DELCATH SYSTEMS, INC
CLINICAL STUDY PROTOCOL

Protocol: PHP-OCM-301A

EudraCT No. 2015-000417-44

Version 1.0- USA
22 June 2018

A Single-arm, Multi-Center, Open-Label Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment in Patients with Hepatic-Dominant Ocular Melanoma

Confidential Statement

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INVESTIGATOR'S AGREEMENT

I hereby agree to:

- Conduct the study as outlined in this protocol with reference to national/local regulations and current International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guidelines.
- Discuss and agree upon any modification to the protocol with Delcath Systems, Inc. or representatives hereof.
- Fully co-operate with monitoring and auditing and allow access to all documentation by authorized individuals representing Delcath Systems, Inc. or health authorities.

To be signed by Principal Investigator:

Signature	Date
Print Name	
Title	
Name of Facility	

SPONSOR APPROVAL PAGE

A Single-arm, Multi-Center, Open-Label Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment in Patients with Hepatic-Dominant Ocular Melanoma

APPROVED BY:

Medical:

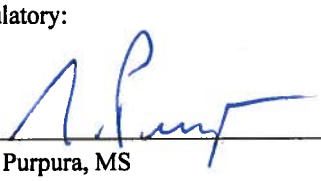


JUN 22, 2018

Johnny John, MD
VP, Medical Affairs

Date

Regulatory:



6/22/18

John Purpura, MS
Executive VP, Global Head Operations

Date

Clinical Operations/Project Management:



JUN 22, 2018

Nathalie Riebel, PMP, MBA
Associate Vice President, Head Clinical Operations

Date

PROCEDURES IN CASE OF EMERGENCY

Role in Study	Name	Address and Telephone Number
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SYNOPSIS

Name of Sponsor/Company:
Delcath Systems, Inc.

Name of Investigational Product: Melphalan Hydrochloride for Injection for use with the Hepatic Delivery System (Melphalan/HDS)

Name of Active Ingredient: Melphalan hydrochloride

Title of Study: A Single-arm, Multi-Center, Open-Label Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment in Patients with Hepatic-Dominant Ocular Melanoma

Objectives:

Primary Objective:

- Objective Response Rate (ORR) (complete response + partial response) as determined by Independent Central Review Committee (IRC).

Secondary Objectives:

- Duration of Response (DOR) as determined by Independent Central Review Committee.
- Disease Control Rate (DCR) as determined by Independent Central Review Committee.
- Overall Survival (OS).
- Progression Free Survival (PFS) as determined by Independent Central Review Committee.

Exploratory Objectives:

- Time to Objective Response (TOR) as determined by Independent Central Review Committee.
- ORR, DOR, DCR, PFS and TOR as determined from the Investigator-assessed objective response.
- Hepatic progression-free survival (hPFS) as determined by Independent Central Review Committee.
- Hepatic objective response rate (hORR) as determined by Independent Central Review Committee.
- To document the quality of life (QOL).
- To evaluate the safety of treatment with Melphalan/HDS in patients with hepatic-dominant metastatic ocular melanoma.
- To explore relationships between melphalan exposure and common or serious adverse reactions and clinical outcomes.
- To characterize the local and systemic exposure of melphalan administered by the HDS.

Methodology:

The study will consist of 3 phases:

Screening/Baseline Phase: Screening assessments will be conducted within 28 days prior to the eligibility date to determine each patient's overall eligibility and baseline characteristics. These assessments will include medical history, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status (PS), 12-lead electrocardiogram (ECG), echocardiogram (ECHO), vital signs, full hematology and biochemistry, Quality of Life questionnaire, radiologic assessments of baseline disease status and concomitant medications.

For patients with a history of liver surgery or major vasculature surgery, an angiogram evaluation of their vasculature will be performed for compatibility for Percutaneous Hepatic Perfusion (PHP) prior to confirming eligibility.

Eligibility date: This is the date on which all screening assessments have been completed and the patient is determined to be eligible for the trial.

Re-screening: If not all screening assessments are able to be completed within the 28 days prior to the eligibility date due to scheduling difficulties at the site (e.g. unable to schedule CT scan within time-frame), re-screening is permitted for those assessments that occur outside the 28 day window. Prior to re-screening the site should notify the Sponsor and/or the Sponsor's designee to identify which re-screening assessments needs to be completed e.g. laboratory.

Re-screening will also be permitted for those patients that were consented on the PHP-OCM-301 study but were not randomized to a treatment arm.

Treatment Phase: The treatment phase of the study will be conducted as described in Section 6.1. The first study treatment should occur within 14 days of the eligibility date. Eligible patients will be treated with Melphalan/HDS 3.0 mg/kg Ideal Body Weight (IBW). Melphalan/HDS treatment will be administered every 6 weeks for a total of 6 cycles with an acceptable delay of another 2 weeks before the next planned treatment to allow for recovery of melphalan-related toxicity, if needed. Tumor response will be assessed every 12 weeks ($\pm$ 2 weeks) until disease progression. The assessment scans will be reviewed by an Independent Central Review Committee (IRC), but patient management will be according to the principal investigator (PI) assessment of images and clinical needs. Patients with progressive disease (PD) will be discontinued from study treatment, and will continue to be followed until death. Melphalan/HDS treatment will also be discontinued if recovery from treatment-related toxicity requires more than 8 weeks from the last treatment. An end-of-treatment visit (EOT) will be conducted approximately 6 to 8 weeks following the final study treatment. Ongoing treatment related adverse events (TEAEs) at the end-of-treatment visit (EOT) will be followed until the severity is within one of the three following parameters:

1- Symptoms are resolved or return to baseline,
2- CTCAE Grade $\leq$ 1 or can be explained,
3- Patient death.

The maximum possible duration of the study treatment phase for any patient will be 12 months.

NOTE: Active Melphalan/HDS patients (currently in treatment) on PHP-OCM-301 will continue treatment on PHP-OCM-301A following the re-consenting process.

Follow-up Phase: Once the patient has completed the end-of-treatment (EOT) visit in accordance with the schedule of events they will enter the follow-up phase. If the disease has not progressed at the EOT (Section 6.2), the patient will need to continue with disease assessment visits every 12 weeks (+ 2 weeks) until disease progression is documented. If the disease has progressed before or at the EOT their follow-up is to be by phone every 3 months for survival status until death.

NOTE: Patients on PHP-OCM-301 that have completed treatment and are entering or are already in the follow-up phase will be followed-up for survival and disease progression (as applicable) on PHP-OCM-301A following the re-consenting process.

For the purpose of study report preparation, an interim database lock for analysis is planned approximately 24 months after the last patient's last treatment. Long-term follow-up will continue in

patients who survived longer than 24 months after the last patient last treatment. Data from the long-term follow-up will eventually be integrated with the interim locked database and will be summarised separately to be reported in a study report addendum.

Number of Patients (planned): Approximately 50 patients will be treated.

Criteria for Inclusion:

Patients must meet all of the following criteria for study entry:

1. Male or female patients ≥ 18 years of age.
2. Patients must weigh ≥ 35 kg (due to possible size limitations with respect to percutaneous catheterization of the femoral artery and vein using the Delcath Hepatic Delivery System).
3. 50% or less histologically or cytologically-proven ocular melanoma metastases in the parenchyma of the liver.
4. Disease in the liver must be measurable by computed tomography (CT) and/or magnetic resonance imaging (MRI).
5. Evidence of limited extrahepatic disease on preoperative radiological studies is acceptable if the life-threatening component of disease is in the liver. Limited extrahepatic disease is defined in this protocol as follows: metastasis in bone, subcutaneous, lung or lymph nodes that is amenable to resection or radiation and has a defined treatment plan. Patients with extra-hepatic tumor burden which does not have a defined treatment plan (i.e. monitor or is unable to be resected or radiated) must not be included in the trial.
6. Scans used to determine eligibility (CT scan of the chest/abdomen/pelvis and MRI of the liver) must be performed within 28 days prior to eligibility. An MRI of the liver is required at screening to validate that CT accurately reflects the extent of disease in the liver. For patients with MRI intolerance, a 3-phase liver CT is to be done in place of liver MRI.
7. Patients must not have had chemotherapy, radiotherapy, chemoembolization, radioembolization, or immunoembolization for their malignancy within 30 days prior to treatment and must have recovered from all side effects of therapeutic and diagnostic interventions except those listed in Appendix B of the study protocol.
8. Patients receiving anti programmed cell death protein 1 (PD-1) immunotherapy such as pembrolizumab or nivolumab, or human cytotoxic T-lymphocyte antigen 4 blocking antibody such as ipilimumab must have completed treatment 8 weeks prior to study eligibility.
9. Patients must have an ECOG PS of 0-1 at screening.
10. Patients must have adequate hepatic function as evidenced by total serum bilirubin ≤1.5 x the upper limit of normal (ULN) and a prothrombin time (PT) within 2 seconds of the upper normal limit. Aspartate aminotransferase/alanine aminotransferase (AST/ALT) must be ≤ 2.5 x ULN.
11. Patients must have a platelet count > 100,000/μL, hemoglobin ≥ 10.0 gm/dL, white blood cell count (WBC) > 2,000/uL, absolute neutrophil count ≥ 1.5 x 10^9/L, and a serum creatinine ≤ 1.5 mg/dL unless the measured creatinine clearance is > 40 mL/min/1.73 m^2.
12. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (β-human chorionic gonadotropin) within 7 days prior to eligibility.
13. Provided signed informed consent.

Criteria for Exclusion:

Patients who meet any of the following criteria will be excluded from study entry:

1. Patients with Child-Pugh Class B or C cirrhosis or with evidence of portal hypertension by history, endoscopy, or radiologic studies.
2. Those with New York Heart Association functional classification II, III or IV active cardiac conditions, including unstable coronary syndromes (unstable or severe angina, recent

myocardial infarction), worsening or new-onset congestive heart failure, significant arrhythmias and severe valvular disease must be evaluated for risks of undergoing general anesthesia.

3. History or evidence of clinically significant pulmonary disease that precludes the use of general anesthesia.
4. Women of childbearing potential (WOCBP) i.e. fertile meaning not permanently sterilized and having had a menstrual period within the past 12 months) unable to undergo hormonal suppression to avoid menstruation during treatment.
5. WOCBP and fertile males (not permanently sterile by bilateral orchiectomy) unwilling or unable to use highly effective contraception method from consent to at least 6 months after the last administration of study treatment (e.g. combined hormonal contraception; progestogen-only hormonal contraception; Intrauterine device, intrauterine hormone-releasing system; bilateral tubal occlusion, vasectomized partner or sexual abstinence).
6. Females that are pregnant or are breastfeeding.
7. Patients taking immunosuppressive drugs; however, oral corticosteroids ≤ 10 mg/ day are allowed.
8. Patients who are unable to be temporarily removed from chronic anti-coagulation therapy.
9. Patients with active bacterial infections with systemic manifestations (malaise, fever, leucocytosis) are not eligible until completion of appropriate therapy.
10. Patients with severe allergic reaction to iodine contrast, which cannot be controlled by premedication with antihistamines and steroids.
11. Patients with a history of or known hypersensitivity to melphalan or the components of the Melphalan/HDS system.
12. Patients with latex allergy.
13. Patients with a history of hypersensitivity to heparin or the presence of heparin-induced thrombocytopenia.
14. Patients with a history of bleeding disorders or evidence of intracranial abnormalities which would put them at risk for bleeding with anti-coagulation (e.g., strokes, active metastases).
15. Patients with a history of gastrinoma, NOTE: For patients with a history of liver surgery or major vasculature surgery, a CT angiogram or MR angiogram is required during screening to assure the patient does not have hepatic vasculature incompatible with perfusion, hepatofugal flow in the portal vein or known unresolved venous shunting.
16. Known varices at risk of bleeding, including medium or large esophageal or gastric varices, or active peptic ulcer.
17. Patients with prior Whipple's procedure.
18. Patients with brain metastases or presence of other intracranial lesions at risk for bleeding by history or baseline radiologic imaging.
19. Patients with an active infection, including Hepatitis B and Hepatitis C infection. Patients with anti-hepatitis B core antibody (HBc) positive, or hepatitis B surface antigen (HBsAg) but DNA negative are exception(s).
20. Uncontrolled endocrine disorders including diabetes mellitus, hypothyroidism, or hyperthyroidism.
21. Received any investigational agent for any indication within 30 days prior to first treatment.
22. Not recovered from side effects of prior therapy to ≤ Grade 1 (according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v. 4.03). Certain side effects that are unlikely to develop into serious or life–threatening events (e.g. alopecia) are allowed at > Grade 1.

23. Cancers other than ocular melanoma for which the patient is currently under treatment or still deemed to be not cancer free.

Investigational Product, Dosage and Mode of Administration:
Melphalan hydrochloride for injection 3.0 mg/kg ideal body weight (IBW) (maximum dose of 220 mg per treatment) infused into the hepatic artery via the Hepatic Delivery System (HDS).
Duration of Treatment: Up to 6 cycles, with a maximum interval of 8 weeks between cycles.

Criteria for Evaluation:
Efficacy Outcome Measures
Primary efficacy outcome measure:

- Objective Response Rate (ORR) (complete response + partial response) as determined by Independent Central Review Committee

Secondary efficacy outcome measures:

- Duration of Response (DOR) as determined by Independent Central Review Committee
- Disease Control Rate (DCR) determined by Independent Central Review Committee
- Overall Survival (OS)
- Progression Free Survival (PFS) as determined by Independent Central Review Committee

Exploratory outcome measures:

- Time to objective response (TOR) as determined by Independent Central Review Committee
- ORR, DOR, DCR, PFS and TOR as determined from the Investigator-assessed objective response
- Hepatic Progression Free Survival (hPFS) as determined by Independent Central Review Committee
- Hepatic Objective Response Rate (hORR) as determined by Independent Central Review Committee
- Quality of life (QOL)
- To evaluate the safety of treatment with Melphalan/HDS in patients with hepatic-dominant metastatic ocular melanoma
- To explore relationships between melphalan exposure and common or serious adverse reactions and clinical outcomes
- To characterize the local and systemic exposure of melphalan administered by the HDS

Safety Outcome Measures
Safety will be assessed by monitoring AEs and serious adverse events (SAEs); the association with any study treatment will be assessed and severity will be graded using CTCAE v.4.03. Other safety assessments will include clinical laboratory tests (including hematology and chemistry), vital signs (including temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, and mean arterial pressure (MAP), electrocardiograms (ECGs) and echocardiograms (ECHOs).
Pharmacokinetic Outcome Measures
Melphalan pharmacokinetics (total and free concentrations) will be assessed to calculate the following PK parameters using standard noncompartmental analysis and population PK methods: observed maximum concentration (C_{max}), time of maximum concentration (T_{max}), observed terminal elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve from time-zero to the time of the last measurable concentration ($AUC_{0\text{-}last}$), area under the plasma concentration time curve from time zero extrapolated to infinity ($AUC_{0\text{-}\infty}$), and total systemic clearance (CL). Exploratory exposure-response analyses evaluating relationships between melphalan exposure and common or serious adverse reactions and clinical outcomes will be conducted.

Statistical Methods:

Sample size determination: The planned sample size for this study is 50 patients. Patient data from this study will be combined with patient data from study PHP-OCM-301 to obtain at least 80 Melphalan/HDS-treated patients to estimate the ORR. Assuming the combined ORR is 0.210, this provides a maximum width of the 95% confidence interval of ± 0.113 around the point estimate of ORR assuming the ORR is 0.210, giving a 95% lower bound of 0.097. This lower bound of 0.097 exceeds the upper bound of the 95% confidence interval of a historically-derived control, which is 0.083.

Data from protocol PHP-OCM-301 will be pooled with the data collected under the current protocol for the primary analysis of efficacy in the intent-to-treat (ITT) population and for safety analysis in the Safety population. A **PHP301A group** will consists of at least 50 patients from PHP-OCM-301A and a **PHP301 group** will include approximately 30 patients from PHP-OCM-301 to yield at least 80 total patients in the **PHP group** for the ITT analysis. The BAC group from PHP-OCM-301 will be summarized as well. Efficacy and safety data from Melphalan/HDS treatment for the PHP301A and PHP301 groups will be summarized separately, also, as a secondary analysis.

The ITT population for PHP-OCM-301A is defined as all patients who have a date of eligibility (i.e. signed informed consent and met all qualification criteria for Melphalan/HDS treatment).

The Safety population is defined as all patients for whom a study treatment or procedure is attempted, regardless of whether they receive treatment. All safety analyses will be based on the safety population. Summary statistics for continuous efficacy variables will include the mean, standard deviation, median and range (minimum/maximum). Categorical efficacy variables will be presented as frequency counts and percentages and 95% CI. Time-to-event variables will be summarized using Kaplan-Meier methods (median, 95% CI, number of events, number censored, Kaplan-Meier figures). Data listings will be created to support each table and to present all data.

Efficacy Analysis: The primary efficacy endpoint ORR will be characterized by the point estimate and corresponding 95% confidence interval for each group (PHP, PHP301A, PHP301 and BAC).

Safety Analysis: The Medical Dictionary for Regulatory Activities (Version 15 or higher) will be used to classify all AEs with respect to system organ class and preferred term. TEAEs will be summarized for by treatment group (PHP, PHP301A, PHP301 and BAC).

TEAEs for the PHP group will also be divided based on period of onset in three periods: peri-procedure (day of planned procedure to 3 days post-procedure or hospital discharge, whichever is earlier); post-procedure (end of peri-procedure to day prior to the date of the next treatment cycle), post-study drug treatment (an AE that the patient's personal physician believes could be related to prior study drug treatment or procedures with an onset date more than 30 days after the last administration of melphalan), and overall TEAEs. AEs will also be summarized by causality: procedure, device, melphalan, BAC, multiple, or unrelated to any.

Shift tables will be generated for key hematologic, coagulation, chemistry and liver function laboratory parameters.

Table 1: Schedule of Assessments

Study Procedure	Screening/ Baseline: Days Prior to Eligibility <28 days to eligibility		Scheduling of PHP procedure Logistic planning and ordering	Melphalan/HDS Treatment Period (6-week repeating cycle) per Individual Cycle Calendar							End of Study Treatment (EOT) 6-8 wks after last Mel/HDS	Follow-up Period (until death)
				Week 1		Week 2		Week 3	Week 4	Week 6 (or last week of the cycle)		
	≤ 28	≤ 14	Up to -14 days to Day 1	Mel/HDS Day 1	Post-Mel/ HDS	Study Day 8	Study Day 11 or 12	Study Day 15 ± 2	Study Day 22 ± 2	Study Day 42 ± 2		
Informed Consent [A]	X[-42A]											
Eligibility date [B]		X[B]										
Medical History	X											
Physical exam		X				X		X			X	
Vital signs		X		X		X		X			X	
CT of C/A/P	X											
MRI of Liver [C]	X[C]											
MRI or CT of Brain	X											
Endoscopy [D]	X[D]											
Bone Scan [E]	X[E]											
Pregnancy Test [F]		X[F]								X[F]	X[F]	
ECOG PS		X						X			X	
12-lead ECG [G]		X[G]		X[G]	X[G]					X[G]		
ECHO [H]		X[H]		X[H]						X[H]		
Hematology, Chemistry		X		X	X	X	X	X	X	X	X	
Urinalysis		X								X		
PT/INR, PTT		X		X	X							
Troponin-I or T [I]		X[I]		X[I]	X[I]							
Angiogram [J]		X[J]								X[J]		
Disease assessments [K]										X[K]		X[K]
Melphalan/HDS				X								

Study Procedure	Screening/ Baseline: Days Prior to Eligibility <28 days to eligibility		Scheduling of PHP procedure Logistic planning and ordering	Melphalan/HDS Treatment Period (6-week repeating cycle) per Individual Cycle Calendar							End of Study Treatment (EOT) 6-8 wks after last Mel/HDS	Follow-up Period (until death)
				Week 1		Week 2		Week 3	Week 4	Week 6 (or last week of the cycle)		
	≤ 28	≤ 14	Up to -14 days to Day 1	Mel/HDS Day 1	Post-Mel/ HDS	Study Day 8	Study day 11 or 12	Day 15 ± 2	Day 22 ± 2	Day 42 ± 2		
Quality of Life		X								X	X	
G-CSF Prophylaxis [L]					X[L]							
AE assessment	X	X		X	X	X	X	X	X	X	X	X
Concomitant meds	X	X		X	X	X	X	X	X	X	X	
PK sampling [M]				X[M]	X[M]							
Survival status and chronic treatment-related toxicities [N]												X[N]

Footnotes for the Schedule of Assessments

Abbreviations: AE = adverse event; β-HCG = β-human chorionic gonadotropin; CT = computed tomography; CT C/A/P = computed tomography of the chest/abdomen/pelvis; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte-colony-stimulating factor; INR = international normalized ratio; Melphalan/HDS = melphalan hydrochloride for injection for use with the Hepatic Deliver System; MRI = magnetic resonance imaging; PK = pharmacokinetic; PHP = percutaneous hepatic perfusion; PS = performance status; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event.

For full details on all assessment see text in Study Assessments and Procedures (Section 6)

A. Informed consent: Informed consent must be obtained prior to any protocol-specific procedures, but may be obtained no more than 15 days prior to screening procedures.

B. Eligibility date: Recording of the eligibility date is required. This is the date at which all the screening and baseline assessments have been completed and the patient is deemed eligible for treatment (replaces the randomization date from protocol number PHP-OCM-301).

C. MRI of the liver (or 3-phase CT of the liver for patients intolerant to MRI) is required at screening to validate that CT accurately reflects the extent of disease in the liver. If the screening CT c/a/p and MRI of the liver (or 3-phase CT of the liver) are consistent, then the site to chooses which tumor modality to be used for all subsequent evaluation

D. Endoscopy (for patients with a history of or suspected of peptic ulcer disease) to check for varices at risk of bleeding (e.g., large esophageal or gastric varices, varices with red sign) or active peptic ulcers with or without exposed vessels at risk of bleeding).

E. Radionuclide bone scan for patients with known or suspected bone metastases, including previous irradiated bone metastases.

F. A serum β-HCG pregnancy test within 7 days prior to eligibility for females of childbearing potential (i.e., have had a menstrual period within the past 12 months). Pregnancy test is to be repeated at the completion of the 3rd cycle of Melphalan/HDS and at end of study treatment unless the end of treatment visit is within 30 days from the last pregnancy test at the End of Treatment visit.

G. Screening: 12-lead ECG will be completed within 14 days to prior eligibility.

   Treatment Period: For each Melphalan/HDS treatment:

   - Prior to hydration Pre-Treatment or Week 6, Day 7 ± 2 (study day 42 of previous cycle)
   - Morning of Melphalan/HDS infusion Day 1 but prior to treatment
   - Within 2 hours after the completion of Melphalan/HDS infusion
   - Daily in the morning while patient is hospitalized
   - 7 days (± 2 days) following hospital discharge

H. ECHO will be completed within 28 days prior to the eligibility date and on the day prior or morning of each Melphalan/HDS cycle (the ECHO does not need to be repeated if it is within 5 days of Day 1 of each cycle). Additional studies may be obtained when medically indicated

I. Troponin-I or T levels will be checked at the following time points:

   - At Screening within 14 Days of eligibility
   - Prior to hydration (on the day before Melphalan/HDS treatment)
   - Morning of, but before Melphalan/HDS treatment
   - At completion of Melphalan/HDS hemofiltration
   - Every 8 hours for the first 24 hours post Melphalan/HDS treatment

- Daily while in hospital until normalization
- If not normalized at discharge, 7 days (± 2 days) following hospital discharge and repeat weekly until stabilization.
- If elevated troponin-I or T result should be reviewed with ECG, cardiac enzymes and cardiology consultation as needed

J. CT or MRI based visceral angiogram for patients with a history of liver surgery or major vasculature to validate that the patient's hepatic vasculature is compatible with catheterization for Melphalan/HDS and embolization. Angiogram and embolization (when required) are to be repeated on Day 1 of each Melphalan/HDS cycle.

K. Disease Assessments (Tumor response) will be assessed every 12 weeks (± 2 weeks) beginning after the date of the first treatment until disease progression.

- If the patient receives only 1 treatment, the disease assessment scans are to be conducted beginning 12 weeks after the date of that treatment. Abdominal imaging by CT (or MRI) is required until progressive disease is documented. Additional studies may be obtained when clinically indicated.

L. Patients must receive granulocyte stimulating growth factor prophylaxis 24 to 72 hours after Melphalan/HDS treatment. The choice of agent is at the discretion of the treating physician

M. Pharmacokinetic blood samples will be taken in Cycle 1 (Chart 3), and in subsequent Cycles (Chart 4).

N. All treated patients are to be contacted by phone every 3 months for survival status until death.

Please refer to Chart 1 and Chart 2 for laboratory evaluations at screening, prior and during each Melphalan/HDS cycle and post each Melphalan/HDS cycle

Chart 1: Pre-treatment Lab Assessments and Day 1

	≤14 Days	Day -1	Day 1					
		Prior to hydration	Pre-procedure at time 0	Completion of Hemofiltration	After anti-coagulation reversal	Post-procedure 5 minutes before all vascular accesses have been removed	3 hours after completion of washout	Every 8 hours for the first 24 hours post-Mel/HDS treatment (8/16/24 hours post-PHP)
CBC	X		X		X		X	
Chemistry	X						X	
PT/INR, PTT	X		X		X	X	X	
LFTs	X						X	
Troponin-I or T	X	X	X	X				X

Abbreviations: CBC = complete blood cell count; INR = international normalized ratio; LFT = liver function test (includes ALT, AST, alkaline phosphatase, total and direct bilirubin, and albumin); PT = prothrombin time; PTT = partial thromboplastin time.

Chart 2: Lab Assessments During Hospitalization and After Discharge

	Daily During Hospitalization	After Discharge from Hospital		
		Every 4 (+/- 1day) Days (during first two weeks)	Weekly (starting at week 3, or more frequently if Grade 3/4 toxicities are observed)	If not normalized at discharge, collect at 7 days ± 2 days following hospital discharge and repeat weekly until stabilization
CBC	X	X	X	
Chemistry	X			
PT/INR/PTT	X			
LFTs	X		X	
Troponin-I or T	X			X

Abbreviations: CBC = complete blood cell count; INR = international normalized ratio; LFT = liver function test (includes ALT, AST, alkaline phosphatase, total and direct bilirubin, and albumin); PT = prothrombin time; PTT = partial thromboplastin time.

Chart 3. Cycle 1 Pharmacokinetic Sampling

	During Infusion			Hemofiltration/washout			Post hemofiltration									
	10 min	**20 min**	**30 min**	**10 min**	**20 min**	**30 min**	**5 min**	**10 min**	**15 min**	**30 min**	**1 hr**	**2 hr**	**3 hr**	**3.5 hr**	**5 hr**	**6 hr**
Intensive Group (n = 20) (US sites only)																
Pre-filter	X	X	X	X	X	X										
Post-filter	X	X	X	X	X	X										
Systemic	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Sparse Group (all other patients[1])																
Pre-filter	X	X	X	X	X	X										
Post-filter	X	X	X	X	X	X										
Systemic			X			X	X[2,4]		X[3,4]		X[5]			X[6]		

1. Patients not enrolled into the intensive sampling group will be placed into the sparse sampling group
2. One sample 5-10 minutes after completion of hemofiltration
3. One sample 15-30 minutes after completion of hemofiltration
4. The 5-10 minute and 15-30 minute samples should be at least 10 minutes apart
5. One sample between 1-3 hours after completion of hemofiltration
6. One sample between 3-6 hours after completion of hemofiltration

Chart 4. Cycles 2-6 Pharmacokinetic Sampling (all patients)

	During Infusion			Hemofiltration/washout			Post hemofiltration									
	10 min	**20 min**	**30 min**	**10 min**	**20 min**	**30 min**	**5 min**	**10 min**	**15 min**	**30 min**	**1 hr**	**2 hr**	**3 hr**	**3.5 hr**	**5 hr**	**6 hr**
Pre-filter			X			X										
Post-filter			X			X										
Systemic			X			X	X[1,3]		X[2,3]		X[4]			X[5]		

1. One sample 5-10 minutes after completion of hemofiltration
2. One sample 15-30 minutes after completion of hemofiltration
3. The 5-10 minute and 15-30 minute samples should be at least 10 minutes apart
4. One sample between 1-3 hours after completion of hemofiltration
5. One sample between 3-6 hours after completion of hemofiltration