drugs that are selected have a high first pass extraction by the liver. This allows for favorable liver/systemic drug ratios, limiting normal liver and systemic exposure. Up to a 10-fold increase in drug concentration to the tumor can be achieved with this approach.

An alternative, more selective approach is TACE. A number of chemotherapy agents in combination with sponges or emulsified oil particles have been tested. The advantage of TACE is that a higher concentration of chemotherapy can be delivered more selectively to the macroscopic tumor. Embolization causes ischemia and tumor necrosis and longer retention times

of the cytotoxic agent, potentially improving efficacy. Because embolization causes tissue ischemia, TACE is exclusively limited to focal liver applications. Since TACE selectively targets only macroscopic tumors, they are subject to recurrence due to neo-angiogenesis of the tumor blood supply.

An investigational regional therapy, hepatic perfusion of high-dose melphalan directly into the liver via an open-surgical procedure known as isolated hepatic perfusion (IHP), has been demonstrated to control disease and extend survival for patients with unresectable hepatic metastases [Alexander et al, 2000; Alexander et al, 2003; Noter et al, 2004; Rizell et al, 2008]. IHP takes approximately 8 hours to complete and the IHP recovery period is protracted with patients spending 2 to 3 days in an intensive care unit (ICU) immediately after the procedure followed by an additional 10 to 15 days in the hospital prior to discharge. IHP has not been widely adopted as a treatment because it is an open-surgical procedure that is limited to one-time-only treatment. PHP, discussed below, was developed to replace IHP.

There is a critical unmet medical need for effective treatment options for patients with unresectable, metastatic ocular melanoma. Based on the metastatic pattern seen in ocular melanoma patients, a liver-directed therapy could prolong survival. Optimal treatment must involve treatment of the entire liver to control macroscopic and microscopic metastases, must overcome the innate resistance to systemic chemotherapy seen with ocular melanoma, and must be repeatable.

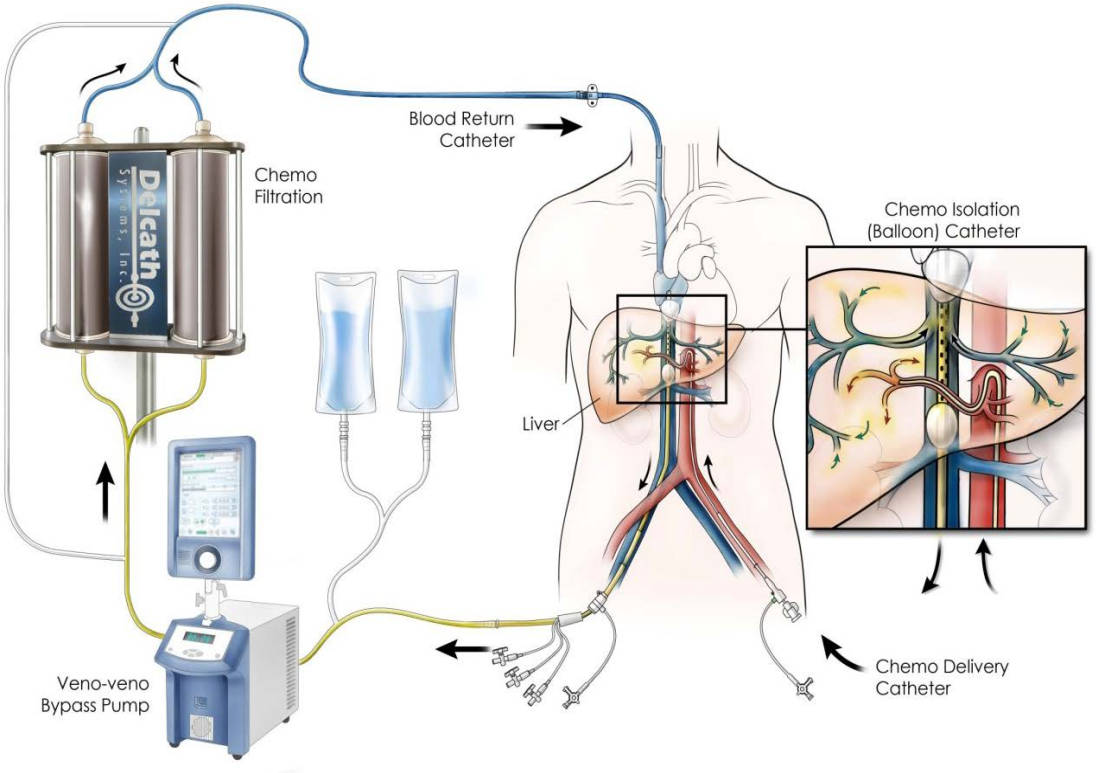
4. MELPHALAN/PHP: PROCEDURE AND TREATMENT

This section provides a high-level overview of how the PHP procedure, the device, and melphalan were used, as specified in the clinical study protocols, during the conduct of the clinical development program. The protocol, additional lessons learned during the clinical development program, and the use of experienced proctors from NCI during clinical development to train new investigational sites forms the basis for a proposed U.S. Training Program that dictates how the procedure must be performed and how melphalan and the device must be used by trained medical experts at qualified hospital sites.

4.1. Overview of the PHP Procedure

A schematic overview of the PHP procedure is provided in Figure 1. In the PHP procedure, melphalan is delivered directly into the hepatic artery via a catheter in the proper hepatic artery. A double-balloon catheter is positioned in the retrohepatic inferior vena cava to isolate and collect hepatic venous outflow which is sent through an extracorporeal filtration system to lower the concentration of melphalan in the blood before being returned to the systemic circulation via an internal jugular vein sheath. Once the extracorporeal circuit is established, melphalan is administered as a 30-minute infusion via the hepatic artery with simultaneous extracorporeal blood filtration. Extracorporeal filtration continues for an additional 30 minutes after infusion to filter any melphalan that is released from the liver after completion of melphalan infusion.

Figure 1: Overview of Melphalan/PHP Treatment



4.2. PHP Procedure Team

The PHP procedure requires a multi-disciplinary procedural team with the knowledge and skills required to care for patients who undergo melphalan/PHP treatment. Table 6 lists the members of the procedural team and their role during treatment. The interventional radiologist leads the procedural team.

The objective of the proposed mandatory training is to train all team members on the overall procedure, to train each individual expert on their specific role during the procedure, and to identify and proactively manage risks before, during, and following the procedure. The mandatory training program is extensive and is comprised of three components: didactic "classroom" training by experienced procedural experts, viewing a video of a live case to provide a visual aid for the didactic material, and experiential training for the first two cases or more if needed until the team demonstrates the aptitude to independently perform cases. The Training Program must be completed prior to shipment of the melphalan/PHP system and documented through certification of the hospital site and team members (see Section 10.3.3). The interventional radiologist, surgical or medical oncologist, anesthesiologist, and perfusionist will each individually be certified after completion of the mandatory training. The hospital can only receive product after being certified by hospital qualification criteria and ensuring that only appropriately-trained and certified team members participate in the procedural aspects and administration of melphalan/PHP treatment.

Table 6: Melphalan/PHP Procedure Team

Team Member	Responsibilities
Interventional radiologist	Leads procedural team during the procedure by communication and coordination with the entire procedural team
Surgical or medical oncologist	Complete management of patient
Anesthesiologist	Sedation, analgesia, and hemodynamic support
Perfusionist	Establishing, monitoring, and controlling the extracorporeal circuit
Certified healthcare provider for chemotherapy delivery	Melphalan administration
Interventional radiology staff	Assists in procedure and imaging
Pharmacist	Melphalan preparation

4.3. Overview of Patient Hospitalization for PHP Procedure

Patients are typically hospitalized for 4 days for melphalan/PHP treatment. The PHP procedure is conducted in an interventional radiology suite under general anesthesia and takes approximately 3 hours to complete. After completion of the PHP procedure, the patient is observed in the ICU, surgery recovery unit, or surgical ward by the interventional radiologist, anesthesiologist, and additional staff for 24 to 48 hours after treatment for the following:

- Monitoring for evidence of systemic toxicity secondary to the perfusion procedure
- Monitoring hemodynamic stability
- Ensuring that coagulation is normalizing

4.3.1. Screening for the PHP Procedure

In order to avoid serious injury, illness, or deaths, patient selection criteria must be followed with respect to anatomical structure, extent of liver tumor burden, and propensity for adverse events due to underlying disease conditions (see Section 10.2).

Prior to the PHP procedure, there are laboratory assessments, imaging tests, and treatments (ie, gastroduodenal embolization if required) that must be performed to ensure patient eligibility for melphalan/PHP treatment (see Section 10.2).

4.3.2. Preparation for PHP Procedure

The patient is admitted to the hospital by the medical or surgical oncologist the night before for preparation for the procedure. IV hydration is started to ensure an adequate fluid pre-load before the procedure. Proton pump inhibitors are administered to prevent gastritis which could occur as a result of regional melphalan absorption during the procedure. Patients with a history of hepatobiliary surgery or ablative procedures are given antibiotics prophylactically to prevent infections.

4.3.3. Support during the PHP Procedure

Heparin is administered by the anesthesiologist to maintain the activated clotting time at therapeutic levels. Heparin is administered at the direction of the interventional radiologist

before he/she isolates the liver and prior to the initiation of the extracorporeal circuit by the perfusionist. Vital signs are monitored continuously throughout the procedure by the anesthesiologist.

All patients will experience hypotension at two points during the procedure:

- When balloons are inflated within the inferior vena cava causing decreased cardiac return since blood flow from the lower body is temporarily obstructed
- When the extracorporeal circuit is connected to the body

The blood pressure drop is managed with pre-hydration and IV vasopressors until blood pressure normalizes. Vasopressors are administered by the anesthesiologist to maintain a mean arterial pressure >65 mmHg to prevent ischemic injury to the heart and brain. Patient responsiveness to the vasopressor is checked prior to balloon inflation.

The melphalan infusion is not started by the interventional radiologist until mean arterial pressure is >65 mmHg. Vasopressor support is weaned during the 30-minute melphalan infusion and is not required after conclusion of the procedure.

Arterial patency is assessed by the interventional radiologist several times during the PHP procedure by injection of contrast media into the hepatic artery catheter to ensure that there is no vasospasm of the hepatic artery that could result in melphalan reflux into proximal GI branches. Nitroglycerin is administered by the interventional radiologist by intra-arterial injection if hepatic spasm is seen and the infusion of melphalan is suspended until the spasm resolves. The procedure is terminated by the interventional radiologist if the spasm does not resolve with nitroglycerin administration.

4.3.4. Support Immediately After the PHP Procedure

Protamine, fresh frozen plasma and/or cryoprecipitate are administered immediately after the procedure to correct coagulopathy and to facilitate sheath removal. Platelets and red blood cells may be transfused by the interventional radiologist, as required, to correct thrombocytopenia and anemia that are a consequence of platelet and red blood cell sequestration by the filters. Some patients require electrolyte administration to correct electrolyte imbalances. One or two doses of furosemide may be necessary to counter edema as a result of IV hydration.

4.3.5. Hospitalization Discharge

Total hospitalization for the PHP procedure is approximately 3 to 5 days, but may vary depending on the medical needs of the patient. The patient is discharged from the hospital once anticoagulation, liver function abnormalities, thrombocytopenia, and anemia are corrected. The following are recommendations for discharge:

- Prothrombin time (PT) within 2 seconds of upper limit of normal (ULN)
- Activated partial thromboplastin time (aPTT) within normal range
- Platelets >75,000/μL without platelet transfusion or >100,000/ μL with transfusion
- Hemoglobin >10 g/dL

4.3.6. Post Hospitalization Care

Patients must be closely monitored on an outpatient basis after hospital discharge. When following-up patients after their discharge from the hospital, it is important for the oncologist to monitor for possible melphalan and procedure-related toxicities, including bone marrow suppression. The interventional radiologist who is part of the procedure team plays a unique leadership role in communicating the safe use conditions for melphalan/PHP treatment and coordinating with oncologists and other key healthcare providers responsible for patient follow-up care and monitoring for post-procedure toxicities.

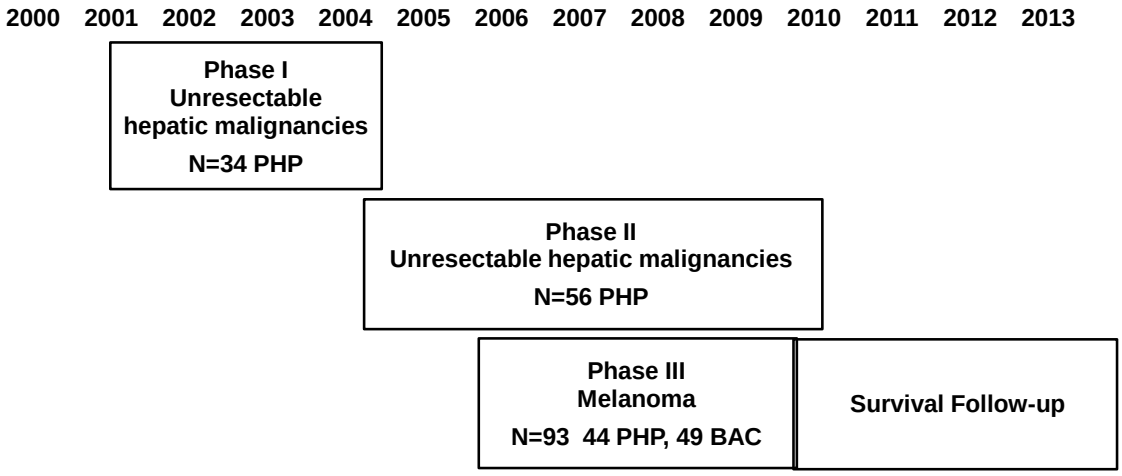
5. CLINICAL DEVELOPMENT PROGRAM

An overview of the clinical development program is provided in Figure 2. Three studies were conducted: a Phase 1, Phase 2, and pivotal Phase 3 study. The Phase 1 and Phase 2 studies were conducted at NCI and the pivotal Phase 3 study was initiated at NCI and expanded to include an additional 9 sites. The NCI procedural treatment team trained the treatment teams at the other investigational sites.

Blood samples for analysis of melphalan pharmacokinetics were collected in all of the studies; these data are provided in Appendix A.

Compassionate use and expanded access programs are ongoing in the U.S.

Figure 2: Clinical Development Program



6. PHASE 1 STUDY 01-C-0215

6.1. Study Design

The Phase 1 study, 01-C-0215, was an open-label, dose-escalation study at NCI in patients with unresectable hepatic metastases from a variety of solid tumors (ie, ocular melanoma, cutaneous melanoma, and other tumor types). Key eligibility criteria for the study are listed in Appendix B.

The objective of the Phase 1 study was to determine the dose-limiting toxicities (DLT) and MTD of melphalan administered by PHP. Patients were hospitalized for treatment for up to 3 to 5 days every 4 weeks for up to 4 treatments. Prior to cycle 3, patients must have shown evidence of stable disease (SD) or better.

The first two cohorts (cohort 1 and cohort 2; 6 patients/cohort) were enrolled into a 2.0 mg/kg IBW dose cohort, with subsequent cohorts receiving melphalan doses that increased by 0.5 mg/kg IBW (ie, 2.5 mg/kg, 3.0 mg/kg, 3.5 mg/kg). The starting dose of 2.0 mg/kg IBW was based on the use of a melphalan dose of 1.5 mg/kg in IHP, the open-surgical procedure that was the predecessor to PHP.

Six patients were planned to be enrolled and treated in the 2.0 mg/kg cohort, but the dose cohort was expanded during study conduct to gain additional experience with the technical aspects of the procedure and the events associated with it. At each subsequent dose level, three patients were treated as part of the dose escalation.

The definition of a DLT is provided in Table 7. If any DLTs occurred at any dose level during the first PHP treatment in 1 patient, as many as 6 patients were treated at that dose level to determine the degree of toxicity. The dose level at which 2 patients experienced a DLT during the first treatment was to be considered dose limiting. Six patients were then to be treated at the next lower dose level to define that dose as the MTD. Up to a total of 12 patients were to receive the MTD. Any patient in a dose cohort who experienced a DLT had their melphalan dose reduced to the next lower dose level for subsequent PHP treatments.

Table 7: DLT Definition

Event	Description
Grade 4 neutropenia	>72 hours duration or associated with neutropenic fever
Grade 3 thrombocytopenia	>72 hours duration or associated with a hemorrhage requiring transfusion
Grade 4 hemoglobin	>7 days duration
Grade 3 or 4 major nonhematologic organ toxicity	Not correctable within 24 hours (1 day) of the procedure (excluding fever, nausea, and weight gain). Acute systemic toxicity that corrected within 24 hours of treatment was not considered dose limiting

Hepatic response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) scan 4 weeks after cycle 2 of treatment. Hepatic responses were categorized by the investigator as complete response (CR), partial response (PR), SD, or progressive disease (PD) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, with a modification to restrict target lesions to the liver and to allow up to 10 target liver lesions.

After completion or withdrawal from treatment, patients entered the Follow-up Phase during which they were evaluated for disease progression (if not already present) every 3 months for the first 2 years, every 4 months for the third year, and as clinically indicated thereafter.

6.2. Phase 1 Results

A total of 34 patients were enrolled at NCI in the Phase 1 study: 14 in the 2.0 mg/kg cohort; 3 in the 2.5. mg/kg cohort; 11 in the 3.0 mg/kg cohort; and 6 in the 3.5 mg/kg cohort. Twelve patients with ocular melanoma, 3 patients with cutaneous melanoma, and 19 patients with other solid tumor types were enrolled.

6.2.1. Demographics and Baseline Characteristics

Demographics and baseline disease characteristics were similar across the dose cohorts. The majority of the patients were white. More males (18 patients) than females (16 patients) were enrolled in the study. Median age was 50.0 years. Median time since diagnosis of the primary tumor was 33.2 months and the median time since diagnosis of hepatic metastasis at study entry was 9.2 months.

Table 8: Demographics and Baseline Characteristics in Phase 1 Study (ITT Population)

	Melphalan Dose (mg/kg IBW)				
	Overall	2.0	2.5	3.0	3.5
Age (years)					
Median (range)	50.0 (17-74)	48.5 (28-74)	44.0 (32-45)	50.0 (17-70)	54.5 (38-59)
Sex, n (%)					
Male	18 (52.9)	8 (57.1)	0	6 (54.5)	4 (66.7)
Female	16 (47.1)	6 (42.9)	3 (100.0)	5 (45.5)	2 (33.3)
Race, n (%)					
White	29 (85.3)	13 (92.9)	2 (66.7)	9 (81.8)	5 (83.3)
Black or African American	1 (2.9)	0	0	1 (9.1)	0
Asian	2 (5.9)	1 (7.1)	0	1 (9.1)	0
Unknown	2 (5.9)	0	1 (33.3)	0	1 (16.7)
ECOG Performance Status, n (%)					
0	28 (82.4)	14 (100.0)	3 (100.0)	5 (45.5)	6 (100.0)
1	5 (14.7)	0	0	5 (45.5)	0
Unknown	1 (2.9)	0	0	1 (9.1)	0
Primary tumor location, n (%)					
Eye	12 (35.3)	5 (35.7)	2 (66.7)	3 (27.3)	2 (33.3)
Skin	3 (8.8)	1 (7.1)	0	2 (18.2)	0
Other	19 (55.9)	8 (57.1)	1 (33.3)	6 (54.5)	4 (66.7)
Median time since diagnosis of primary tumor (range) (months)	33.2 (3.3-457.9)	40.8 (16.5-201.2)	23.5 (16.7-40.5)	26.5 (4.1-412.6)	33.2 (3.3-457.9)
Median time since diagnosis of liver metastasis (range) (months)	9.2 (0.6-49.7)	17.5 (0.6-49.7)	1.5 (1.4-8.7)	10.5 (2.0-29.1)	4.8 (1.6-33.3)

6.2.2. Exposure

The median number of attempted treatment cycles in the Phase 1 study was 2.0 and the majority of patients (69.7%) completed ≥ 2 cycles of treatment. Overall, 39.4% of patients completed ≥4 cycles of treatment.

6.2.3. Overview of Adverse Events

The majority of patients in all cohorts had at least one adverse event and 79% of patients had at least one grade 3/4 adverse event (Table 9).

No deaths due to adverse events occurred in the study. Overall, 42.4% of patients had at least one serious adverse event. Four patients prematurely discontinued the study due to an adverse event.

Table 9: Overview of Adverse Events in the Phase 1 Study (Safety Population)

Type of Event, n (%)	All Doses (N=33)	2.0 mg/kg (N=14)	2.5 mg/kg (N=3)	3.0 mg/kg (N=10)	3.5 mg/kg (N=6)
Adverse event	28 (84.8)	11 (78.6)	3 (100.0)	9 (90.0)	5 (83.3)
Grade 4 adverse event	18 (54.5)	7 (50.0)	1 (33.3)	6 (60.0)	4 (66.7)
Serious adverse event	14 (42.4)	8 (57.1)	0	4 (40.0)	2 (33.3)
Adverse event resulting in death	0	0	0	0	0
Adverse event leading to treatment discontinuation	3 (9.1)	1 (7.1)	0	2 (20.0)	0

6.2.4. Phase 1 DLTs and MTD

To determine which patients had significant melphalan-related toxicities and therefore DLTs, the NCI investigators reviewed each patient's adverse events on a weekly basis and adjudicated the toxicities to determine the DLTs and to support dose escalation. In the DLT determination, the investigators considered the protocol definition of a DLT and additional factors such as the time of event onset relative to melphalan administration, other adverse events that occurred within the same time frame, and the clinical consequences associated with the event (ie, medical interventions required to treat the event, could the patient continue PHP treatment without delay).

Three patients had DLTs as determined by the investigators: 2 patients at 3.5 mg/kg and 1 patient at 3.0 mg/kg (Table 10). Thus, 3.0 mg/kg was determined as the MTD of melphalan delivered by PHP since only 1 patient had a DLT at this dose. All of the DLTs were events related to bone marrow suppression, including neutropenia, febrile neutropenia, leukopenia, and thrombocytopenia.

Table 10: DLTs in Phase 1 Study

	Melphalan Dose			
	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
Decreased neutrophil count	0	0	-	2
Decreased white blood cell count	0	0	1	1
Decrease platelet count	0	0	1	2
Febrile neutropenia	0	0	1	1

6.2.5. Antitumor Activity

Exploratory analyses of efficacy, including hPFS and hOR were performed in the Phase 1 study using investigator assessments and an Intent-to-Treat (ITT) population, defined as all enrolled patients. Meaningful antitumor effects were seen in the liver of the ocular melanoma patients in the Phase 1 study.

Four ocular melanoma patients had a hepatic objective response: 3 patients with a CR and 1 patient with a PR (Table 11). An additional 3 patients had SD.

Median hPFS for ocular melanoma patients was approximately 9 months.

Table 11: hOR and hPFS in Phase 1 Study (ITT Population)

	Ocular Melanoma (N=12)	Cutaneous Melanoma (N=3)	Other Tumor Types (N=19)
hOR, n (%)	4 (33.3)	0	0
Complete response, n (%)	3 (25.0)[a]	0	0
Partial response, n (%)	1 (8.3)[b]	0	0
Stable disease, n (%)	3 (25.0)[c]	1 (33.3)	7 (36.8)
Median hPFS (months)	8.9	2.1	2.9

Note: Response was assessed using RECIST version 1.0, with a modification to restrict target lesions to the liver and to allow up to 10 target liver lesions.

[a]Complete responses were seen in 1 patient in the 2.0 mg/kg group, 1 patient in the 2.5 mg/kg group, and 1 patient in the 3.5 mg/kg group.

[b]The partial response was seen in the 3.0 mg/kg group.

[c]Stable disease was seen in 2 patients in the 2.0 mg/kg group and 1 patient in the 3.5 mg.kg group.

7. PHASE 2 STUDY 04-C-0273

7.1. Study Design

The Phase 2 study 04-C-0273 was an open-label study conducted at NCI in parallel with the pivotal Phase 3 study DSI MEL 2005-001. The study population in the Phase 2 study consisted of patients with unresectable primary (hepatocellular cancer or intrahepatic cholangiocarcinoma) or metastatic hepatic malignancies, including adenocarcinoma (ACC) of the GI tract, ocular or cutaneous melanoma, or neuroendocrine tumors (NET) (with the exception of gastrinoma). The study was originally designed to examine the efficacy of melphalan/PHP treatment in several non-melanoma tumor types; however the protocol was amended during study conduct to include a melanoma cohort who had received prior melphalan treatment and thus, were ineligible for the Phase 3 study. All patients were also required to have minimal to no extrahepatic metastases and to satisfy the additional key eligibility criteria listed in Appendix B.

The primary objective of the Phase 2 study was to determine the response rate and duration of response for melphalan/PHP treatment. Secondary objectives were to determine the patterns of recurrence, hPFS, and OS, to evaluate the safety and tolerability of melphalan/PHP treatment, and to evaluate the filter efficiency/PK (see Appendix A).

Patients were treated with a melphalan dose of 3.0 mg/kg IBW in 4-week cycles for a maximum of 4 cycles. Treatment could be delayed for up to an additional 4 weeks to allow for resolution or reduction of toxicity to ≤grade 2. A melphalan dose reduction to 2.5 mg/kg IBW was allowed during treatment for patients who experienced any of the following:

- Grade 4 neutropenia of >5 days duration with growth factor support or associated with neutropenic fever
- Grade 4 thrombocytopenia of >5 days duration or associated with a hemorrhage that required a transfusion
- A grade 4 hemoglobin level of >48 hours duration
- Grade 3 or 4 major non-hematologic organ toxicity not corrected within 24 hours of the procedure (excluding fever, nausea, and weight gain); for hepatic toxicity, grade 4

bilirubin of any duration, and doubling of liver function test values (AST, ALT, and total bilirubin) above the baseline value

Melphalan/PHP treatment was to be permanently discontinued if patients had persistent toxicity that had not resolved to grade 2 or less by 8 weeks following treatment.

Hepatic response was assessed by CT or MRI scans 4 weeks after cycles 2 and 4. Hepatic responses were categorized by the investigator as CR, PR, SD, or PD using RECIST version 1.0, with a modification to restrict target lesions to the liver and to allow up to 10 target liver lesions. Prior to starting cycle 3, patients must have shown evidence of SD or better and no abnormalities in a MRI scan of the brain. The primary efficacy endpoint was hOR and duration. Secondary efficacy endpoints included hPFS and OS.

7.2. Phase 2 Results

A total of 56 patients were enrolled at NCI: 20 in the ACC cohort, 8 in the primary hepatic malignancies cohort, 4 in the melanoma cohort, and 24 in the NET cohort. All patients in the melanoma cohort had ocular melanoma.

7.2.1. Demographics and Baseline Disease Characteristics

The four primary tumor cohorts were generally similar with respect to demographic and baseline disease characteristics (Table 12). Most of the patients were white. More males (32 patients) than females (24 patients) were enrolled in the study. Median age was 53 years. The median time since diagnosis of the primary tumor ranged from 5.39 months in the primary hepatic tumor cohort to 71 months in the melanoma cohort. The melanoma cohort previously received melphalan either via IHP or PHP.

Table 12: Demographics and Baseline Disease Characteristics in Phase 2 Study (ITT Population)

	Overall	MEL (N=4)	ACC (N=20)	HCC (N=8)	NET (N=24)
Age (years)					
Median (min-max)	53.0 (21-72)	41.5 (35-59)	56.5 (22-63)	61.0 (48-63)	48.0 (21-72)
Sex, n (%)					
Male	32 (57.1%)	4 (100.0%)	8 (40.0%)	5 (62.5%)	15 (62.5%)
Female	24 (42.9%)	0	12 (60.0%)	3 (37.5%)	9 (37.5%)
Race, n (%)					
White	48 (85.7%)	4 (100.0%)	18 (90.0%)	6 (75.0%)	20 (83.3%)
Black or African American	3 (5.4%)	0	0	2 (25.0%)	1 (4.2%)
Asian	3 (5.4%)	0	2 (10.0%)	0	1 (4.2%)
Unknown	1 (1.8%)	0	0	0	1 (4.2%)
Missing	1 (1.8%)	0	0	0	1 (4.2%)
Median time since diagnosis of primary tumor (range) (months)	28.71 (0.5-301.8)	70.88 (48.2-95.2)	27.47 (8.3-195.4)	5.39 (0.9-52.8)	35.04 (0.5-301.8)
Median time since diagnosis of liver metastasis (range) (months)	19.91 (0.3-99.3)	20.47 (9.2-32.7)	22.49 (7.3-51.4)	6.98 (2.5-52.8)	18.56 (0.3-99.3)

7.2.2. Antitumor Activity

Meaningful antitumor effects were seen in the liver of the ocular melanoma patients in the Phase 2 study. Three of the four ocular melanoma patients had a hOR (all PRs) with a median hPFS of approximately 9 months (Table 13). Median survival for these patients was approximately 2 years (Table 13).

Table 13: hOR, hPFS, and OS in the Phase 2 Study (ITT Population)

	MEL (N=4)	ACC (N=20)	HCC (N=8)	NET (N=24)
hOR, n (%)	3 (75.0)	0	1 (12.5)	10 (41.7)
Complete response	0	0	0	0
Partial response	3 (75.0)	0	1 (12.5)	10 (41.7)
Stable disease	1 (25.0)	4 (20.0)	4 (50.0)	6 (25.0)
Median hPFS (range) (months)	9.10 (3.1+, 15.3)	4.04 (1.2+, 25.3)	5.60 (2.7, 12.2)	16.82 (2.1, 64.1)
Median OS (range) (months)	22.54 (5.7, 35.3+)	5.83 (1.7, 33.3)	9.12 (3.4, 20.5)	31.87 (2.4, 81.1)

A plus sign (+) next to the minimum/maximum indicates the observed time was a censored observation

8. PHASE 3 STUDY DSI MEL 2005-001

8.1. Study Design

The Phase 3 study DSI MEL 2005-001 was a pivotal, randomized, controlled, multicenter study conducted at 10 centers in the U.S. in patient with histologically- or cytologically-confirmed cutaneous or ocular melanoma with metastases predominantly in the liver. The objectives of the Phase 3 study were to evaluate and assess the efficacy, safety, and tolerability of melphalan/PHP treatment versus BAC selected by the investigator.

8.1.1. Primary and Secondary Efficacy Endpoints

The primary efficacy endpoint was hPFS by IRC assessment. Secondary efficacy endpoints included the following:

- hPFS by investigator assessment, defined as the time from the date of randomization to the first observation of hepatic disease progression, or death due to any cause, by IRC assessment
- Overall progression free survival (PFS), defined as the time from the date of randomization to the first observation of disease progression (either hepatic or extrahepatic) or death due to any cause, by investigator assessment
- hOR, defined as a complete or partial best confirmed hepatic response (CR or PR) recorded from randomization until the time of disease progression, by IRC and investigator assessment
- OS defined as the time from the date of randomization to death due to any cause

Hepatic response in both treatment groups was assessed by CT or MRI scans at the investigational site at 6 and 12 weeks post baseline and then every 8 weeks for the remainder of

time on therapy. Response was assessed by both the investigators and the IRC using RECIST, with a modification to restrict target lesions to the liver and to allow up to 10 target liver lesions.

For the IRC assessment, two board-certified radiologists performed blinded, independent reviews of individual patient's scans. If a discrepancy in reviewer evaluations occurred in either date of progression, best overall hepatic response, or date of first confirmed response, a third board-certified radiologist (ie, an adjudicator) independently assessed the discrepant case and determined which of the two primary radiologist assessments was a more accurate representation of outcome. Thus, in the case of adjudication, the assessment reflected an agreement on outcome between two of three experts. The review process, criteria, and roles of the IRC were outlined in an IRC charter.

8.1.2. Patient Population

The Phase 3 study population consisted of patients with unresectable hepatic metastases from ocular or cutaneous melanoma. Study eligibility criteria are listed in Appendix B. Key inclusion criteria included the following:

- Histologically- or cytologically-confirmed ocular or cutaneous melanoma
- Measurable disease by CT and/or MRI
- Limited extrahepatic disease if the life-limiting component of disease was in the liver. Acceptable extrahepatic disease included, but was not limited to the following:
  - Up to 4 pulmonary nodules each <1 cm in diameter
  - Retroperitoneal lymph nodes <3 cm in diameter
  - Skin or subcutaneous metastases fewer than 10 in number and <1 cm in diameter
  - Asymptomatic bone metastases that were or could be palliated with external beam radiation therapy
  - A solitary metastasis to any site that could be resected
- For patients with 50% or greater tumor burden by medical imaging, a biopsy of the non-involved parenchyma to show that it was histologically normal
- Women who were premenopausal (have had a period within the last 12 months) had to receive appropriate hormonal suppression to prevent potential bleeding as a result of the procedure
- Eastern Cooperative Oncology Group (ECOG) performance status of <3 at screening and on the day before treatment
- Adequate hepatic function, defined as:
  - Total serum bilirubin of <3.0 mg/dL
  - AST/ALT ≤ 10 times ULN
- Adequate hematologic function, defined as:
  - Platelet count >75,000/μL

- Hemoglobin ≥9 g/dL (correctable with transfusion)
- Absolute neutrophil count ≥1,300/μL
- PT within 2 seconds of ULN

Key exclusion criteria included the following:

- Childs B or C cirrhosis or evidence of portal hypertension by history, endoscopy, or radiologic studies
- History of congestive heart failure with a left ventricular ejection fraction <40%
- Previously treated with regional hepatic therapy with melphalan
- History of bleeding disorders (eg, nose bleeds, bleeding ulcers) or evidence of intracranial abnormalities that put the patient at risk for bleeding with anticoagulation (eg, stroke, active metastases)
- History of gastrinoma or a Whipple procedure

Eligible patients were stratified at randomization by study center and type of melanoma (cutaneous versus ocular) and then randomized in a 1:1 ratio to either PHP treatment with melphalan or BAC.

8.1.3. Melphalan Dose and Dose Modifications

Patients were treated with a melphalan dose of 3.0 mg/kg IBW in 4-week cycles for a maximum of 6 cycles. Treatment could be delayed for up to an additional 4 weeks to allow for resolution or reduction of toxicity to ≤grade 2. A melphalan dose reduction to 2.5 mg/kg IBW was allowed during treatment for patients who experienced any of the following:

- Grade 4 neutropenia of >5 days duration with growth factor support or associated with neutropenic fever
- Grade 4 thrombocytopenia of >5 days duration or associated with a hemorrhage that required a transfusion
- A grade 4 hemoglobin level of >48 hours duration
- Grade 3 or 4 major non-hematologic organ toxicity not corrected within 24 hours of the procedure (excluding fever, nausea, and weight gain). For hepatic toxicity, grade 4 bilirubin of any duration. Doubling of other liver function tests above the baseline value (eg, AST, ALT, and total bilirubin)

Melphalan/PHP treatment was to be permanently discontinued if patients had persistent toxicity that had not resolved to grade 2 or less by 8 weeks following treatment.

The number of PHP treatments received was dependent on individual hepatic response (patients with SD were limited to 4 treatments) and systemic toxicity.

8.1.4. BAC Control Arm

The control arm in the Phase 3 study was a BAC arm. A standardized BAC regimen was not specified in the protocol, thereby allowing the investigator to determine the most appropriate

treatment course for each patient. Allowed BAC treatments were supportive care or active treatment, including systemic or regional chemotherapy, hepatic artery embolization, or any therapy considered appropriate, including investigational therapies. This was considered the most ethical control group for this study because, at study initiation, there were no approved treatments for patients with unresectable metastatic melanoma in the liver.

Patients in the BAC group were treated using the standard treatment schema for the therapy selected.

8.1.5. Safety Assessments

Safety assessments included adverse events, serious adverse events, deaths, premature withdrawals due to adverse events, adverse events that resulted in or prolonged hospitalization, adverse events leading to treatment delay or dose modification, adverse events of special interest, clinical laboratory tests (hematology, serum chemistry, liver function, and urinalysis), and vital signs. Patients in the PHP group were treated and followed for safety at the investigational site whereas patients in the BAC group were able to receive treatment and follow-up care by a local oncologist and returned to the investigational site periodically for imaging assessments. Laboratory monitoring was conducted more frequently in the PHP group than in the BAC group.

Note: Expanded criteria for determining the seriousness of an adverse event were applied at NCI that were not used at the non-NCI sites; NCI enrolled approximately 50% of the patients in the Phase 3 study. At NCI, some grade 4 labs, primarily neutrophils and platelets, were reported as serious adverse events, irrespective of whether or not the laboratory result triggered a medical intervention, was potentially life-threatening, or required or prolonged hospitalization. Thus, many laboratory abnormalities that are not associated with clinical sequelae were reported as serious adverse events at this site.

8.1.6. Crossover Group

Patients in the BAC group were allowed to crossover to PHP treatment at the time of documented hepatic progression by the investigator. For patients who crossed over from BAC to PHP, a complete CT scan of the chest, abdomen, and pelvis and a MRI of the liver were conducted within 10 days prior to initiation of PHP treatment to establish a second baseline. Crossover patients had to satisfy all inclusion/exclusion criteria prior to being treated with PHP (see Appendix B). Patients could receive up to 6 cycles of treatment. Hepatic response was assessed by both the IRC and investigators.

8.1.7. Statistical Assumptions, Sample Size, and Analysis Methods

The Phase 3 study was powered to detect a median difference of approximately 4 months using the assumption that the median time of hPFS was 4 months for patients randomized to the BAC group and 7.73 months for patients randomized to the PHP group and there was a 21.7% nonevent rate (ie, hepatic disease progression or death). The assumed difference of 4 months was discounted to 3.73 months to account for the expected number of patients randomized to the PHP group who were not able to be treated (for any reason, including vascular anatomy unsuitable for PHP treatment). A total of 73 hepatic events or a total of 46 patients per treatment group were required to detect the targeted difference with 80% power.

hOR was powered at 88% under the assumption that the success rate was 10% for patients randomized to the BAC group and 40% for patients randomized to the PHP group.

The primary analysis of efficacy occurred when the protocol-specified 73 events of progressive liver disease by investigator assessment were observed (April 30, 2010).

Efficacy data were analyzed for the overall population, the ocular melanoma subpopulation, and the crossover population using an ITT Population, defined as all randomized patients.

hPFS, overall PFS, and OS were summarized using Kaplan-Meier methods and compared between treatment groups using a nonparametric log-rank test. The estimate of the Hazard Ratio (HR) is from the Cox model with fixed effect for treatment.

hOR was defined as a confirmed CR or PR as assessed by the IRC or investigator. hOR rates were compared between the PHP and BAC groups using Fischer's Exact Test.

Sensitivity analyses for hPFS were planned to confirm that results seen for the primary analysis of hPFS were not influenced by certain aspects of study conduct or how the primary analysis was conducted. The following sensitivity analyses were conducted using the log-rank test and the Cox model with a single fixed effect for randomized treatment:

- Correcting for early scans
- Converting censored observations to events of hPFS
- Using a censoring mechanism consistent with that in Table C of FDA guidance, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007*)*
- Including only patients in the BAC group who received active therapy and excluding patients who received supportive care
- Using the earliest documented time to progression from the IRC or investigator assessment
- Restricting crossover to BAC patients with IRC-confirmed progression

The following prespecified subgroups were analyzed for hPFS by IRC assessment using a Cox model with fixed effects for randomized treatment (PHP versus BAC), the subgroup variable, and the interaction between the subgroup variable and randomized treatment:

- Investigative site (NCI versus non-NCI)
- Primary tumor site (ocular versus cutaneous)
- Age (65 years and $\geq$ 65 years)
- Gender (females and males)
- Baseline tumor burden (<50% and $\geq$50%)

All other efficacy endpoints (ie, hPFS by investigator assessment, hOR, and OS) were also analyzed for the ocular melanoma subpopulation.

8.2. Phase 3 Patient Disposition

A total of 93 patients were randomized: 44 to the PHP group and 49 to the BAC group. Forty-eight patients in the BAC group experienced hepatic disease progression and were eligible to crossover to PHP treatment. Of these patients, 28 crossed over to treatment with PHP.

Eight patients were alive as of February 2013: 2 in the PHP group, 2 in the BAC group, and 4 in the crossover group.

8.3. Phase 3 Demographics and Baseline Disease Characteristics

Demographics and baseline disease characteristics were well-balanced between the PHP and BAC groups (Table 14). The median age for all patients was 56 years; 52% of patients were female and 48% were male. Most patients were white.

Most patients had ocular melanoma (89%). Ten patients with cutaneous melanoma were enrolled: 5 in the PHP group and 5 in the BAC group. Approximately half of the patients had no extrahepatic metastasis. When present, the most common site of extrahepatic metastasis was the lung.

The median time since diagnosis of the primary tumor was longer in the PHP group (49.2 months) than in the BAC group (38.1 months). The median time since diagnosis of liver metastasis in both groups was approximately 2 months.

Approximately 30% of patients in both groups received prior systemic therapy; chemotherapy and immunotherapy were the most frequent prior systemic therapies.

Table 14: Demographics and Baseline Disease Characteristics-Phase 3 Study (ITT Population)

	Overall (N=93)	PHP (N=44)	BAC (N=49)
Age (years)			
Median (range)	56.0 (31-77)	55.0 (33-74)	56.0 (31-77)
Sex, n (%)			
Male	45 (48.4)	23 (52.3)	22 (44.9)
Female	48 (51.6)	21 (47.7)	27 (55.1)
Race, n (%)			
White	92 (98.9)	44 (100.0)	48 (98.0)
Black or African American	1 (1.1)	0	1 (2.0)
ECOG Performance Status, n (%)			
0	70 (75.3)	28 (63.6)	42 (85.7)
1	19 (20.4)	13 (29.5)	6 (12.2)
Primary tumor location, n (%)			
Eye	83 (89.2)	39 (88.6)	44 (89.8)
Skin	10 (10.8)	5 (11.4)	5 (10.2)
Median time since diagnosis of primary tumor (range) (months)	39.3 (1-292)	49.2 (3-292)	38.1 (1-162)
Median time since diagnosis of liver metastasis (range) (months)	2.053 (0.03-44.06)	1.906 (0.03-44.06)	2.136 (0.07-28.94)
Prior systemic therapy, n (%)	29 (31.2)	14 (31.8)	15 (30.6)
Chemotherapy	18 (19.4)	8 (18.2)	10 (20.4)
Immunotherapy	16 (17.2)	8 (18.2)	8 (16.3)

8.4. BAC Treatments

Most patients (82%) in the BAC group received active treatment, with temozolamide (41%) and chemoembolization (22%) the most common active treatments (Table 15). The number of different therapies used in the Phase 3 study attests to the lack of a standard of care for patients with unresectable liver metastases from ocular melanoma.

Table 15: Treatments in the BAC Group

Treatment	N (%)[1]
Systemic Chemotherapy	24 (49.0)
Temozolomide	20 (40.8)
Carboplatin/Paclitaxel	3 (6.1)
Dacarbazine	1 (2.0)
Chemoembolization	11 (22.4)
Carmustine[2]	3 (6.1)
Doxo/Cis/Mitomycin	3 (6.1)
Cisplatin	2 (4.1)
Doxorubicin/Cisplatin	2 (4.1)
Doxorubicin	1 (2.0)
RadioEmbolization	3 (6.1)
Yttrium Y-90 Sirspheres	3 (6.1)
Combination Sys/Embo[3]	1 (2.0)
Surgery	1 (2.0)
Supportive Care	9 (18.4)

[1]One patient who did not have a BAC therapy reported in the eCRF reported as Supportive Care in this summary.
[2]Patient 012-354 received two cycles of interarterial carmustine followed by one cycle of inter-arterial paclitaxel.
[3]Patient 03-259 received seven cycles of inter-arterial gemcitabine combined with IV paclitaxel.

8.5. Efficacy

8.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint in the Phase 3 study was hPFS by IRC assessment. Results shown below are from the primary data analysis cut-off of April 2010.

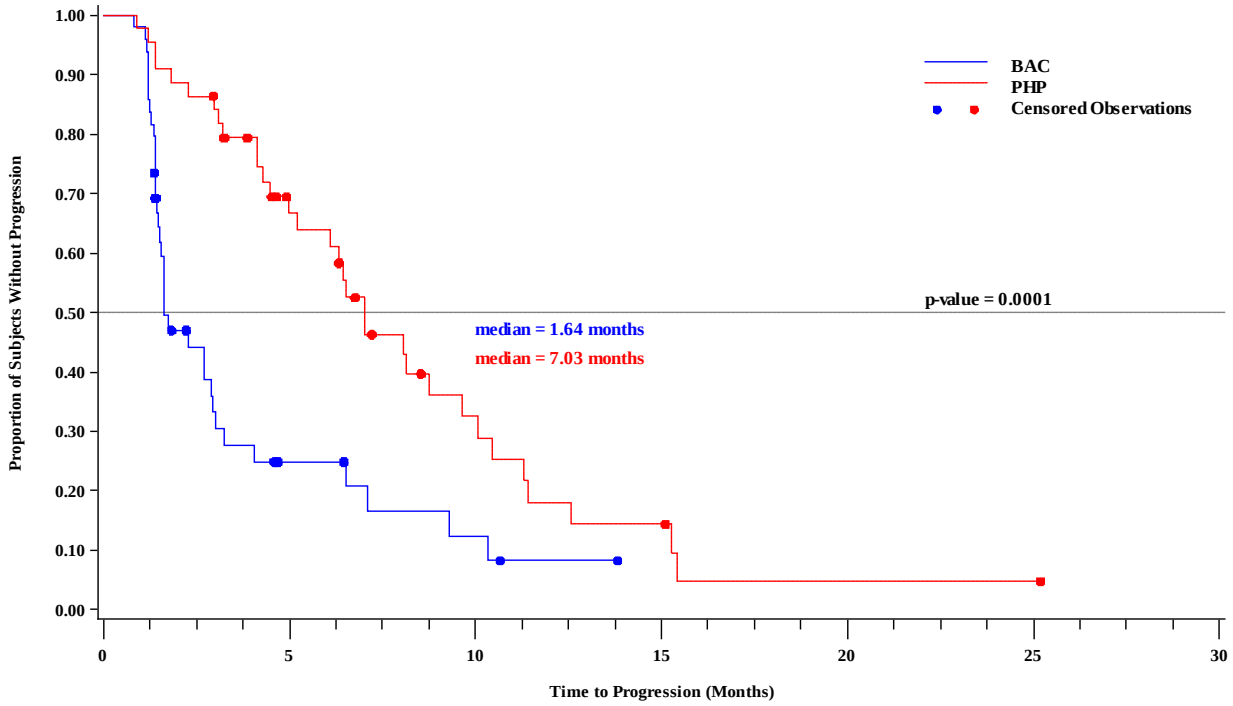
In the overall population, a clinically meaningful and statistically significant improvement in hPFS by IRC assessment was observed in the PHP group compared to the BAC group (Table 16). Median hPFS by IRC assessment was 1.64 months (95% CI: 1.48, 2.92) in the BAC group compared to 7.03 months (95% CI: 5.22, 9.66) in the PHP group, with a corresponding HR of 0.39 (95% CI: 0.24, 0.64). The Kaplan-Meier curves of event rates for hPFS show a clear, early separation of the curves that remain separate, with a 5-month difference at the median (Figure 3). Thus, the primary efficacy endpoint for the study was met.

Table 16: hPFS in the Overall Population in the Phase 3 Study: IRC Assessment (ITT Population)

	PHP (N=44)	BAC (N=49)
Patients with hepatic progression n (%)	32 (72.7%)	36 (73.5%)
Median[a] (95% CI) time to hepatic progression (months)	7.03 (5.22, 9.66)	1.64 (1.48, 2.92)
Min, Max time to hepatic progression (months)	0.9, 25.2+	0.8, 13.8+
P-value from log-rank test	0.0001	
Hazard ratio[b] (95% CI)	0.39 (0.24, 0.64)	

[a]Median and confidence interval (CI) are based on the Product-Limit estimate of survival curve.
[b]Estimate of the hazard ratio is from the Cox model with fixed effect for treatment.
Plus sign indicates a censored observation.

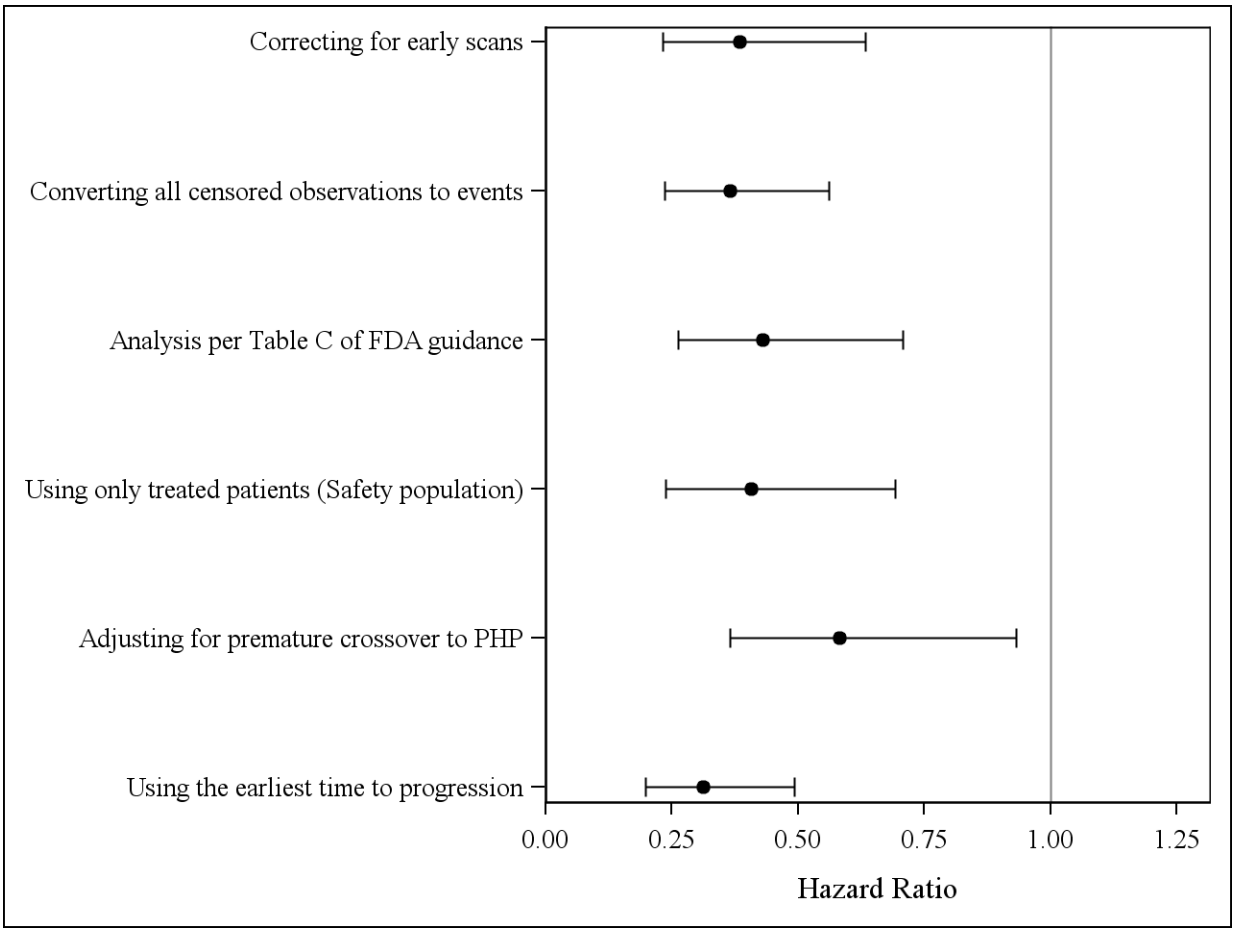
Figure 3: Kaplan Meier Curve of hPFS in the Overall Population in the Phase 3 Study: IRC Assessment (ITT Population)



8.5.1.1. Sensitivity Analyses

The robustness of the hPFS benefit for PHP treatment is evidenced by the consistency of results for the prespecified sensitivity analyses which all show a significant PHP treatment effect (Figure 4).

Figure 4: Forest Plot for hPFS: Sensitivity Analyses in the Phase 3 Study (ITT Population, IRC Assessment)

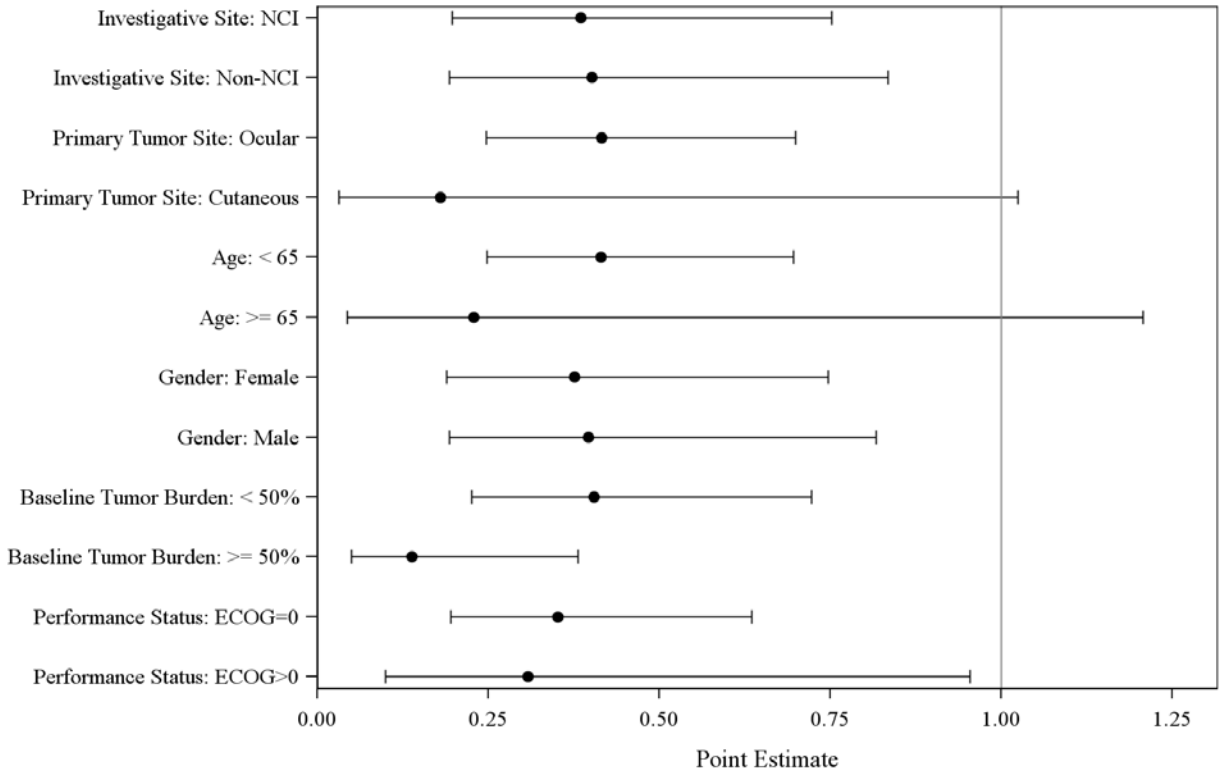


Note: Table C of FDA guidance, "*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007)*"

8.5.1.2. Subgroup Analyses

The robustness of the hPFS benefit for PHP treatment is evidenced by the consistency of results for the prespecified subgroup analyses which all show a significant PHP treatment effect (Figure 5).

Figure 5: Forest Plot for hPFS: Subgroup Analyses in the Phase 3 Study (ITT Population, IRC Assessment)



8.5.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints included hPFS by investigator assessment, hOR rate by both IRC and investigator assessment, overall PFS, and OS. The secondary efficacy results shown below are from the primary data analysis cut-off of April 2010.

8.5.2.1. hPFS by Investigator Assessment

A clinically meaningful and statistically significant improvement in hPFS by investigator assessment was also observed in the PHP group compared to the BAC group (Table 17). Median hPFS by investigator assessment was 1.64 months (95% CI: 1.45, 2.27) in the BAC group compared to 8.05 months (95% CI: 5.78, 8.90) in the PHP group, with a corresponding HR of 0.28 (95% CI: 0.18, 0.45).

IRC and investigator assessments of hPFS were consistent with 72.7% concordance for the PHP group and 63.2% concordance for the BAC group (Table 18).

Table 17: hPFS in the Overall Population in the Phase 3 Study: Investigator Assessment (ITT Population)

	PHP (N=44)	BAC (N=49)
Patients with hepatic progression n (%)	34 (77.3%)	48 (98.0%)
Median[a] (95% CI) time to hepatic progression (months)	8.05 (5.78, 8.90)	1.64 (1.45, 2.27)
Min, Max time to hepatic progression (months)	0.9, 28.9+	0.8, 16.4
P-value from log-rank test	< 0.0001	
Hazard ratio[b] (95% CI)	0.28 (0.18, 0.45)	

[a]Median and confidence interval (CI) are based on the Product-Limit estimate of survival curve.
[b]Estimate of the hazard ratio is from the Cox model with fixed effect for treatment.
Plus sign indicates a censored observation.

Table 18: IRC and Investigator Concordance for hPFS in the Phase 3 Study

	% Patients	
	PHP (N=44)	BAC (N=49)
IRC and investigator agree	72.7	63.2
IRC and investigator disagree	13.6	22.4
IRC no hepatic progressive disease, investigator hepatic progressive disease	9.1	22.4
IRC hepatic progressive disease, investigator no hepatic progressive disease	4.5	0
Scan couldn't be read by IRC (poor quality or missing)	13.6	14.3

8.5.2.2. hOR Rate

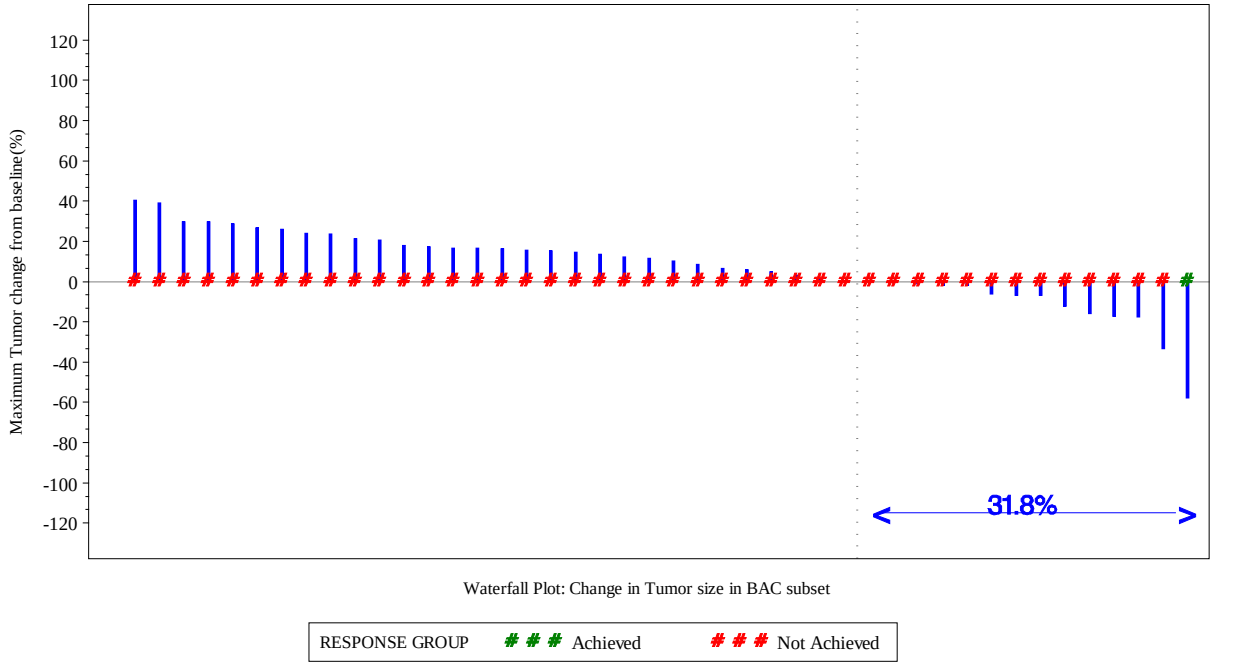
In the overall population, there was a statistically significant ($p < 0.0001$) improvement in the hOR rate by IRC assessment with PHP treatment (36.4%) compared to BAC treatment (2.0%) (Table 19). The investigators' assessment of the hOR rate was consistent with the IRC's. All of the hORs were PRs.

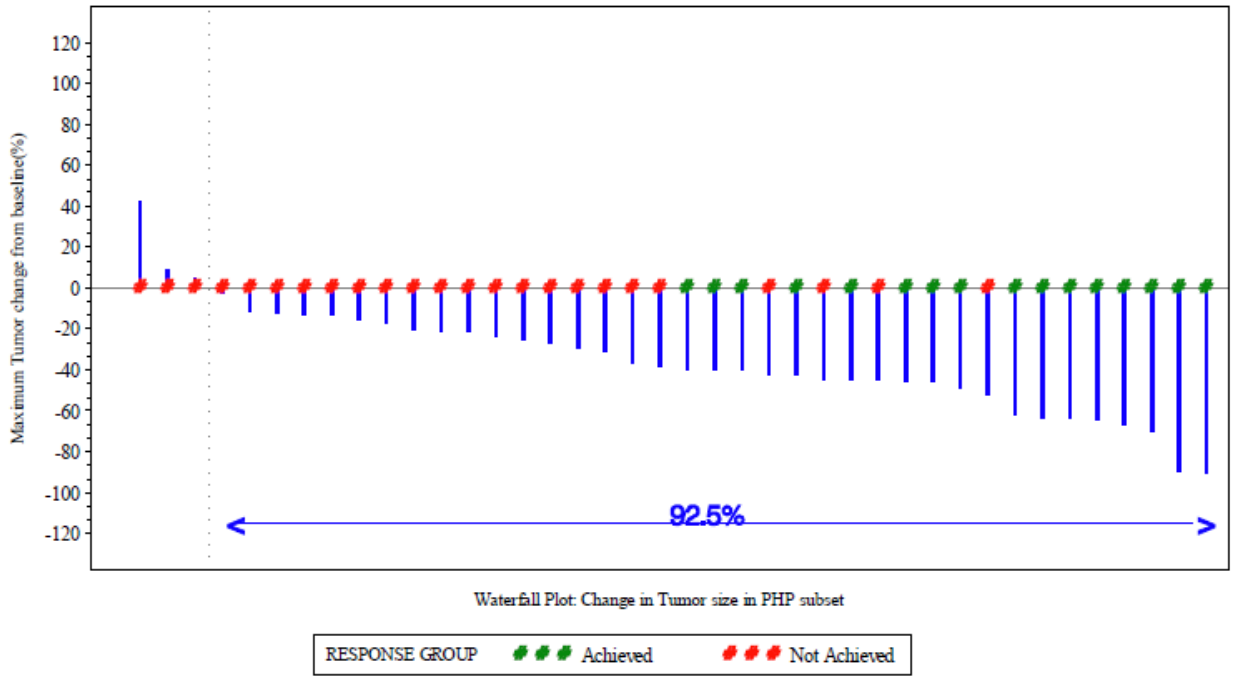
Table 19: hOR by IRC and Investigator Assessment in the Overall Population in the Phase 3 Study (ITT Population)

	Overall Population		
	PHP (N=44)	BAC (N=49)	p-value
hOR IRC (%)	36.4	2.0	<0.0001
hOR Investigator (%)	38.6	2.0	<0.0001

IRC assessment of maximum percent change in tumor size (ITT population) at the primary data cut-off date is shown in Figure 6. In the PHP group, 92% of patients had some shrinkage in tumor size compared to 32% of patients in the BAC group. Moreover, nearly half of the patients randomized to PHP had a >30% reduction in the size of their lesions with 16 of these patients having confirmed reductions by a follow-up radiologic assessment.

Figure 6: Waterfall Plot of Maximum Percent Change in Hepatic Tumor Size by Treatment in the Phase 3 Study (ITT Population, IRC Assessment)





Note: Green bars represent achievement of any response and red bars represent no response at all.

8.5.2.3. Overall PFS

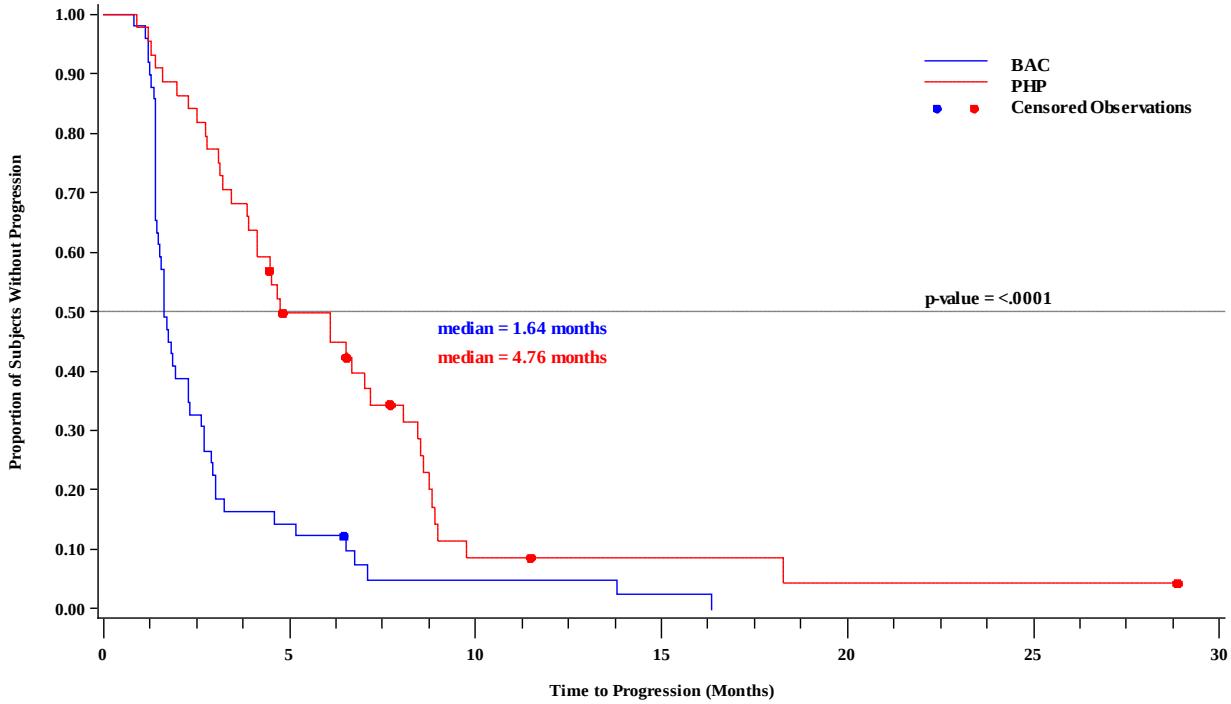
Median time to overall progression or death was 4.76 months in the PHP group compared to 1.64 months in the BAC group, a statistically significant ($p < 0.0001$) 3-month prolongation (Table 20). The HR for disease progression or death was 0.36 which represents a 64% decrease in the hazard of overall disease progression or death. Kaplan-Meier curves of event rates for overall PFS show a clear, early separation of the curves that remain separate (Figure 7).

Table 20: Overall PFS in the Overall Population in the Phase 3 Study: Investigator Assessment (ITT Population)

	PHP (N=44)	BAC (N=49)
Patients with overall progression n (%)	38 (86.4%)	48 (98.0%)
Median[a] (95% CI) time to overall progression (months)	4.76 (3.88, 7.16)	1.64 (1.45, 2.27)
Min, Max time to overall progression (months)	0.9, 28.9+	0.8, 16.4
P-value from log-rank test	<0.0001	
Hazard Ratio[b] (95% CI)	0.36 (0.23, 0.56)	

[a]Median and confidence interval (CI) are based on the Product-Limit estimate of survival curve.
[b]Estimate of the hazard ratio is from the Cox model with fixed effect for treatment.
Plus sign indicates a censored observation.

Figure 7: Kaplan Meier Curve of Overall PFS in the Overall Population in the Phase 3 Study: IRC Assessment (ITT Population)



8.5.2.4. Overall Survival

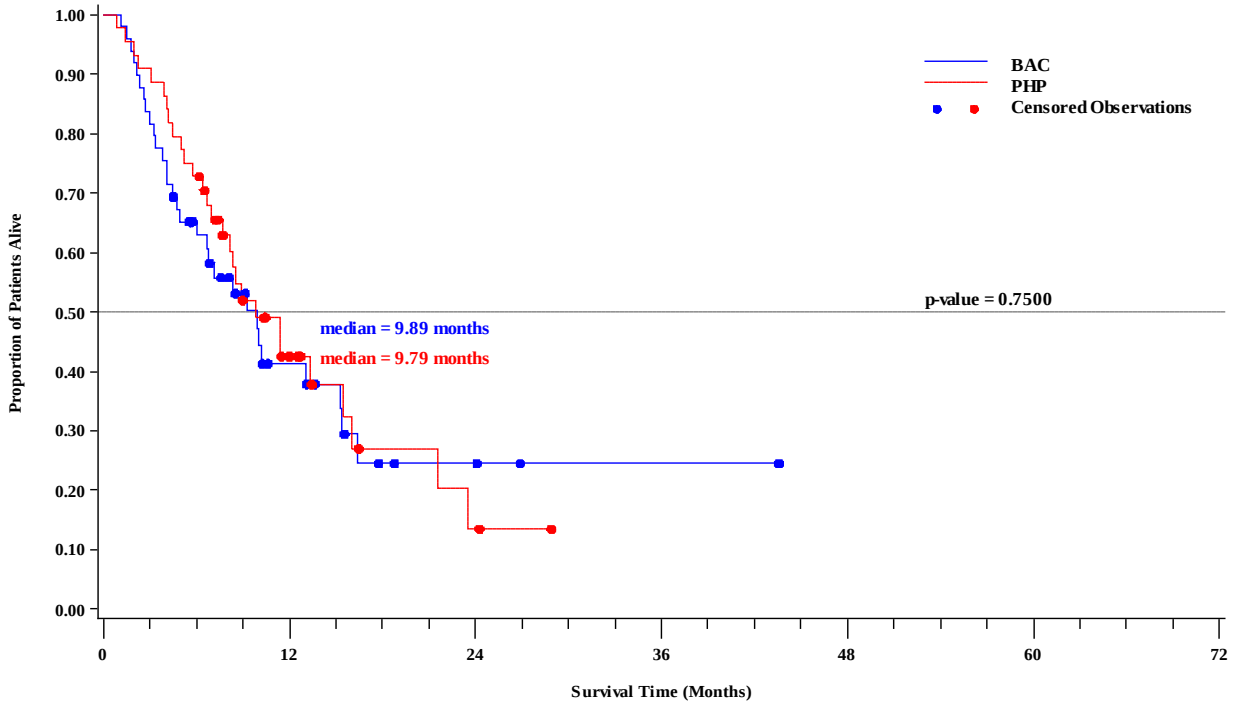
In the overall population, median survival was similar in the PHP and BAC groups at the primary (Table 21) data analysis cut-off. Kaplan-Meier curves of OS in the PHP and BAC groups separated early in the study, but ultimately overlapped (Figure 8). These results are confounded by the high number of BAC patients (28/49 patients; 57.1%) who crossed over to PHP treatment. At the time of the primary April 2010 cut-off there were 16 PHP, 5 BAC and 14 BAC cross-over patients.

Table 21: Overall Survival Results in Overall Population in the Phase 3 Study (ITT Population)[a]

	PHP (N=44)	BAC (N=49)
Patients who died, n (%)	28 (63.6%)	30 (61.2%)
Median (95% CI) time to death (months)[b]	9.79 (6.93, 15.44)	9.89 (6.01, 15.28)
Min, Max time to death (months)	0.9, 28.9+	1.1, 43.6+
P-value from log-rank test	0.7500	
Hazard Ratio[c] (95% CI)	0.92 (0.55, 1.54)	

[a]Primary analysis cut off of April 2010.
[b]Median and confidence interval (CI) are based on the Product-Limit estimate of survival curve.
[c]Estimate of the hazard ratio is from the Cox model with fixed effect for treatment.

Figure 8: Kaplan-Meier Curves of Overall Survival in the Overall Population in the Phase 3 Study (ITT Population)



Note: Primary analysis cut off of April 2010.

8.5.3. Supportive Efficacy Results: Ocular Melanoma Subgroup

The primary and secondary efficacy endpoints were also analyzed for the ocular melanoma subgroup.

The primary and secondary efficacy results, including all sensitivity and subgroup analyses, were highly statistically significant and clinically meaningful in the ocular melanoma subgroup (Table 22).

Table 22: Efficacy in Ocular Melanoma Subgroup in Phase 3 Study DSI MEL 2005-001

	Ocular Melanoma	
	PHP	BAC
hPFS by IRC		
Median (95% CI) in months	7.03 (4.99, 9.66)	1.64 (1.41, 2.69)
HR (95% CI)	0.42 (0.25, 0.72)	
p-value	0.0011	
hPFS by Investigator		
Median (95% CI) in months	7.89 (5.22, 8.84)	1.64 (1.41, 2.27)
HR (95% CI)	0.31 (0.19, 0.50)	
p-value	<0.0001	
hOR by IRC (%)	35.9	2.3
p-value	<0.0001	
hOR by Investigator (%)	41.0	2.3
p-value	<0.0001	
OS		
Median (95% CI) in months	9.79 (6.70, 15.44)	9.89 (4.50, 15.41)
HR (95% CI)	0.98 (0.57, 1.68)	
p-value	0.9413	

8.5.4. Exploratory Efficacy Analyses

8.5.4.1. Crossover Group

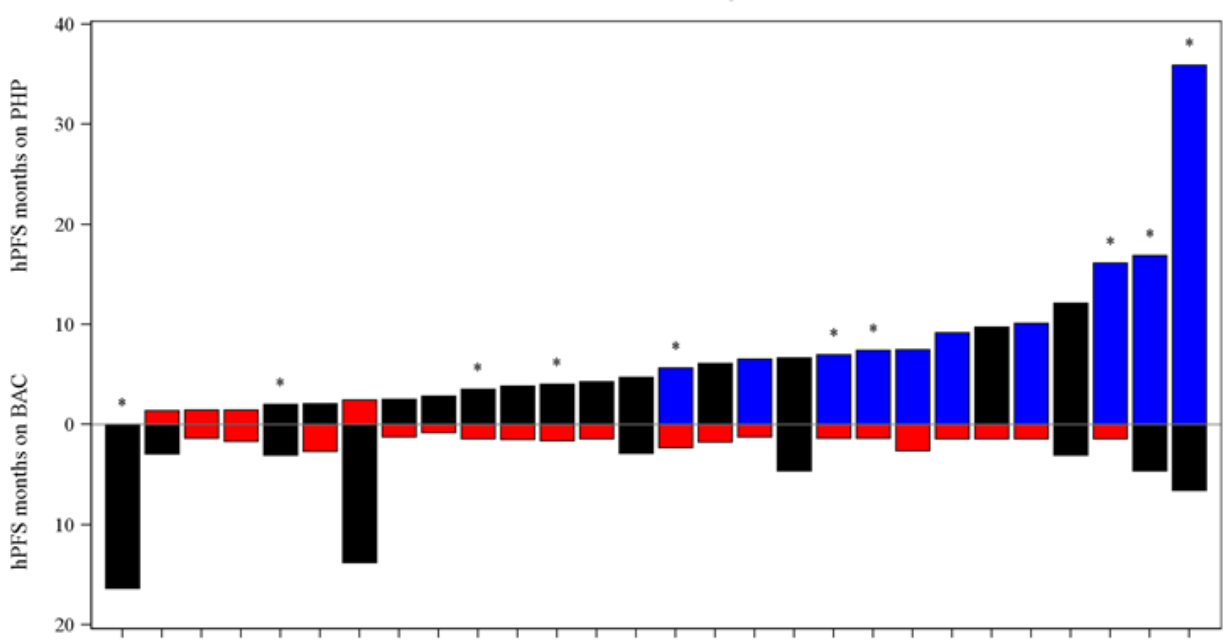
The crossover group was not a prespecified subgroup for efficacy analyses because it wasn't known how many patients in the BAC group would qualify for and chose to crossover to PHP treatment after hepatic progression. However, because of the substantial number of patients (28 patients) who crossed over from BAC to PHP treatment, exploratory efficacy analyses were performed for the crossover group. In general, the efficacy results seen in the crossover group were similar to those in the PHP group (Table 23).

Table 23: Efficacy in Crossover Group in Phase 3 Study DSI MEL 2005-001

Endpoint	Crossover Group
hPFS by IRC	
Median (95% CI) in months	8.44 (3.06, 11.17)
hPFS by Investigator	
Median (95% CI) in months	6.70 (3.88, 9.72)
hOR by IRC (%)	28.6
hOR by Investigator (%)	35.7
OS	
Median (95% CI) in months	15.28 (9.89,-)

Investigator assessment of hPFS for each of the 28 BAC patients who crossed over before and after cross over at the primary data cut-off date are shown in Figure 9. None of the patients who crossed over from BAC to PHP had a best hepatic response of PR while on BAC treatment, but 10 of the patients had a best hepatic response of PR while on PHP.

Figure 9: Investigator hPFS Before and After Crossover (ITT Crossover Population)

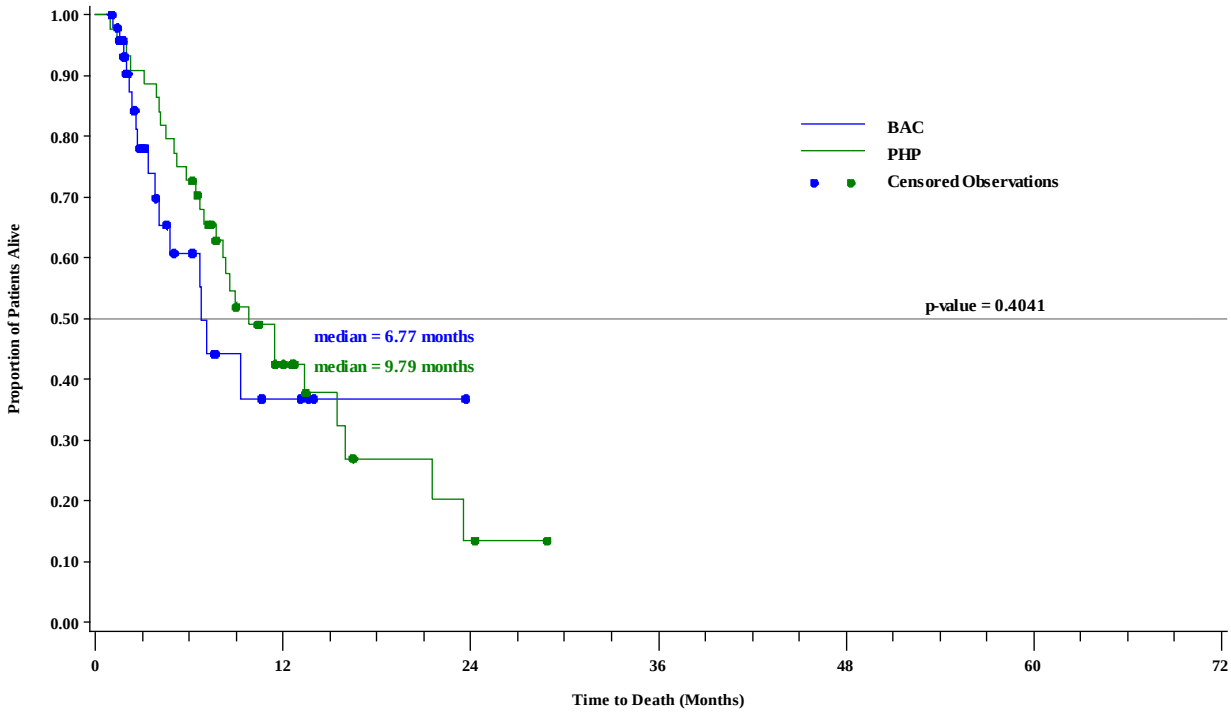


Note: Red bars represent progression of disease, black stable disease, and blue partial response. Asterisks show best response when censored for PHP.

8.5.4.2. Other Exploratory Analyses

Exploratory analyses of OS were conducted. One exploratory analysis examined whether there was a difference in OS when BAC patients were censored at crossover. Kaplan-Meier curves of OS censored at the time of crossover show an early separation of the curves that remain separate (Figure 10).

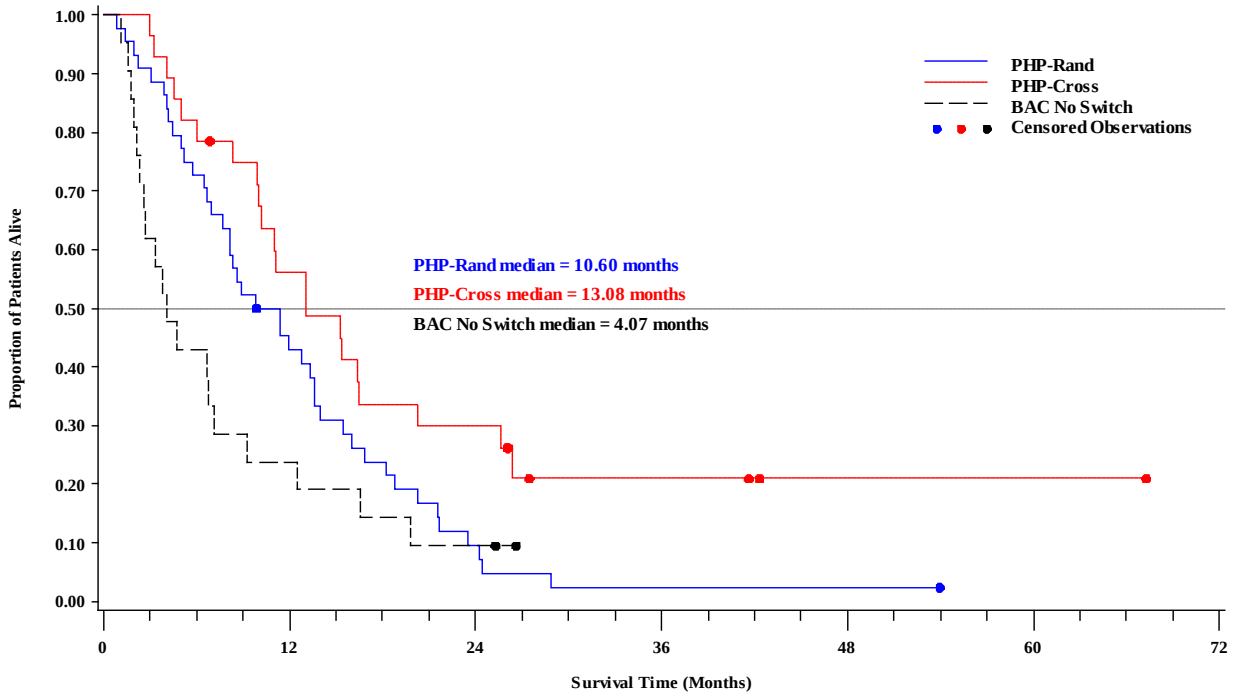
Figure 10: Kaplan-Meier Curve of Overall Survival Censored for BAC Patients at the Time of Crossover in the Phase 3 Study (ITT Population)



Note: BAC = Best Alternative Care. PHP = Percutaneous Hepatic Perfusion (with Melphalan). Baseline is the date of randomization.
Patients Randomized to BAC who crossed over to PHP were censored at the time of crossover. footnote4

An additional exploratory analysis was conducted to examine OS for patients who crossed over from BAC to melphalan/PHP treatment upon hepatic progression versus non-crossovers. The Kaplan-Meier curve of OS in the crossover group was similar to that seen for the PHP group, suggesting that survival of the crossover group was like that observed in the PHP group; a heavier tail was observed for the curve of the crossover group versus the curve of the PHP group because of a number of survivors in the crossover group (Figure 11).

Figure 11: Kaplan-Meier Curve of Overall Survival for Crossovers and Non-Crossovers in the Phase 3 Study (ITT Population)



8.6. Efficacy Conclusions

The Phase 3 study, DSI MEL 2005-001, met its primary endpoint of hPFS by IRC assessment in both the overall patient population and the ocular melanoma subgroup. The magnitude of the hPFS improvement observed with melphalan/PHP treatment is both statistically significant and clinically meaningful. The 5-month median advantage of melphalan/PHP treatment in hPFS in melanoma patients is clinically meaningful given the short median time to hepatic progression or death in the comparator BAC arm (melphalan/PHP, 7.03 months; BAC, 1.64 months).

hPFS results were consistent between the IRC and investigator assessments. The robustness of the hPFS benefit with melphalan/PHP was observed across all sensitivity and subgroup analyses.

Melphalan/PHP treatment also resulted in statistically significant and clinically meaningful improvements in the hOR rate compared to BAC.

A treatment benefit for melphalan/PHP treatment over BAC was not seen for OS; this is likely due the high number of BAC patients who experienced hepatic progression and crossed over to PHP treatment.

Ocular melanoma patients and patients who crossed over from BAC to PHP treatment at the time of hepatic progression showed similar median hPFS times and hOR rates as the PHP group in the overall population.

The ocular melanoma subgroup in the uncontrolled Phase 1 01-C-0215 study and Phase 2 study 04-C-0273 showed similar median hPFS times and hOR rates as the Phase 3 study, providing supportive evidence of efficacy.

Collectively, these data provide compelling evidence of a clinical benefit for melphalan/PHP in patients with unresectable metastatic ocular melanoma in the liver.

9. SAFETY OF MELPHALAN/PHP TREATMENT

9.1. Overview of the Safety Database

The primary presentation of safety data is a pool of the Phase 2 (N=52) and the Phase 3 studies because these studies used the same melphalan dose (3.0 mg/kg), the same safety-related inclusion criteria (see Appendix B), and similar safety monitoring schedules. The multiple tumor histologies present in the Phase 2 study compared to the Phase 3 study are not expected to impact the safety profile. The pooled population includes data from a total of 121 patients, including the following:

- 42 patients with ocular or cutaneous melanoma from the randomized PHP group in the Phase 3 study
- 28 patients with ocular or cutaneous melanoma who crossed over from BAC treatment to PHP treatment in the Phase 3 study
- 51 patients with multiple tumor histologies in the Phase 2 study

Data from the Phase 1 study were not pooled with the Phase 2 and Phase 3 data because of the range of melphalan doses used in the Phase 1 study. However, the safety profile for melphalan/PHP treatment in this study was consistent with that observed in the Phase 2 and Phase 3 studies.

Safety data are presented for a Safety Population, defined as all patients for whom a study treatment or procedure was attempted. In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported. Thus, the adverse event analyses are focused on adverse events of grade 3 or greater.

9.2. Exposure

In both the pooled and the Phase 3 populations, the median number of completed cycles of PHP treatment was three (Table 24). The median cumulative melphalan dose was higher for the Phase 3 study compared to the pooled population.

Table 24: Extent of Exposure (Safety Population)

	Pooled (N=121)	Phase 3 (N=42)	Phase 2 (N=56)
Number of completed cycles			
N	116	40	
Median	3.0	3.0	2.0
Range	1-7	1-6	1-7
Cumulative melphalan dose (mg)			
N	116	40	
Median	449.5	527.5	414.0
Range	81-1430	159-1025	81-1099

9.3. Overview of Adverse Events

An overview of adverse events is provided in Table 25. Almost all patients (95%) in the PHP group had at least one adverse event. Most (80%) of these adverse events were serious adverse events. Serious adverse events are discussed in Section 9.6.

Five deaths in the PHP group were considered related to treatment and resulted from adverse events: four in the Phase 3 study, including one in the crossover group and one in the Phase 2 study. Deaths are discussed in Section 9.5.

Approximately 40% of patients had one or more adverse events leading to treatment discontinuation. Adverse events leading to treatment discontinuation are discussed in Section 9.6.

Table 25: Overview of Adverse Events (Safety Population)

	Pooled (N=121)	
Type of Event, n (%)	All	Grade 4
Adverse event	115 (95.0)	110 (90.9)
Serious adverse event	101 (83.5)	88 (72.7)
Adverse event resulting in death	5 (4.1)	-
Adverse event leading to treatment discontinuation	46 (38.0%)	24 (19.8%)

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

9.4. Common Adverse Events

9.4.1. Overall Study Period

The most common adverse events were hematologic events, including thrombocytopenia, neutropenia, febrile neutropenia, and anemia, and increases in liver function tests (bilirubin, AST, and ALT) (Table 26). Thrombocytopenia, neutropenia, and febrile neutropenia were predominantly grade 4 events whereas anemia was predominantly a grade 3 event.

Table 26: Common (>15% of patients) Adverse Events (Safety Population)

	Pooled (N=121)		
Type of event, n (%)	All	Grade 3/4	Grade 4
Platelets decreased	111 (91.7%)	111 (91.7%)	95 (78.5%)
Neutrophils decreased	106 (87.6%)	106 (87.6%)	87 (71.9%)
Hemoglobin decreased	98 (81.0%)	97 (80.2%)	16 (13.2%)
Albumin decreased	46 (38.0%)	46 (38.0%)	0
AST increased	40 (33.1%)	40 (33.1%)	11 (9.1%)
White blood cells decreased	34 (28.1%)	34 (28.1%)	21 (17.4%)
Bilirubin increased	26 (21.5%)	26 (21.5%)	10 (8.3%)
ALT increased	25 (20.7%)	25 (20.7%)	2 (1.7%)
Febrile neutropenia	22 (18.2%)	21 (17.4%)	9 (7.4%)

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

9.4.2. Peri-and Post-Procedure Adverse Events

The relationship of the most common adverse events to either the procedure or to melphalan can be determined by examining the timing of the events. Adverse events were analyzed by two procedural periods:

- Peri-procedure period defined as from the date of the planned procedure until the earlier of 3 days or patient discharge from the hospital. Events during this period are more likely to be device-/procedure-related adverse events
- Post-procedure period, defined as the time from the end of the peri-procedure period until the day prior to the next treatment cycle or 30 days after the date of the final melphalan/PHP treatment. Events reported during the post-procedure period are more likely to be melphalan-related adverse events.

Common adverse events during the peri-procedure period were consequences consistent with hepatic-directed therapies and the technical aspects of the PHP procedure (Table 27). The most common adverse events during the peri-procedure period were hematologic events, including thrombocytopenia and anemia; hypoalbuminemia, and liver enzyme elevations (ie, AST, ALT, and bilirubin increased).

The adverse event profile during the post-procedure period was characterized predominantly by adverse events related to bone marrow suppression. The most common adverse events during the post-procedure period were neutropenia, thrombocytopenia, anemia, white blood cell count decreased, febrile neutropenia, and liver enzyme elevations (ie, AST, ALT, and bilirubin increased); these events are discussed further in Section 9.10.

Table 27: Common (>15% of Patients) Adverse Events: Peri- and Post-Procedure Periods (Safety Population)

Event, n (%)	Overall	Peri	Post
Platelet Count Decreased	111 (91.7%)	89 (73.6%)	97 (80.2%)
Neutrophil Count Decreased	106 (87.6%)	5 (4.1%)	105 (86.8%)
Hemoglobin Decreased	98 (81.0%)	75 (62.0%)	71 (58.7%)
Blood Albumin Decreased	46 (38.0%)	43 (35.5%)	7 (5.8%)
AST Increased	40 (33.1%)	30 (24.8%)	16 (13.2%)
White Blood Cell Count Decreased	34 (28.1%)	3 (2.5%)	34 (28.1%)
Blood Bilirubin Increased	26 (21.5%)	17 (14.0%)	18 (14.9%)
ALT Increased	25 (20.7%)	12 (9.9%)	14 (11.6%)
Febrile Neutropenia	22 (18.2%)	0	22 (18.2%)

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

9.5. Treatment-Related Deaths

Five deaths in the clinical development program were considered treatment-related and resulted from adverse events: 4 in the Phase 3 study (3 in the PHP group and 1 in the crossover group) and 1 in the Phase 2 study (Table 28). There were no adverse events leading to death in the BAC group in the Phase 3 study. The treatment-related deaths were a consequence of either the PHP procedure, melphalan, or both the procedure and melphalan.

Table 28: Adverse Events Resulting in Death in Melphalan/PHP Clinical Development Program

Study Treatment Group	Age (years)	Sex	Cause of Death	Study Day	Cycle	Comment
Phase 2 PHP	67	M	GI hemorrhage Ruptured right hepatic artery	74	1	Prior Whipple procedure • Liver abscess, liver dysfunction • Renal insufficiency • Aspiration pneumonia, acute respiratory distress syndrome
Phase 3 PHP	56	M	Hepatic failure	42	1	Disease burden (>90%) • Hepatorenal syndrome • Myelosuppression
Phase 3 Crossover	62	M	Gastric perforation	151	2	Melphalan infused during hepatic artery spasm • Melphalan reflux • GI bleeding
Phase 3 PHP	54	F	Streptococcal sepsis	60	2	Grade 4 hypoxia, grade 3 anemia, grade 4 thrombocytopenia, grade 4 neutropenia
Phase 3 PHP	66	M	Neutrophil count decreased	94	2	• Herpes simplex infection of the mouth • Pulmonary edema

9.5.1. Procedure-Related Deaths

Three of the deaths were attributable to the PHP procedure or the direct local effects of melphalan during the procedure.

The death due to upper GI hemorrhage in the Phase 2 study was in a male patient with pancreatic NET who had a prior Whipple procedure and consequent abnormal architecture of the upper GI tract, its vasculature, and biliary tree. Following his first cycle of melphalan/PHP treatment, the patient was repeatedly hospitalized for liver abscess and GI bleeding which was complicated by aspiration pneumonia, respiratory distress, and renal failure on Day 74. An autopsy revealed a ruptured right hepatic artery as the primary cause of death.

The death due to hepatic failure occurred in a male patient in the Phase 3 study during the first cycle of melphalan/PHP treatment. Following melphalan/PHP treatment, this patient experienced fluid overload, myelosuppression, and hepatorenal syndrome. An autopsy revealed that this patient's death was related to underlying disease burden since his liver tissue was >90% tumor.

The death due to gastric perforation occurred in a male patient in the Phase 3 study who crossed over to melphalan/PHP treatment after hepatic progression on BAC. After his second cycle of melphalan/PHP treatment, the patient had evidence of GI bleeding. During an endoscopy to investigate the GI bleed, a gastric ulcer was perforated. An exploratory laparotomy was performed and a gastric perforation was repaired. However, during the laparotomy, the patient went into cardiopulmonary arrest and died. An autopsy revealed two gastric ulcers which likely resulted from the infusion of melphalan during a hepatic artery spasm with consequent misperfusion into the GI vasculature.

All of these deaths were followed by protocol amendments during the clinical development program, including excluding patients with a prior Whipple procedure; requiring a liver biopsy to confirm normal liver tissue if the tumor burden was >50%; and recommending the administration of nitroglycerin if hepatic artery spasm was seen during the PHP procedure, to not infuse melphalan until the spasm resolved, and to terminate the PHP procedure if the spasm did not resolve with nitroglycerin administration. These amendments have been incorporated into the patient selection criteria and risk management measures that are proposed for melphalan/PHP treatment (see Section 10.2.2 and Section 10.2.4).

9.5.2. Deaths due to Complications of Neutropenia

Two patients died during the melphalan/PHP clinical development program because of complications of neutropenia during their second cycle of treatment.

A 54-year old female patient in the Phase 3 study died of streptococcal sepsis. This patient experienced myelosuppression at cycle 1, but her melphalan dose was not reduced to 2.5 mg/kg IBW for cycle 2. The patient was readmitted to the hospital on Day 11 of cycle 2 with hypoxia, pancytopenia, and sepsis and started on a multi-antibiotic regimen. The patient died of sepsis on Day 13.

In addition, a 66-year old male patient in the Phase 3 study died of neutropenic complications in cycle 2. This patient experienced myelosuppression in cycle 1 and had his melphalan dose reduced to 2.5 mg/kg IBW for cycle 2. The patient was hospitalized from day 13 to day 23 of cycle 2 with pneumonia and neutropenia and was readmitted on day 33 of cycle 2 with grade 4 pancytopenia, a necrotic herpes simplex infection of the mouth, and pulmonary edema. The patient died on Day 40 of cycle 2.

Prophylactic administration of colony-stimulating factors was not mandated during the clinical development program and only a small percentage of patients received prophylactic growth factors during either the first (5%) or subsequent treatment cycles (12%). Approximately 60% of patients received growth factors for treatment of neutropenia. Prophylactic administration of colony-stimulating factors is proposed as a risk management measure (see Section 10.2.5).

9.6. Serious Adverse Events

Approximately 80% of patients had a serious adverse event (Table 29; Appendix C for a summary of serious adverse events reported in >2 patients). The most common serious adverse events were neutropenia, thrombocytopenia, and febrile neutropenia.

Table 29: Serious Adverse Events (≥10% of Patients) (Safety Population)

Event, n (%)	Pooled (N=121)
Any SAE	101 (83.5%)
Neutrophil count decreased	71 (58.7)
Platelet count decreased	62 (51.2)
Febrile neutropenia	20 (16.5)
Hemoglobin decreased	13 (10.7)

In the Phase 3 study, a higher percentage of serious adverse events was reported in patients enrolled at NCI versus the non-NCI sites, reflecting the differing serious adverse event reporting conventions at the respective sites (Table 30) (see Section 8.1.5).

Table 30: Serious Adverse Events (≥10% of Patients): NCI versus Non-NCI Sites in the Phase 3 Study (Safety Population)

	Phase 3 PHP Group		
Event, n (%)	Overall (N=42)	NCI (N=19)	Non-NCI (N=23)
Any SAE	33 (78.6)	18 (94.7)	15 (65.2)
Neutrophil count decreased	19 (45.2)	15 (78.9)	4 (17.4)
Platelet count decreased	16 (38.1%)	11 (57.9)	5 (21.7)
Hemoglobin decreased	6 (14.3%)	4 (21.1)	2 (8.7)
Febrile neutropenia	6 (14.3%)	3 (15.8)	3 (13.0)

9.7. Adverse Events Prolonging or Resulting in Hospitalization

Approximately 25% of patients had an adverse event that prolonged their hospitalization for the PHP procedure, with a median duration of hospitalization of 5.5 days compared to a median duration of hospitalization for study treatment of 4.0 days (Table 31). The reasons for prolonged hospitalization were varied (Table 32).

Table 31: Hospitalization Duration

Type of Hospitalization	
Hospitalization to receive treatment	
Median Duration	4.0
Minimum Duration	1
Maximum Duration	29
Treatment Hospitalizations Prolonged due to an AE	
Median Duration of total hospitalization	5.5
Minimum Duration	2
Maximum Duration	29
Hospitalizations due to an AE	
Median Duration	5.0
Minimum Duration	1
Maximum Duration	60

AE: adverse event

Table 32: Adverse Events Prolonging Hospitalization (Safety Population)

	All	Grade 4
Blood Bilirubin Increased	3 (2.5)	2 (1.7)
Platelet Count Decreased	3 (2.5)	2 (1.7)
Hemoglobin Decreased	2 (1.7)	1 (0.8)
Hypotension	2 (1.7)	1 (0.8)
Hypoxia	2 (1.7)	1 (0.8)
Pulmonary Edema	2 (1.7)	2 (1.7)
Pyrexia	2 (1.7)	0
Thrombosis	2 (1.7)	1 (0.8)
Abdominal Pain	1 (0.8)	1 (0.8)
AST Increased	1 (0.8)	1 (0.8)
Atrial Fibrillation	1 (0.8)	0
Blood Creatinine Increased	1 (0.8)	0
Bronchospasm	1 (0.8)	1 (0.8)
Cerebral Ischemia	1 (0.8)	1 (0.8)
Cholecystitis Chronic	1 (0.8)	0
Cholangitis	1 (0.8)	0
Gastric Ulcer	1 (0.8)	0
Hematoma	1 (0.8)	0
Myocardial Infarction	1 (0.8)	0
Pneumothorax	1 (0.8)	0
Post Procedural Hemorrhage	1 (0.8)	0
Subendocardial Ischemia	1 (0.8)	1 (0.8)
Small Intestinal Hemorrhage	1 (0.8)	0
Vaginal Hemorrhage	1 (0.8)	1 (0.8)
Vena Cava Thrombosis	1 (0.8)	0
Ventricular Tachycardia	1 (0.8)	0

Approximately 50% of patients were rehospitalized following discharge for treatment of an adverse event, with a median duration of hospitalization of 5 days (Table 31). The most common reasons for a rehospitalization were thrombocytopenia, neutropenia, febrile neutropenia, and anemia (Table 33).

Table 33: Adverse Events Requiring Hospitalization (Safety Population)

	All	Grade 4
Platelet Count Decreased	27 (22.3)	27 (22.3)
Neutrophil Count decreased	18 (14.9)	17 (14.0)
Febrile Neutropenia	18 (14.9)	9 (7.4)
Hemoglobin Increased	9 (7.4)	2 (1.7)
Constipation	3 (2.5)	0
Neutropenic Infection	3 (2.5)	0
Blood Bilirubin Increased	2 (1.7)	1 (0.8)
Dehydration	2 (1.7)	0
Hemorrhage Intracranial	2 (1.7)	1 (0.8)
Pulmonary Embolism	2 (1.7)	2 (1.7)
Abdominal Pain Upper	1 (0.8)	0
ALT Increased	1 (0.8)	1 (0.8)
Allergic Transfusion Reaction	1 (0.8)	0
AST Increased	1 (0.8)	1 (0.8)
Bile Duct Stone	1 (0.8)	0
Cholecystitis	1 (0.8)	0
Costochondritis	1 (0.8)	0
Edema Peripheral	1 (0.8)	0
Endocrine Disorder	1 (0.8)	0
Gastric Ulcer	1 (0.8)	0
Gastritis	1 (0.8)	0
Hematuria	1 (0.8)	0
Jejunal Perforation	1 (0.8)	0
Liver Abscess	1 (0.8)	0
Pancytopenia	1 (0.8)	1 (0.8)
Perirectal Abscess	1 (0.8)	0
Pericardial Effusion	1 (0.8)	1 (0.8)
Pneumonia	1 (0.8)	1 (0.8)
Pleural Effusion	1 (0.8)	0
Pulse Absent	1 (0.8)	0
Rectal Abscess	1 (0.8)	0
Retinal hemorrhage	1 (0.8)	0
Spinal Cord Compression	1 (0.8)	1 (0.8)
Subclavian Vein Thrombosis	1 (0.8)	0
Thrombosis	1 (0.8)	1 (0.8)
Urethral Hemorrhage	1 (0.8)	0
Urinary Tract Infection	1 (0.8)	0
Vaginal Hemorrhage	1 (0.8)	0
Vena Cava Thrombosis	1 (0.8)	1 (0.8)
Vomiting	1 (0.8)	0
While Blood Cell Count Decreased	1 (0.8)	1 (0.8)

9.8. Adverse Events Leading to Treatment Withdrawal

Approximately 40% of patients discontinued treatment (ie, did not receive 4 cycles of treatment in Phase 2 study or 6 cycles of treatment in the Phase 3 study) because of an adverse event (Table 34). The most frequent adverse event resulting in treatment discontinuation was thrombocytopenia. Most of the discontinuations for thrombocytopenia occurred after either cycle 2 or cycle 3 of treatment.

Table 34: Adverse Events Leading to Treatment Withdrawal (Safety Population)

Event, n (%)	Pooled (N=121)
Any AE resulting in treatment discontinuation	46 (38.0)
Frequent (>2 patients) AEs resulting in treatment discontinuation	
Platelet count decreased	19 (15.7)
Neutrophil count decreased	9 (7.4)
Blood bilirubin increased	5 (4.1)

9.9. Adverse Events Leading to Cycle Delays and Dose Reductions

Approximately 60% of patients had a treatment delay, defined as an extension of the cycle length beyond a 4-6 week interval (Table 35). The median delay was 6 days.

Table 35: Treatment Delays (Safety Population)

	Pooled (N=121)
Patients with > 1 cycle melphalan/PHP, n (%)	92 (76)
Any cycle delayed, n (%)	53 (57.6)
Median delay (days)	6

Approximately 20% of patients had a melphalan dose reduction from 3.0 mg/kg IBW to 2.5 mg/kg IBW (Table 36). The most frequent reasons for dose reductions were thrombocytopenia and neutropenia.

Table 36: Melphalan Dose Reductions (Safety Population)

	Pooled (N=121)
Patients with > 1 cycle melphalan/PHP, n (%)	92 (76)
Any dose reduction, n (%)	27 (22.3)
Common reasons for dose reductions[1]	
Platelet count decreased	16 (13.2)
Neutrophil count decreased	12 (9.9)
Febrile neutropenia	5 (4.1)

[1]Three or more patients in the pooled PHP population

9.10. Adverse Events of Special Interest

Adverse events of special interest for melphalan/PHP treatment were selected based upon their clinical significance and the need for appropriate monitoring and prompt intervention if they occur in order to avoid serious complications and deaths. In order to assess the overall incidence of these events in the pooled database, a broad definition of terms was used to define the adverse event of special interest.

9.10.1. Cardiovascular Events

Hypotension will occur during the PHP procedure at balloon inflation and when the filter cartridges of the extracorporeal circuit come on line. Hypotension must be proactively managed by the anesthesiologist in order to mitigate the risk of ischemic injury to the heart and brain.

In order to comprehensively assess the incidence of cardiovascular events during the clinical development program, multiple terms relating to cardiovascular events were grouped, including a standardized Medical Dictionary for Regulatory Affairs (MedDRA) query of embolic and thrombotic events, arterial and embolic and thrombotic events, venous plus additional terms from the cardiac and central nervous system, and thromboembolic system organ classes. A definition for cardiovascular events is provided in Appendix D.

An overview of cardiovascular events is provided in Table 37. Twenty-nine patients (24%) had a cardiovascular event (Table 37). Cardiovascular events were more frequent in the peri-procedure period than the post-procedure period (Table 38).

Table 37: Overview of Cardiac Events (Safety Population)

	Pooled (N=121)
Type of Event, n (%)	
Cardiac adverse event	29 (24)
Grade 4 cardiac adverse event	14 (11.6)
Serious cardiac adverse event	21 (17.4)
Cardiac adverse event resulting in death	0
Cardiac adverse event leading to treatment discontinuation	10 (8.3)

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

Cardiovascular events were grouped into five categories to aid interpretation:

- Arrhythmias
- Cardiac ischemia/infarct
- Thromboembolism
- Cerebral ischemia/infarct
- Cerebral hemorrhage

Six patients had arrhythmias reported. Two patients had clinically significant events related temporally to the filters coming on line that resolved with medical management. One patient had ventricular tachycardia that led to withdrawal from study treatment. The second patient had atrial fibrillation leading to an aborted procedure, but this patient went on to have six further cycles of melphalan/PHP treatment. One additional patient had atrial fibrillation on day 16 of cycle 4 that resolved with cardioversion. There were two cases of sinus tachycardia; both cases resolved. Neither case of sinus tachycardia led to withdrawal of treatment, with one of these patients having two further cycles of melphalan/PHP treatment. An additional patient with sinus tachycardia is discussed under cardiac ischemic events below.

Seven patients, 5 with a cardiovascular history, experienced events categorized as cardiac ischemia/infarct. Six of these 7 patients were at the same study site and all were in the Phase 3 study. All 7 patients had troponin 1 elevations (five grade 4 and two grade 3) and 4 of the patients had events at multiple cycles. Six patients had clinical events concurrent with the troponin elevations: 1 patient with myocardial infarction, 1 patient with subendocardial ischemia, 1 patient with grade 4 pulmonary edema who was treated for acute coronary syndrome, 2 patients with ST changes on ECG, and 1 patient with associated grade 2 fatigue and dyspnea. All acute events resolved and none of these events led to withdrawal of study treatment, although the patient who had a myocardial infarction was eventually withdrawn due to ventricular tachycardia (noted under arrhythmias above).

Seven patients had thromboembolic events. Pulmonary emboli were reported for 3 patients (two were objectively documented by CT angiography); all of the pulmonary emboli resolved with treatment, but the patients were withdrawn from study treatment. There was one right leg deep vein thrombosis, documented by ultrasound and resolving on treatment; this patient had five additional cycles of melphalan/PHP treatment. One non-occlusive inferior vena cava thrombus was noted during preparation for the second cycle of melphalan/PHP treatment; this event resolved on treatment, but the patient was withdrawn from study treatment. There were two cases of indwelling catheter-related thrombi that resolved with catheter removal. One patient with catheter-related thrombi went on to five additional cycles of melphalan/PHP treatment and the other patient with catheter-related thrombi was withdrawn from study treatment for an unrelated reason.

Seven patients in the pooled population had cerebral ischemic/infarct events. Three patients had infarcts on brain CT or MRI; two of the patients were asymptomatic and one patient had slurred speech and dyspraxia that resolved. All of the patients with infarcts on brain CT or MRI were withdrawn from study treatment. Another patient had infarcts in the setting of brain metastases on day 88 of cycle 2; the patient died of this progression of disease on Day 95. The other events were a transient ischemic attack documented on MRI on day 78 (cycle 2), and two grade 1 transient ischemic events: a facial paresis on day 1 and a blurred vision on day 10 post-procedure. All three events resolved.

For the purposes of the cardiac adverse events of special interest analysis, cerebral hemorrhages were included in the cardiovascular tables, but are discussed in the hemorrhage/bleeding section (see Section 9.10.3).

Risk mitigation requirements for cardiovascular events are provided in Section 10.2.1.

Table 38: Cardiovascular Events: Peri- and Post-Procedure Periods (Safety Population)

	All Grades	Grade 3/4		
Event, n (%)	Overall (N=121)	Overall (N=121)	Peri-Procedure (N=121)	Post-Procedure (N=121)
Any cardiovascular AE	29 (24.0)	21 (17.4)*	13 (10.7)	7 (5.8)
Troponin increased	6 (5.0)	6 (5.0)	6 (5.0)	0
Hypotension	4 (3.3)	2 (1.7)	2 (1.7)	0
Cerebral ischemia	3 (2.5)	3 (2.5)*	1 (0.8)	0
Sinus tachycardia	3 (2.5)	0	0	0
Thrombosis	3 (2.5)	3 (2.5)	2 (1.7)	2 (1.7)
Troponin I increased	3 (2.5)	3 (2.5)	3 (2.5)	0
Dizziness	2 (1.7)	0	0	0
Hemorrhage intracranial	2 (1.7)	1 (0.8)	0	1 (0.8)
Pulmonary embolism	2 (1.7)	2 (1.7)	0	2 (1.7)
Vena cava thrombosis	2 (1.7)	2 (1.7)	1 (0.8)	1 (0.8)
Acute myocardial infarction**	1 (0.8)	0	0	0
Atrial fibrillation	1 (0.8)	0	0	0
Chest discomfort	1 (0.8)	0	0	0
Electrocardiogram T wave abnormal	1 (0.8)	0	0	0
Electrocardiogram T wave inversion	1 (0.8)	0	0	0
Facial paresis	1 (0.8)	0	0	0
Hemorrhagic transformation stroke	1 (0.8)	0	0	0
Lacunar infarction	1 (0.8)	0	0	0
Myocardial infarction**	1 (0.8)	0	0	0
Pericardial effusion	1 (0.8)	1 (0.8)	0	1 (0.8)
Pulse absent	1 (0.8)	0	0	0
Pupillary reflex impaired	1 (0.8)	1 (0.8)*	0	0
Somnolence	1 (0.8)	1 (0.8)*	0	0
Subclavian vein thrombosis	1 (0.8)	1 (0.8)	0	1 (0.8)
Subendocardial ischemia	1 (0.8)	1 (0.8)	1 (0.8)	0
Ventricular tachycardia	1 (0.8)	1 (0.8)	1 (0.8)	0
Vision blurred	1 (0.8)	0	0	0
Visual impairment	1 (0.8)	0	0	0

*Event(s) occurring more than 30 days after the last treatment cycle were not attributed to the post-procedure period.
**One patient in the Phase 3 study (patient 5-600) had an acute myocardial infarction (non-ST segment elevation and myocardial infarction) and the same patient had a myocardial infarction (elevated troponin and non-T wave myocardial infarction) reported on the same date and time.
Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

9.10.2. GI Events

Misperfusion of melphalan into GI vessels can occur either because vessels were not embolized or there was reflux of melphalan into GI branches.

In order to comprehensively assess the incidence of GI events, multiple terms relating to GI events were grouped, including a standardized MedDRA query of GI nonspecific inflammation and dysfunction conditions and GI perforation, ulceration, hemorrhage or obstruction. A definition for GI events is provided in Appendix D.

An overview of GI events is provided in Table 39. Thirty patients (24.8%) had a GI event (Table 39). GI events were more frequent in the peri-procedure period than the post-procedure period (Table 40).

Two patients (1.7%) died because of GI event. One patient in the Phase 2 study died of a ruptured right hepatic artery and one crossover patient died of a gastric perforation in the Phase 3 study. Following these deaths, the clinical protocols were amended to exclude patients with a prior Whipple procedure, to recommend the intra-arterial administration of nitroglycerin if hepatic artery spasm was seen during the PHP procedure, and to not infuse melphalan until the spasm resolved. These amendments have been incorporated into the risk mitigation requirements that are proposed for GI events (Section 10.2.2).

Six patients (5.0%) discontinued study treatment because of a GI event, including bile duct stone, cholecystitis, cholecystitis chronic, duodenal perforation, duodenal ulcer, gastric ulcer, and pancreatitis.

Table 39: Overview of GI Adverse Events (Safety Population)

	Pooled (N=121)
Type of Event, n (%)	All
GI adverse event	30 (24.8)
Grade 4 GI adverse event	1 (0.8)
Serious GI adverse event	14 (11.6)
GI adverse event resulting in death	2 (1.7)
GI adverse event leading to treatment discontinuation	6 (5.0)

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

In the pooled population, there were 11 patients with events of gastritis, ulceration, perforation, and bleeding.

Five patients (4%) had gall bladder adverse events, including cholangitis, bile duct stone, cholecystitis, chronic cholecystitis, and cholelithiasis. Chronic cholecycstistis, choleliathis, and bile duct stone were pre-existing conditions that were potentially exacerbated by melphalan/PHP treatment. In addition, one patient with a prior Whipple procedure experienced cholangitis; this patient also experienced a jejunal perforation possibly due to melphalan mis-infusion because of anatomical changes due to the prior Whipple procedure. Two patients had cholecystitis that might be related to melphalan/PHP treatment; this is a known effect of regional liver treatments [Gates et al, 1999].

Approximately 67% of patients had the gastroduodenal artery branches pre-embolized to prevent reflux of melphalan into the GI vasculature. Additionally, 67% of patients were administered nitroglycerin to alleviate a spasm of the hepatic artery and prevent melphalan reflux into the GI vasculature.

Risk mitigation requirements for GI events are provided in Section 10.2.2.

Table 40: GI Events: Peri- and Post-Procedure Periods (Safety Population)

	All Grades	Grade 3/4		
Event, n (%)	Overall (N=121)	Overall (N=121)	Peri-procedure (N=121)	Post-procedure (N=121)
Any GI AE	30 (24.8)	13 (10.7)	5 (4.1)	9 (7.4)
Nausea	10 (8.3)	3 (2.5)	1 (0.8)	2 (1.7)
Vomiting	7 (5.8)	3 (2.5)	0	3 (2.5)
Abdominal pain	6 (5.0)	3 (2.5)	1 (0.8)	2 (1.7)
Duodenal ulcer	3 (2.5)	1 (0.8)	0	1 (0.8)
Gastric ulcer	3 (2.5)	1 (0.8)	0	1 (0.8)
Arterial spasm	2 (1.7)	1 (0.8)	1 (0.8)	0
Cholecystitis	2 (1.7)	1 (0.8)*	0	0
Non-cardiac chest pain	2 (1.7)	0	0	0
Abdominal pain upper	1 (0.8)	3 (2.5)*	0	0
Bile duct stone	1 (0.8)	0	0	0
Cholangitis	1 (0.8)	1 (0.8)	1 (0.8)	0
Cholecystitis chronic	1 (0.8)	0	0	0
Cholelithiasis	1 (0.8)	0	0	0
Duodenal perforation	1 (0.8)	1 (0.8)*	0	0
Flank pain	1 (0.8)	0	0	0
Gastritis	1 (0.8)	0	0	0
Gastrointestinal hemorrhage	1 (0.8)	1 (0.8)	0	1 (0.8)
Hematemesis	1 (0.8)	0	0	0
Hematochezia	1 (0.8)	0	0	0
Intra-abdominal hemorrhage	1 (0.8)	1 (0.8)	0	1 (0.8)
Jejunal perforation	1 (0.8)	1 (0.8)	0	1 (0.8)
Pancreatitis	1 (0.8)	1 (0.8)	0	1 (0.8)
Small intestinal hemorrhage	1 (0.8)	1 (0.8)	1 (0.8)	0

*Event(s) occurring more than 30 days after the last treatment cycle were not attributed to the post-procedure period.
Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

9.10.3. Bleeding Events

Bleeding complications can occur during the peri-procedure period due to the anticoagulation required for performance of the procedure and because of hemofiltration-related thrombocytopenia. Bleeding complications can occur during the post-procedure period due to melphalan-related thrombocytopenia.

In order to comprehensively assess the incidence of bleeding during the clinical development program, multiple terms relating to bleeding events were grouped using the standardized MedDRA query of hemorrhage terms (see Appendix D).

An overview of bleeding events is provided in Table 41.

Table 41: Overview of Bleeding Events (Safety Population)

	Pooled (N=121)
Type of Event, n (%)	
Bleeding adverse event	16 (13.2)
Grade 4 bleeding adverse event	3 (2.5)
Serious bleeding adverse event	10 (8.3)
Bleeding adverse event resulting in death	1 (0.8)
Bleeding adverse event leading to treatment discontinuation	4 (3.3)

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

Four patients (3.3%) had a grade 3/4 bleeding event in the peri-procedure period (Table 42). All of the patients with grade 3/4 peri-procedure bleeding events were thrombocytopenic at the time of the event, with the exception of the patient with a hematoma. Treatments for peri-procedural bleeding included transfusions of packed red blood cells, fresh frozen plasma, and platelets.

Four patients (3.3%) had a grade 3/4 bleeding event in the post-procedure period, including intracranial hemorrhage, retinal hemorrhage, vaginal hemorrhage, and GI hemorrhage (Table 42). All of the patients with post-procedure grade 3/4 bleeding events were thrombocytopenic at the time of the bleeding event. Treatments for post-procedural bleeding included transfusions of packed red blood cells, fresh frozen plasma, and platelets.

Two intracranial hemorrhages occurred in patients with brain metastases; one of these patients died. The protocols were subsequently amended to exclude patients with active intracranial metastases or brain lesions with a propensity to bleed.

Four patients discontinued study treatment because of a bleeding event, including intracranial hemorrhage (2 patients; mentioned above), hemorrhagic transformation stroke (1 patient), and hepatic hemorrhage (1 patient).

Risk mitigation requirements for bleeding are provided in Section 10.2.3.

Table 42: Bleeding Adverse Events: Peri- and Post-Procedure Periods (Safety Population)

	All grades	Grade 3/4		
Event, n (%)	Overall (N=121)	Overall (N=121)	Peri-procedure (N=121)	Post-procedure (N=121)
Any bleeding AE	16 (13.2)	8 (6.6)	4 (3.3)	4 (3.3)
Hematoma	2 (1.7)	1 (0.8)	1 (0.8)	0
Epistaxis	2 (1.7)	0	0	0
Hemorrhage intracranial	2 (1.7)	1 (0.8)	0	1 (0.8)
Retinal hemorrhage	2 (1.7)	1 (0.8)	0	1 (0.8)
Ecchymosis	1 (0.8)	0	0	0
Hematemesis	1 (0.8)	0	0	0
Post procedural hemorrhage	1 (0.8)	1 (0.8)	1 (0.8)	0
Small intestinal hemorrhage	1 (0.8)	1 (0.8)	1 (0.8)	0
Vaginal hemorrhage	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
Gastrointestinal hemorrhage	1 (0.8)	1 (0.8)	0	1 (0.8)
Hematochezia	1 (0.8)	0	0	0
Hematuria	1 (0.8)	1 (0.8)	0	1 (0.8)
Intra-abdominal hemorrhage	1 (0.8)	1 (0.8)	0	1 (0.8)
Pulmonary hemorrhage	1 (0.8)	1 (0.8%)	0	1 (0.8)
Rectal hemorrhage	1 (0.8)	0	0	0
Urethral hemorrhage	1 (0.8)	0	0	0
Hemorrhage transformation stroke	1 (0.8)	0	0	0
Hepatic hemorrhage	1 (0.8)	1 (0.8)*	0	0

*Event(s) occurring more than 30 days after the last treatment cycle were not attributed to the post-procedure period.
Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

9.10.4. Hepatic Events

In order to comprehensively assess the incidence of hepatic events during the clinical development program, multiple terms relating to hepatic events were grouped using a standardized MedDRA query of drug-related hepatic disorders that excluded liver-related bleeding disorders and liver neoplasms. A definition for hepatic events is provided in Appendix D.

An overview of hepatic events is provided in Table 43. Overall, 53 patients (43.8%) had a hepatic event (Table 43). Hepatic events in the peri- and post-procedure periods consisted predominantly of laboratory changes in liver function tests reported as adverse events, including elevated hepatic transaminases and hyperbilirubinemia (Table 44). Elevated hepatic transaminases with or without hyperbilirubinemia is a known adverse effect associated with liver-directed therapies and with melphalan.

Table 43: Overview of Hepatic Adverse Events (Safety Population)

	Pooled (N=121)
Type of Event, n (%)	
Hepatic adverse event	53 (43.8)
Grade 4 hepatic adverse event	18 (14.9)
Serious hepatic adverse event	11 (9.1%)
Hepatic adverse event resulting in death	1 (0.8)
Hepatic adverse event leading to treatment discontinuation	7 (5.8)

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

One patient in the Phase 3 study died of hepatic failure during the first cycle of melphalan/PHP treatment. Following treatment, this patient experienced fluid overload, myelosuppression, and hepatorenal syndrome. An autopsy revealed that this patient's death was related to underlying disease burden since his liver tissue was >90% tumor. The protocols were amended following this patient's death to require a biopsy of the non-involved parenchyma to show that it is histologically normal in patients with 50% or greater tumor burden by medical imaging.

Seven patients (5.8%) discontinued study treatment because of a hepatic event, including increased blood bilirubin, AST increased, ALT increased, and hepatic failure.

Risk mitigation requirements for hepatic events are provided in Section 10.2.4.

Table 44: Hepatic Adverse Events: Peri- and Post-Procedure Periods (Safety Population)

	All grades	Grade 3/4		
Event, n (%)	Overall (N=121)	Overall (N=121)	Peri-Procedure (N=121)	Post-Procedure (N=121)
Any Hepatic AE	53 (43.8)	52 (43.5)	37 (30.6)	30 (24.8)
AST increased	40 (33.1)	40 (33.1)	30 (24.8)	16 (13.2)
Blood bilirubin increased	26 (21.5)	26 (21.5)	17 (14.0)	18 (14.9)
ALT increased	25 (20.7)	25 (20.7)	12 (9.9)	14 (11.6)
Ascites	2 (1.7)	1 (0.8)	0	1 (0.8)
Blood bilirubin unconjugated increased	1 (0.8)	0	0	0
Hepatic failure	1 (0.8)	1 (0.8)	0	1 (0.8)
Hepatic pain	1 (0.8)	1 (0.8)	1 (0.8)	0

Note: In the melphalan/PHP clinical development program, grade 1 and grade 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalization discharge, were not required to be reported.

9.10.5. Bone Marrow Suppression

Bone marrow suppression is the most significant toxicity associated with melphalan/PHP treatment as it occurred in most patients and resulted in two deaths from complicated neutropenia.

9.10.5.1. Neutropenia

Post-procedural neutropenia occurred in 105 patients (87%) with 71 patients (58.7%) with a serious event of neutropenia. A median neutrophil nadir of 0.1 x 10^9 cells/L occurred on day 11 of the treatment cycle. Median neutrophil recovery was seen in 8 days.

Complicated neutropenia (ie, febrile neutropenia or neutropenic infection) occurred in 25 patients (20.7%) and was the underlying cause of two of the deaths in the clinical development program. A 54-year old female patient in the Phase 3 study died of streptococcal sepsis. This patient experienced myelosuppression at cycle 1, but her melphalan dose was not reduced to 2.5 mg/kg IBW for cycle 2. The patient was readmitted to the hospital on Day 11 of cycle 2 with hypoxia, pancytopenia, and sepsis and started on a multi-antibiotic regimen. The patient died of sepsis on Day 13.

In addition, a 66-year old male patient in the Phase 3 study died of neutropenic complications in cycle 2. This patient experienced myelosuppression in cycle 1 and had his melphalan dose reduced to 2.5 mg/kg IBW for cycle 2. The patient was hospitalized from day 13 to day 23 of cycle 2 with pneumonia and neutropenia and was readmitted on day 33 of cycle 2 with grade 4 pancytopenia, a necrotic herpes simplex infection of the mouth, and pulmonary edema. The patient died on Day 40 of cycle 2.

Eighteen patients (15%) were rehospitalized for treatment of neutropenia (Table 33). Nine patients (7.4%) discontinued study treatment because of neutropenia.

Prophylactic administration of colony-stimulating factors was not mandated during the clinical development program and only a small percentage of patients received prophylactic growth factors during either the first (5%) or subsequent treatment cycles (12%). Approximately 60% of patients received growth factors for treatment of neutropenia.

Overall, 33.1% of patients were prescribed antibiotics for the treatment of infections. Antibiotic use was similar across the treatment cycles.

9.10.5.2. Thrombocytopenia

Post-procedural thrombocytopenia occurred in 97 patients (80.2%) (Table 27). The median nadir platelet count associated with post-procedural thrombocytopenia was 10 x 10^9 cells/L (range, 0 to 332 x 10^9 cells/L), which was reached in a median time of 12 days from cycle baseline. Treatments for post-procedural thrombocytopenia included platelet transfusions with platelet recovery in a median time of 16 days.

Twenty-seven patients (22.3%) were rehospitalized for thrombocytopenia, primarily for platelet transfusions (Table 33). Ten patients (8.3%) were discontinued from study treatment because of post-procedure thrombocytopenia. Most of the discontinuations for thrombocytopenia occurred after either cycle 2 or cycle 3 of treatment.

Thrombocytopenia resulted in 4 cases (3.3%) of bleeding events in the post-procedure period, including intracranial hemorrhage, retinal hemorrhage, vaginal hemorrhage, and GI hemorrhage (see Section 9.10.3)

9.10.5.3. Anemia

Post-procedural anemia occurred in 71 patients (58.7%). Median nadir hemoglobin levels associated with post-procedural anemia were 77 g/L (range, 0.08 to 126 g/L) which were reached in a median time of 9 days from cycle baseline.

Approximately 56% of patients received a packed red blood cell transfusion and 18% received erythropoietin with a median time to recovery of hemoglobin levels in 5 days.

Nine patients (7.4%) were rehospitalized for anemia treatment (Table 33).

Four patients (3.3%) were discontinued from study treatment because of post-procedure anemia.

9.11. Compassionate Use and EAP Safety

As of March 2013, 13 patients have been treated in Compassionate Use and 2 patients have been treated in the Expanded Access Program.

9.12. Post-Marketing Safety

As of March 2013, a total of 32 patients have been treated in the EU with melphalan/PHP treatment. One death has been reported. The patient, a 71-year-old female, with a history of ocular melanoma, cardiac disease, diabetes, and hypertension, died of a spontaneous retroperitoneal hemorrhage. At completion of the PHP procedure, protamine sulfate, calculated for the heparin dose given was administered; fresh frozen plasma (16 bags), factor VII (2 vials), factor VIII (2 vials) and factor IX (2 vials) were also administered. The patient's blood pressure did not normalize at the conclusion of the procedure and retroperitoneal bleeding was suspected. A laparotomy was performed, but no active bleeding site was found other than a large retroperitoneal hematoma. Postoperatively, the patient had a PT of 29.3 seconds, an aPTT of 71.6 seconds, an international normalized ratio of 2.54, and platelet count of 65,000 x 10^9/L. The patient was transferred to the ICU and died within 24 hours of procedure completion. An autopsy was performed and the cause of death was noted as multiple hemorrhagic syndrome with multiple micro-hemorrhages noted in the retroperitoneum. Spontaneous retroperitoneal hemorrhage is a known complication of heparin anticoagulation.

9.13. Safety Conclusions

Almost all patients in the PHP group had at least one adverse event. Most (80%) of these adverse events were serious adverse events which included hospitalizations.

There were 5 deaths during the clinical development program that resulted from adverse events, including GI hemorrhage, hepatic failure, gastric perforation, streptococcal sepsis, and neutropenia.

Approximately 40% of patients had one or more adverse events leading to treatment discontinuation.

Melphalan-related bone marrow suppression, including neutropenia (87%), complicated neutropenia (21%), thrombocytopenia (80%), and anemia (59%) occurred. There were two deaths from complicated neutropenia (streptococcal sepsis and neutropenia) in the clinical development program. Thrombocytopenia (22%), febrile neutropenia (15%), and neutropenia (15%) were the most frequent events resulting in rehospitalization. Thrombocytopenia (15.7%) and neutropenia (7.4%) were the most frequent adverse events leading to treatment withdrawal. Most treatment withdrawals due to thrombocytopenia and neutropenia occurred after either the second or third melphalan/PHP treatment.

There is a risk of cardiovascular events with melphalan/PHP treatment because of intra-procedural hypotension. Cardiovascular events occurred in 24% of patients with 17% of patients with a Grade 3/4 cardiovascular event. Cardiovascular events seen during clinical development included arrhythmias, cerebral ischemia/infarct, cardiac ischemia/infarct, thromboembolism, and cerebral hemorrhages; each of these events was reported in a small number of patients. No patients died from a cardiovascular event. Ten patients (8%) were withdrawn from treatment because of a cardiovascular event.

There is a risk of GI events because of misperfusion of melphalan into GI vessels either because vessels were not embolized or there was reflux of melphalan into GI branches. GI events, including gastritis, ulceration, perforation, bleeding, and gall bladder-related events occurred in 25% of patients with 11% of patients with a grade 3/4 GI event. There were two deaths from GI events (ruptured right hepatic artery and gastric perforation) in the clinical development program. Six patients (5%) were withdrawn from treatment because of a GI event.

There is a risk of bleeding events because of the anticoagulation required for performance of the procedure, hemofiltration-related thrombocytopenia, and melphalan-related thrombocytopenia. Bleeding events occurred in 13% of patients with 7% of patients with a grade 3/4 bleeding event. One patient with brain metastases died from an intracranial hemorrhage. Four patients discontinued study treatment because of a bleeding event.

There is a risk of hepatic events as a consequence of underlying disease, liver-directed therapy, and melphalan treatment. Hepatic events occurred in 44% of patients with all of these patients having grade 3/4 events. Hepatic events were predominantly laboratory changes in liver function tests that were reported as adverse events, including elevated hepatic transaminases and hyperbilirubinemia. One patient died of hepatic failure related to underlying disease burden since his liver tissue was >90% tumor. Seven patients (5.8%) discontinued study treatment because of a hepatic event, including increased blood bilirubin, AST increased, alanine aminotransferase ALT increased, and hepatic failure.

10. RISK MANAGEMENT, TRAINING PROGRAM, AND REMS

10.1. Overview

Performance of the PHP procedure requires a skilled procedural team that includes an interventional radiologist, anesthesiologist, perfusionist, medical or surgical oncologist, pharmacist, interventional radiology staff, and a healthcare provider certified for chemotherapy delivery. It is critical to have in-depth knowledge of the drug delivery system, the risks associated with the procedure and melphalan, and the coordination among the procedural team

members during the preparation for and conduct of the procedure. In order to use the melphalan/PHP System, the Procedural Team must successfully complete a melphalan/PHP System Training Program, modeled after the training program used during clinical development and including additional lessons learned from the development program and EU marketing experience. This Training Module is part of the proposed REMS, with elements to assure safe use, to ensure the benefits of melphalan/PHP treatment outweigh the aforementioned risks and procedural complications. In addition, both the hospital and specific members of the procedural team must be certified with the melphalan/PHP System REMS. The purpose of the melphalan/PHP System Training Program, as an important component of the melphalan/PHP System REMS, is to:

- Communicate the indications for use and patient selection criteria for the melphalan/PHP System
- Provide extensive and detailed procedural training so that each team member understands the PHP procedure and their role in each step, including:
  - Pre-procedural preparation
  - Procedural details
  - Post-procedural care
  - Expected complications and their management
- Communicate the requirements to receive and to ensure safe use of the melphalan/PHP System via hospital qualification, hospital certification, and healthcare provider training and certification requirements required for use of the melphalan/PHP System

An overview of the steps and training required for the use of the melphalan/PHP System are provided in Table 45 and discussed below.

Table 45: Overview of Requirements for Use of the Melphalan/PHP System

Hospital Requirements	**Healthcare Provider Requirements**
• Qualified using the Hospital Qualification Criteria	• Completion of didactic training
• Hospital certification with the melphalan/PHP System REMS	• Viewing of a video of a live case
	• Completion of Knowledge Assessment
	• Completion of experiential training
	• Healthcare provider certification with the melphalan/PHP System REMS
Hospital authorized to receive the melphalan/PHP System	

10.2. Risk Mitigation Requirements

The Training Module contains step-by-step information similar to a protocol and the Instructions for Use for a device on important risk mitigation requirements (ie, patient selection, preparation of the patient for the PHP procedure, set up of device, monitoring, treatment) that must be

followed to ensure safe use. Section 10.2.1 to Section 10.2.7 identifies the patient management criteria for each of the identified critical risks.

10.2.1. Cardiovascular Events

Because hypotension will occur during the procedure, vigilant patient selection and patient management are necessary to prevent ischemic injury to the heart and brain. Mandatory proactive risk management measures to avoid cardiovascular complications resulting from intra-procedural hypotension include the following:

- Patient selection, including:
  - New York Heart Association (NYHA) classification 1. Patients with NYHA classification 2, 3, or 4 should not undergo melphalan/PHP treatment
  - Normal baseline ECGs and echocardiograms
  - Normal troponin levels
- Pre-procedural monitoring and management, including:
  - Adequate fluid pre-load before balloon inflation
  - Monitoring of blood pressure continuously during the procedure and performance of a vasopressor response test before balloon inflation
  - Administration of vasopressors to maintain a mean arterial pressure >65 mmHg at balloon inflation and when the filters come on line
- Post-procedural monitoring and management, including:
  - Echocardiograms, prior to each treatment cycle and 30 days after the end of treatment
  - 12-lead ECG, prior to hydration, the morning of the PHP procedure, within 2 hours following completion of the PHP procedure, and then daily until hospitalization discharge
  - Troponin immediately following the procedure, every 6 hours for 24 hours following completion of the procedure, and then daily until hospitalization discharge

  Any echocardiogram or ECG abnormalities or troponin elevations will be followed until resolution and clinical judgment used to determine whether or not the patient receives additional cycles of treatment.

10.2.2. GI Events

Mandatory proactive risk management measures to avoid GI complications following melphalan/PHP treatment include the following:

- Patient selection, including:
  - Endoscopy to check for esophageal varices at risk of bleeding (eg, large esophageal or gastric varices, varices with red sign) or active peptic ulcer with or

without exposed vessels at risk of bleeding in patients with a history of peptic ulcer disease

  - A pre-operative visceral angiogram to search for variant hepatic arterial and GI branches that could lead to inadvertent melphalan infusion into these branches

- Pre-procedural monitoring and management, including:
  - Embolization of the gastroduodenal artery and certain branches supplying the pancreas, stomach, or duodenum to avoid melphalan reflux into these branches and GI toxicity
  - Administration of proton pump inhibitors and antibiotics (if the patient has had previous hepatobiliary surgery) the day before the procedure to prevent gastritis and infection, respectively
- Procedural monitoring and management, including:
  - Assessment of arterial patency several times during the PHP procedure to ensure that there is no vasospasm of the hepatic artery that could result in melphalan reflux into proximal GI branches. Administration of nitroglycerin to relieve hepatic arterial spasm. Termination of the procedure if spasm cannot be relieved with nitroglycerin

10.2.3. Bleeding

Mandatory proactive risk management measures to avoid bleeding complications following melphalan/PHP treatment include the following:

- Patient selection, including:
  - Brain MRI at baseline and before every cycle to rule out any tumors or intracranial abnormalities with a propensity to bleed
  - Contraindication for melphalan/PHP treatment in patients with active intracranial metastases or brain lesions with a propensity to bleed
  - Appropriate hormonal suppression to prevent menstruation in premenopausal women (ie, have had a period within the last 12 months)
  - PHP procedure should not be performed in patients with a platelet count <75,000 cells/μL. Correction of prothrombin time and platelet count to clinically acceptable safe limits before treatment
- Post-procedure monitoring and management, including:
  - Protamine, fresh frozen plasma and/or cryoprecipitate administration immediately following the PHP procedure to reverse the anticoagulation required for the procedure
  - Platelet transfusions immediately following the PHP procedure to restore platelets that are sequestered by the hemofiltration cartridges

10.2.4. Hepatic Events

Mandatory proactive risk management measures to prevent hepatic complications following melphalan/PHP treatment include the following patient selection criteria:

- A biopsy of the non-involved parenchyma to show that it is histologically normal in patients with 50% or greater tumor burden by medical imaging
- Contraindication for melphalan/PHP treatment in patients with hepatic failure or portal hypertension (any worse than Childs A)

10.2.5. Neutropenia

Neutropenia must be frequently monitored for and aggressively treated following patient discharge from the hospital to prevent serious complications and deaths. Mandatory proactive risk management measures for neutropenia include the following:

- Prophylactic administration of colony-stimulating factors at each treatment cycle
- Prophylactic administration of antibiotics where required by American Society of Clinical Oncology (ASCO) guidelines
- A melphalan dose reduction to 2.5 mg/kg IBW and cycle delays (for up to an additional 4 weeks) until recovery from toxicities, where necessary, for the next melphalan/PHP treatment

10.2.6. Thrombocytopenia

Thrombocytopenia must be frequently monitored for and aggressively treated following patient discharge from the hospital to prevent serious complications and deaths. Mandatory proactive risk management measures for thrombocytopenia include the following:

- Platelet transfusions in accordance with ASCO guidelines
- A melphalan dose reduction to 2.5 mg/kg IBW and cycle delays (for up to an additional 4 weeks) until recovery from toxicities, where necessary, for the next melphalan/PHP treatment

10.2.7. Anemia

Anemia must be frequently monitored following patient discharge from the hospital. Mandatory proactive risk management measures for anemia include the following:

- Red blood cell transfusions and erythropoietin administration in accordance with ASCO guidelines
- A melphalan dose reduction to 2.5 mg/kg IBW and cycle delays (for up to an additional 4 weeks) until recovery from toxicities, where necessary, for the next melphalan/PHP treatment

10.3. Risk Evaluation and Mitigation Strategy

A REMS for the melphalan/PHP System has been issued by FDA to communicate important safety messages and safe use conditions for melphalan/PHP treatment to healthcare providers by the following:

- Informing healthcare providers of the risks of hepatic failure, gastric ulceration, coagulation/bleeding diatheses, and procedural complications associated with the melphalan/PHP system drug/device combination product
- Ensuring dispensing of the melphalan/PHP system only to specially certified hospitals
- Ensuring only appropriately trained and certified team members (interventional radiologist, anesthesiologist, perfusionist, and medical or surgical oncologist) participate in procedural aspects and administration of melphalan/PHP treatment

The REMS for melphalan/PHP treatment will reinforce the patient selection criteria and the measures that are necessary to prevent serious complications and deaths. The REMS will do this through the following:

- Restricting performance of the PHP procedure to hospitals that meet the REMS requirements
- Restricting the healthcare providers allowed to participate in the PHP procedure (ie, a defined PHP treatment team) at each hospital
- Requiring mandatory training and certification of the PHP treatment team at these hospitals
- Restricting distribution of the melphalan/PHP System to certified hospitals with certified PHP treatment teams

10.3.1. Hospital Certification for PHP Procedure

Performance of the PHP procedure will be restricted to a limited number of hospitals that have the required personnel and equipment to perform the procedure and have been certified with the REMS.

Under the REMS, the hospital will be recertified every 2 years. Certification and recertification will involve the attestation of a person of appropriate authority that the training materials were received and distributed and that only those individuals defined as the PHP treatment team will participate in the PHP procedure (see Section 10.3.2 and Section 10.3.3).

10.3.2. Assignment of the PHP Treatment Team

All hospitals that perform the PHP procedure will be required to define a treatment team for the PHP procedure and to ensure that only these individuals participate in the performance of the PHP procedure. PHP treatment team members must include an interventional radiologist (team leader during the PHP procedure), surgical or medical oncologist, anesthesiologist, perfusionist, certified healthcare provider for chemotherapy delivery, interventional radiology staff, and a pharmacist.

Under the REMS, the interventional radiologist, perfusionist, anesthesiologist, and surgical or medical oncologist will be certified and recertified every 2 years. Certification and recertification will involve each of these individuals attesting that have completed all components of the mandatory training program (see Section 10.3.3), understand the risks associated with melphalan/PHP treatment, and understand that communication and coordination with other healthcare professionals involved in patient therapy is necessary for safe use.

10.3.3. Mandatory Training of the PHP Treatment Team

In order to ensure that the PHP treatment team at each hospital understands the requirements for prevention of serious complications and deaths from melphalan/PHP treatment, each hospital's procedural treatment team will be required to undergo mandatory training on the following:

- Patient selection criteria
- Procedures and preventive measures that must be performed before, during, and following melphalan/PHP treatment
- Required melphalan dose reductions and cycle delays for subsequent treatments
- Coordination of responsibilities for optimal patient care among various specialists (ie, anesthesia, interventional radiology, surgical and medical oncology)
- Careful monitoring of outpatients

Mandatory training will be a multi-step process that consists of the following:

- Didactic (ie, classroom) training to review the patient selection criteria, set-up of the PHP System, the risks associated with melphalan/PHP treatment, and the critical tasks and monitoring that must be performed before, during, and following the PHP procedure to proactively minimize these risks. A training manual that summarizes all the information reviewed in the didactic training will be provided to all members of the treatment team
- Viewing of a video of a patient undergoing the PHP procedure. The video will demonstrate the role of each team member during a PHP procedure and will be viewed after completion of didactic training
- Knowledge assessment about the use and potential risks of melphalan/PHP treatment and each procedural treatment team member's role and responsibilities during the PHP procedure. The knowledge assessment must be completed after didactic training and viewing the video
- Experiential (ie, proctored) training in the performance of the PHP procedure. This training will consist of the performance of the initial cases (at least two cases at a minimum) of the PHP procedure by the procedural treatment team under the supervision of an individual with experience in performing the procedure

10.3.4. Restricted Distribution

Distribution of the melphalan/PHP system will be restricted to the following:

- Hospitals where all components of the mandatory training program have been successfully completed
- Hospitals where both the hospital and procedural treatment team members are certified

11. BENEFIT AND RISK SUMMARY

In the randomized, controlled Phase 3 study, melphalan/PHP treatment resulted in a clinically meaningful and highly statistically significant improvement in hPFS. The safety profile of melphalan/PHP treatment is well characterized and thus, toxicities can be addressed by a combination of patient selection criteria, patient monitoring and appropriate intervention, and dose modification and timing of the next treatment cycle. There are no approved therapies or a standard of care for patients with metastatic, ocular melanoma in the liver that is unresectable. Thus, there is a clear unmet medical need and melphalan/PHP treatment provides a new treatment option for these patients. Key benefits and risks of melphalan/PHP treatment are summarized below.

11.1. Benefits

The efficacy of melphalan/PHP treatment was demonstrated in the pivotal Phase 3 study DSI MEL 2005-001 in patients with ocular melanoma. These data are supported by the anti-tumor effects of melphanal/PHP treatment seen in the Phase 1 (Study 01-C-0215) and Phase 2 (04-C-0273) studies.

Pivotal Study:

- Melphalan/PHP treatment resulted in a statistically significant and clinically meaningful increase in hPFS compared to BAC. The 5-month median improvement in hPFS is noteworthy given the short median hPFS time in the BAC arm (7.03 months with melphalan/PHP treatment versus 1.64 months with BAC)
- The robustness of the hPFS benefit is evidenced by consistent results across the sensitivity and subgroup analyses
- Melphalan/PHP treatment also resulted in statistically significant and clinically meaningful improvements in the hOR rate compared to BAC
- A treatment benefit for melphalan/PHP over BAC was not seen for OS most likely because of the high number of BAC patients who experienced hepatic progression and crossed over to PHP treatment.

Phase 1 and Phase 2 Supportive Studies:

The ocular melanoma subpopulation in the uncontrolled Phase 1 and Phase 2 studies, 01-C-0215 and 04-C-0273, respectively, which showed similar times to hepatic progression or death and hOR rates as the Phase 3 study.

11.2. Risks

The safety database for melphalan/PHP treatment is based on three clinical trials that included 154 patients who received at least one dose of melphalan, ranging from 2.0 mg/kg to 3.5 mg/kg. Of these 154 patients, 121 patients received the recommended melphalan dose of 3.0 mg/kg. The PHP procedure is associated with both procedure-related and melphalan-related risks, including cardiovascular events, GI events, bleeding, hepatic events, and bone marrow suppression.

A Training Program will be implemented for the melphalan/PHP System, as part of the proposed REMS, to ensure the benefits of melphalan/PHP treatment outweigh both the procedure-related and melphalan-related risks. In addition, both the hospital and specific members of the procedural team must be certified with the melphalan/PHP System REMS and distribution of the melphalan/PHP System will be restricted to certified hospitals with certified procedural treatment teams.

11.3. Benefit-Risk Conclusions

There is no standard of care and no approved therapy for patients with unresectable, hepatic metastases from ocular melanoma. Thus, there is an unmet medical need for these patients. Treatment of this patient population with melphalan/PHP has been demonstrated to alter the disease course, as evidenced by the consistent, statistically significant, and clinically meaningful benefits seen with melphalan/PHP treatment across the tumor-related efficacy endpoints in the pivotal Phase 3 study. The toxicities associated with melphalan/PHP treatment need to be viewed within the context of the aggressive natural history of disease in these patients and the ability of melphalan/PHP treatment to alter the disease course. The REMS is designed to maintain a positive risk-benefit for melphalan/PHP treatment.

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APPENDIX A. CLINICAL PHARMACOLOGY

Blood samples for analysis of melphalan pharmacokinetics (PK) were collected in the Phase 1, Phase 2, and Phase 3 studies during the first cycle of treatment from three sampling locations: the peripheral arterial line (systemic) and pre-filter and post-filter in the extracorporeal circuit. Pre-filter samples assess melphalan levels leaving the liver while post-filter samples evaluate melphalan not captured by the filters. Samples were collected immediately prior to and for 1 hour following the start of the melphalan infusion.

Melphalan concentration was determined by high pressure liquid chromatography with ultraviolet detection.

The maximum concentration (C_{max}) was an observed value and area under the curve from time zero to the time of last measured concentration (AUC_{last}) was calculated using the linear trapezoidal method.

Filter efficiency was used to determine the degree of melphalan removal from the hepatic venous circulation. Filter efficiency was estimated by using the AUC_{last} data from the two extracorporeal sampling locations as follows:

$$\% \text{ Filter Efficiency} = \frac{(\text{Pre-filter } AUC_{last}) - (\text{Post-filter } AUC_{last})}{(\text{Pre-filter } AUC_{last})}$$

Pharmacokinetics

PK results for the 3.0 mg/kg dose level were similar across the three studies (Table 46). Pre-filter C_{max} was approximately 4-fold higher than post-filter $C_{max.}$ Systemic C_{max} was approximately 40% lower than post-filter Cmax, presumably due to melphalan dilution throughout the systemic circulation (Table 46).

Table 46: Melphalan C_{max} and AUC_{last} by Sampling Site at a Melphalan Dose of 3.0 mg/kg (PK Population)

	Mean C_{max} (µg/mL) (SD)			Mean AUC_{last} (µg*min/mL) (SD)		
Study	Pre-filter	Post-filter	Systemic	Pre-filter	Post-filter	Systemic
Phase 1 (n=3)	11.8 (6.14)	1.89 (0.481)	1.11 (0.287)	295 (104)	53.8 (19.9)	36.2 (11.4)
Phase 2 (n=20)	11.3 (4.11)	2.42 (0.843)	1.70 (0.767)	293 (106)*	68.7 (20.3)*	53.3 (26.1)*
Phase 3 (n=40)	8.73 (2.97)	2.33 (0.87)	1.43 (0.467)**	265 (86.1)	74.1 (30.0)	50.8 (16.3)**

*n=18;**n=37

Filter Efficiency

Filter efficiency was calculated individually for all patients with PK data to determine the degree of melphalan removal from the hepatic venous circulation.

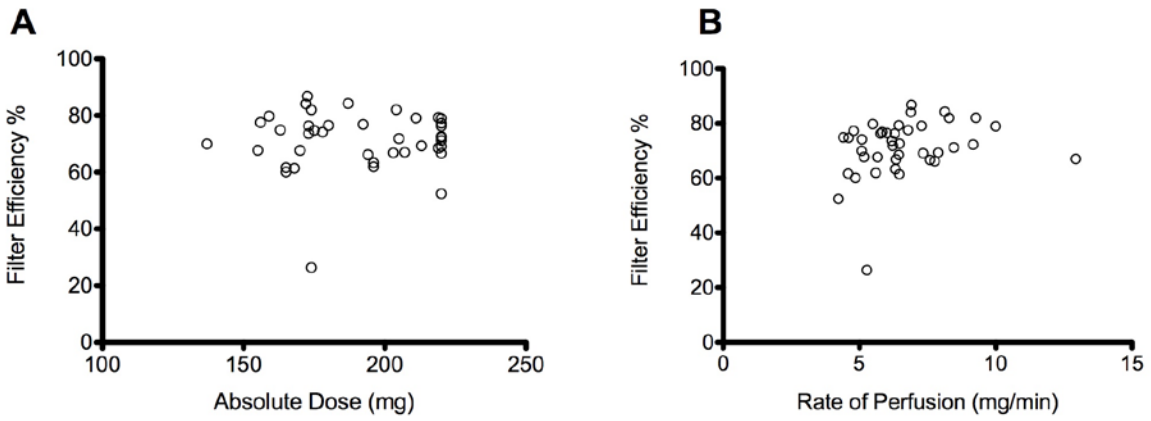
Mean filter efficiency at a melphalan dose of 3.0 mg/kg was consistent across the Phase 1, Phase 2, and Phase 3 studies, ranging between 71-78% (Table 47).

Table 47: Filter Efficiency at a Melphalan Dose of 3.0 mg/kg (PK Population)

	Phase 1	Phase 2	Phase 3
Mean	78.1	73.3	71.2
Range	58.1-93.9	31.8-86.2	26.4-86.8

As shown in the Phase 3 study, filter efficiency was not impacted by the absolute dose of melphalan administered or the rate of melphalan perfusion (Figure 12).

Figure 12: Individual Filter Extraction Efficiency (%) by Absolute Dose and Rate of Perfusion in Phase 3 Study (PK Population)



APPENDIX B. ELIGIBILITY CRITERIA IN PHASE 1, PHASE 2, AND PHASE 3 STUDIES

	DSI MEl 2005-001 Phase 3	Study 04-C-0273 Phase 2	Study 01-C-0215 Phase 1
Tumor type	Included patients with unresectable hepatic metastases from ocular or cutaneous melanoma, predominantly in the parenchyma of the liver Required histologically-normal liver parenchyma on biopsy for patients with 50% or greater tumor burden by medical imaging Limited unresectable extrahepatic disease on pre-operative radiological studies was acceptable if the life-limiting component of progressive disease was in the liver. Limited extrahepatic disease included up to 4 pulmonary nodules each <1 cm in diameter; retroperitoneal lymph nodes <3 cm in diameter; skin or subcutaneous metastases fewer than 10 in number and <1 cm in diameter; asymptomatic bone metastases that were or could be palliated with external beam radiation therapy; or a solitary metastasis to any site that was resectable. Excluded patients with resectable tumor(s) of the liver	Included patients with unresectable primary hepatic malignancies (ie, hepatocellular cancer or intrahepatic cholangiocarcinoma) and unresectable metastatic hepatic malignancies from either GI adenocarcinoma, neuroendocrine tumor (with the exception of gastrinoma), or ocular or cutaneous melanoma, predominantly in the parenchyma of the liver Required histologically-normal liver parenchyma on biopsy for patients with 50% or greater tumor burden by medical imaging Limited unresectable extrahepatic disease on pre-operative radiological studies was acceptable if the life-limiting component of progressive disease was in the liver. Limited extrahepatic disease included up to 4 pulmonary nodules each <1 cm in diameter; retroperitoneal lymph nodes <3 cm in diameter; skin or subcutaneous metastases fewer than 10 in number and <1 cm in diameter; asymptomatic bone metastases that were or could be palliated with external beam radiation therapy; or a solitary metastasis to any site that was resectable. Excluded patients with resectable tumor(s) of the liver	Included patients with unresectable primary hepatic malignancies or unresectable metastatic hepatic malignancies from a non-liver primary site, predominantly in the parenchyma of the liver Excluded patients with resectable tumor(s) of the liver

	DSI MEl 2005-001 Phase 3	Study 04-C-0273 Phase 2	Study 01-C-0215 Phase 1
Adequate hepatic function	Required a total serum bilirubin of < 3.0 mg/dL, AST/ ALT ≤10 times ULN Excluded patients with Childs B or C cirrhosis or evidence of portal hypertension by history, endoscopy, or radiologic studies	Required total serum bilirubin < 2.0 mg/dL, AST/ALT ≤10 times ULN Excluded patients with Child B or C cirrhosis or evidence of portal hypertension by history, endoscopy, or radiologic studies	Required total serum bilirubin ≤2.0 mg/dL Excluded patients with biopsy-proven cirrhosis with evidence of portal hypertension by history, endoscopy, or radiologic studies

	DSI MEl 2005-001 Phase 3	Study 04-C-0273 Phase 2	Study 01-C-0215 Phase 1
Cardiovascular disease	Excluded patients with congestive heart failure with a left ventricular ejection fraction <40%. Significant chronic obstructive pulmonary disorder or other chronic pulmonary restrictive disease	Excluded patients with congestive heart failure with a left ventricular ejection fraction < 40%. Significant chronic obstructive pulmonary disorder or other chronic pulmonary restrictive disease	Excluded patients with congestive heart failure with a left ventricular ejection fraction < 40%. Obstructive pulmonary disease or other chronic pulmonary disease with pulmonary function tests
Bleeding	Required hormonal suppression during treatment (premenopausal women only) Excluded patients who required chronic anticoagulation Excluded patients with a history of bleeding disorders (eg, nose bleeds, bleeding ulcers) or evidence of intracranial abnormalities that put the patient at risk for bleeding with anticoagulation (eg, stroke, active metastases)	Hormonal suppression during treatment (premenopausal women only) Excluded patients who required chronic anticoagulation Excluded patients with a history of bleeding disorders (eg, nose bleeds, bleeding ulcers) or evidence of intracranial abnormalities that put the patient at risk for bleeding with anticoagulation (eg, stroke, active metastases)	Required a platelet count of >100,000 cells/μL Excluded patients who required chronic anticoagulation
Hematologic function	Required a platelet count > 75,000/μL, hemoglobin ≥ 9 g/dL (correctable with transfusion), neutrophil count ≥ 1,300 cells /μL	Required a platelet count of 75,000 cells/μL, hemoglobin > 9 g/dL (correctable with transfusion), a neutrophil count of 1,300 cells/μL	Required a platelet count >100,000 cells/μL, hematrocrit >27%, a neutrophil count >1,300 cells/μL
Renal function	Creatinine ≤ 1.5 mg/dL (unless measured creatinine clearance was >60 mL/min)	Creatinine of 1.5 mg/dL, unless the measured creatinine clearance was >60 mL/min/1.73 m^2	Creatinine <1.5 mg/dL or a creatinine clearance of >60 mL/min
Gastrointestinal	Excluded patients with a history of gastrinoma or a Whipple procedure	Excluded patients with a history of gastrinoma or a Whipple procedure	

APPENDIX C. SERIOUS ADVERSE EVENTS (≥2 PATIENTS)

Event, n (%)	Pooled (N=121)
Any SAE	101 (83.5%)
Frequent (≥ 2 patients) SAEs	
Neutrophil count decreased	71 (58.7)
Platelet count decreased	62 (51.2)
Febrile neutropenia	20 (16.5)
Hemoglobin decreased	13 (10.7)
Blood bilirubin increased	7 (5.8)
AST increased	4 (3.3)
ALT increased	3 (2.5)
Neutropenic infection	3 (2.5)
Cerebral ischemia	3 (2.5)
Gastric ulcer	3 (2.5)
Thrombosis	3 (2.5)
Vomiting	2 (1.7)
Vena cava thrombosis	2 (1.7)
White blood cell count decreased	2 (1.7)
Dehydration	2 (1.7)
Hypoxia	2 (1.7)
Pulmonary embolism	2 (1.7)
Hypotension	2 (1.7)
Cholecystitis	2 (1.7)
Constipation	2 (1.7)
Hemorrhage intracranial	2 (1.7)

APPENDIX D. DEFINITION OF ADVERSE EVENTS OF SPECIAL INTEREST

Adverse Event of Special Interest Category	Definition
Cardiovascular events	PTs within the level 1 SMQ, embolic and thrombotic events, "cardiac arrythmias and ischemic heart disease, plus the PTs pericardial effusion, pulse absent, hypotension, chest discomfort, pupillary reflex impaired, vision blurred, visual impairment, all PTs that contained either "thrombo" or "embo" (excluding thrombocytopenia and aPTT prolonged), and all PTs within the nervous system SOC except headache, migraine, and spinal cord compression
GI events	PTs belonging to the narrow terms list for Level 1 SMQ "GI nonspecific inflammation and dysfunction conditions" and "GI perforation, ulceration, hemorrhage or obstruction. Excludes abdominal distension, constipation, diarrhea, oral pain, perirectal abscess, rectal abscess, rectal hemorrhage, stomatitis
Bleeding	PTs within the level 2 SMQ, hemorrhage terms (excluding laboratory terms)
Hepatic events	PTs within the level 2 SMQ "drug related hepatic disorders - comprehensive search", excluding the level 3 SMQ "liver-related coagulation and bleeding disturbances" and two level 4 SMQs, "liver neoplasms, benign (including cysts and polyps)" and "liver neoplasms, malignant and unspecified
Complicated neutropenia	PTs of febrile neutropenia, neutropenic infection, and neutropenic sepsis

PT: preferred terms; SMQ=standardized MedDRA query; SOC: system organ class