A Phase 2 Study of Transarterial Chemoperfusion Treatment with Cisplatin, Methotrexate and Gemcitabine in Patients with Unresectable Pleural Mesothelioma

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Agents: Cisplatin, Methotrexate, Gemcitabine

Protocol Version 7: March 27, 2018

STUDY SYNOPSIS

Title of Study: A Phase 2 Study of Transarterial Chemoperfusion Treatment with Cisplatin, Methotrexate and Gemcitabine in Patients with Unresectable Pleural Mesothelioma.	
Sponsor: H. Lee Moffitt Cancer Center and Research Institute	
Primary Investigator: Bela Kis, MD, PhD	
Phase of Development: Phase 2	**Study Duration:** 3 years
Primary Objective: To determine the disease control rate of transarterial chemoperfusion treatment with cisplatin, methotrexate and gemcitabine in patients with unresectable malignant pleural mesothelioma (MPM).	
Secondary Objectives: To assess overall survival, progression free survival, severity and frequency of adverse events and quality of life in patients with MPM treated with transarterial chemoperfusion with cisplatin, methotrexate and gemcitabine.	
Rationale: MPM has an extremely poor prognosis with median survival time of less than 12 months. Surgical resection for stage I and stage II MPM is the only curative option. However, the majority of patients present with stage III or IV disease with 85-90% of patients considered unresectable at diagnosis. The largely ineffective current treatment approaches to offer long-term survival and to improve quality of life warrant the search for new therapeutic regimens.	
Study Design: This is an open-label, single arm, phase 2 study with a lead in safety cohort to evaluate the safety and efficacy of transarterial chemoperfusion treatment with cisplatin (35 mg/m^2), methotrexate (100 mg/m^2) and gemcitabine (1000 mg/m^2) in patients with unresectable MPM. During the lead in phase of the study 3 patients will be treated with 50% reduced dose of methotrexate (50 mg/m2) and regular doses of cisplatin (35 mg/m2 BSA) and gemcitabine (1000 mg/m2 BSA). Dose escalation will be contingent upon acceptable safety data obtained during the first three cycles of treatment (12 weeks). If no dose limiting toxicity observed, dose is escalated to methotrexate (100 mg/m2) with cisplatin (35 mg/m2 BSA) and gemcitabine (1000 mg/m2 BSA). The reduced dose level safety cohort will be expanded from 3 to 6 if one of the first 3 patients experiences dose limiting toxicity related to methotrexate. After the 12 weeks of dose limiting toxicity observation period for the final patient in the reduced dose safety cohort is complete, if less than one third of the patients enrolled in that cohort developed dose limiting toxicity, advancement to the regular dose level cohort can begin. If > 2 patients in the safety cohort experience dose limiting toxicity the methotrexate dose will be reduced to 25 mg/m2 and this will be used further in the study. During the chemoperfusion procedure based on the pre-procedural imaging and the angiography findings the chemoperfusion catheter will be placed within a tumor supplying intercostal artery or within the descending aorta slightly proximal to origin of the most cephalad tumor supplying intercostal artery, but below the origin of the left subclavian artery if multiple intercostal vessels are supplying the tumor. For tumors located predominantly anteriorly in the chest the infusion catheter will be placed into the ipsilateral internal mammary artery. For tumors supplied by both intercostal and internal mammary arteries chemoperfusion may be performed for the artery predominantly supplying the tumor or for multiple arteries per primary clinician discretion. Chemoperfusion treatment will be administered in every 4 weeks until the patient's death unless the treatment is terminated earlier due to treatment toxicity or other reasons.	

Number of Subjects (planned): 32

Major Inclusion Criteria:

- Histologically confirmed unresectable MPM.
- Failed first line standard of care chemotherapy or the patient refuses first line chemotherapy.
- Age ≥18 years.
- Estimated life expectancy > 12 weeks.
- ECOG performance status ≤2.
- Adequate organ functions.
- Signed informed consent.

Major Exclusion Criteria:

- Allergic reaction to agent used during the study.
- Known brain metastases or leptomeningeal metastases.
- Uncontrolled severe intercurrent illness.
- Women who are pregnant or breastfeeding.
- Unable to obtain informed consent.

Criteria for Evaluation:

Efficacy Outcome Measures
Primary: Disease control rate measured by modified RECIST for mesothelioma.
Secondary: Overall survival defined as the time from the first day of transarterial chemoperfusion treatment to death. Progression free survival defined as the time from the first day of transarterial chemoperfusion treatment to disease progression based on imaging findings using modified RECIST criteria for mesothelioma.

Safety Outcome Measures
Safety will be assessed by monitoring adverse events and serious adverse events; the association with study treatment will be assessed, and severity will be graded using CTCAE v.4.03.

Quality of Life Measures
Quality of life will be assessed using the modified version of the Lung Cancer Symptom Scale for Mesothelioma questionnaire.

Statistical Methods: This is an open-label, single arm, phase 2 study to evaluate the safety and efficacy of transarterial chemoperfusion treatment in patients with unresectable MPM. The statistical power calculations are based on the Simon's two-stage design. The one-sided and two-sided 95% confidence intervals by Atkinson and Brown will be reported, which accounts for the nature of two-stage design. The secondary endpoints include overall survival and progression free survival which are estimated by the Kaplan-Meier method. For all subjects, descriptive statistics (median, range for continuous variables and frequency and proportion for categorical variables) will be utilized to summarize patients' demographic and clinical variables.

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1. OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to determine the disease control rate of transarterial chemoperfusion treatment with cisplatin, methotrexate and gemcitabine in patients with unresectable malignant pleural mesothelioma using modified RECIST criteria for mesothelioma [1].

1.2 Secondary Objectives

1.2.1 Overall Survival

To assess overall survival (OS) in patients with malignant pleural mesothelioma treated with transarterial chemoperfusion.

1.2.2 Progression Free Survival

To assess progression free survival (PFS), defined as the time from the first day of cisplatin, methotrexate and gemcitabine transarterial chemoperfusion treatment to disease progression (either pleural or extrapleural), based on imaging findings using modified RECIST criteria for mesothelioma [1] or death from any cause.

1.2.3 Safety and Tolerability

To determine the severity and frequency of adverse events related to transarterial chemoperfusion with cisplatin, methotrexate and gemcitabine during the chemoperfusion phase and follow-up phase of the study.

1.2.4 Quality of Life

To assess quality of life in patients with malignant pleural mesothelioma treated with transarterial chemoperfusion.

2. BACKGROUND

2.1 Malignant Pleural Mesothelioma

Malignant mesothelioma is a rare form of cancer that develops from cells of the mesothelium, the lining of the coelomic cavities of the body: the pleura, the peritoneum, the pericardium, and the tunica vaginalis testis. Mesothelioma is classified into three broad histological subtypes: epithelioid, sarcomatoid and mixed, comprising approximately 50% to 70%, 10% to 20%, and 20% to 40% percent of malignant mesothelioma, respectively. Patients with the sarcomatoid and mixed subtypes have worse prognosis compared to the epithelioid subtype [2].

Mesothelioma is associated with asbestos exposure. It was considered a rare disease until 50 years ago, but its incidence dramatically increased due to the widespread use of asbestos in the early to mid-twentieth century. Since the median latency between asbestos exposure and disease onset is 44.6 years, and increases over time in a linear fashion, incidence rates are still rising, with peak incidences expected around 2020 and beyond [3]. Due to the long latency of the onset of disease after exposure to asbestos, mesothelioma typically develops in the sixth or seventh decade of life [4].

Malignant pleural mesothelioma (MPM) is the most common form of mesothelioma (67% to 75%) followed by peritoneal mesothelioma (25% to 33%) [4]. In the US there are approximately 2400 new MPM cases per year [5]. The clinical presentation of MPM at the time of diagnosis is shortness of breath and chest pain in 60% of patients [6]. MPM progresses with local invasion of the thoracic wall including the intercostal nervous structures causes chest pain and the development of chest wall lumps. Loco-regional progression of the tumor results in pneumonia, superior vena cava syndrome, Pancoast or Horner's syndrome, dysphagia, pericardial tamponade, and arrhythmias. In most patients, death occurs as a result of loco-regional progression within the thoracic cavity. Constitutional symptoms (eg, fatigue and weight loss) and lymphatic and hematogenous dissemination occurs late in the disease [7].

Patients with unresectable MPM carry a poor prognosis. The treatment options for unresectable stage III and stage IV MPM are radiation therapy and chemotherapy, but survivals are usually less than a year [6]. These very poor survival statistics necessitates a search for new, more effective therapies.

2.2 Rationale

MPM has an extremely poor prognosis with median survival time of less than 12 months [6]. Surgical resection for stage I and stage II MPM is the only curative option. However, the majority of patients present with stage III or IV disease with 85-90% of patients considered unresectable at diagnosis. The largely ineffective current treatment approaches to offer long-term survival and to improve quality of life warrant the search for new therapeutic regimens.

Isolated lung perfusion, which permits a selective delivery of high-dose chemotherapeutic agents to the tumor, has shown promising results in the treatment of lung metastasis in experimental models [8]. These studies have demonstrated the superiority of isolated lung perfusion to systemic chemotherapy in terms of effectiveness, but despite these results, isolated lung perfusion has not been and likely won't be adopted as a routine clinical treatment because it is a very complex procedure requiring thoracotomy for cannulation of the pulmonary arteries and veins, which is a high morbidity and mortality surgery with a very high associated cost.

Transarterial chemoperfusion of the liver in patients with uveal melanoma metastases demonstrated prolonged survival [9]. Transarterial chemoperfusion through direct injection of drugs into the aorta has been described as a treatment option for advanced pelvic tumors [10].

Vogl et al. recently demonstrated that transarterial chemoperfusion in patients with unresectable MPM significantly improve survival [11]. In contrast to isolated lung perfusion, transarterial chemoperfusion of the lung and pleural cavity can be easily and repeatedly performed percutaneously and it is well tolerated by the patients.

Vogl et al [11] administered mitomycin C with cisplatin, and gemcitabine transarterially to patients with unresectable MPM. The reason why this drug combination was chosen is not explained in their paper. We are proposing transarterial chemoperfusion with cisplatin, metothrexate and gemcitabine in patients with unresectable MPM. This drug combination is different than what was used by Vogl et al. who used mitomycin C with cisplatin, and gemcitabine. We are proposing to use methotrexate instead of mitomycin C because mitomycin C and cisplatin has the same mechanism of action, both are DNA crosslinker agent, and we think that using chemotherapeutic drugs with different mechanism of action may lead to improved clinical response. In addition, folate antimetabolites like methotrexate and pemetrexed are regarded as the most active class of cytotoxic drugs against MPM [12-14]. In our proposed drug combination each drug acts on different steps of the mitotic cycle of cells as cisplatin is a DNA crosslinker, methothrexate is a folate antimetabolite and gemcitabine is a nucleoside analogue.

These drugs were proven to be effective in patients with MPM and have established safety profiles with intraarterial administration. One could argue to use pemetrexed instead of methothrexate since recent reviews [12; 14] showed that the combination of pemetrexed with cisplatin achieves the best overall survival and quality of life in patients with MPM. However, there is no established safety profile of pemetrexed for intraarterial administration.

This proposed transarterial chemoperfusion treatment protocol offers a novel approach to treat patients with unresectable MPM.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed malignant pleural mesothelioma (MPM).

3.1.2 Patients have unresectable MPM or the patient refuses surgery for resectable MPM.

3.1.3 Patients who failed to respond first line standard of care chemotherapy or chemotherapy suspended due to toxicity or other reasons.

3.1.4 Patients who are refusing first line standard of care chemotherapy.

3.1.5 Patients must have measurable disease, by CT or MRI per modified RECIST criteria for mesothelioma . Radiographic tumor assessment must be performed within 28 days prior to the first treatment.

3.1.6 The predominant burden of disease lies in an arterial distribution which is accessible for transarterial chemoperfusion treatment.

3.1.7 Men and women ≥18 years of age.

3.1.8 ECOG performance status ≤2 (Karnofsky ≥60%; see Appendix A).

3.1.9 All baseline laboratory requirements will be assessed and should be obtained within 14 days of first treatment. Screening laboratory values must meet the following criteria:

- leukocytes ≥3,000/μL
- absolute neutrophil count ≥1,500/μL
- platelets ≥100,000/μL
- prothrombin time ≤ 1.5 x upper limit of normal (ULN);
- partial thromboplastin time ≤ 1.5 x institutional ULN;
- total bilirubin ≤ 1.5 x ULN; except subjects with Gilbert syndrome who can have total bilirubin < 3.0 mg/dL)
- aspartate amino transferase ≤2.5 X institutional ULN
- alanine amino transferase ≤2.5 X institutional ULN
- alkaline phosphatase ≤2.5 X institutional ULN
- creatinine within normal institutional limits

OR

- creatinine clearance ≥50 mL/min based on the standard Cockcroft and Gault formula [15].

3.1.10 Women participate in the study must be surgically sterile, post-menopausal, or women of child-bearing potential must agree to use adequate contraception (See Appendix C) prior to study entry and for the duration of study participation and after for a certain amount of time (as defined below) because the therapeutic agents used in this trial and the x-ray used during the transarterial treatment and diagnostic imaging are known to be teratogenic.

The individual methods of contraception and duration should be determined in consultation with the investigator. The duration of mandatory contraception is based on clearance of the investigational drug (5 half-lives after treatment completion). For women, an additional 30 days is required to complete an ovulatory cycle. Calculation of duration of mandatory contraception: The half-life of cisplatin is 20-30 minutes (Appendix E), half-life of metothrexate is 8-15 hours (Appendix F) and half-life of gemcitabine is 42-94 minutes (Appendix G). Thus, contraception is required for up to 5 weeks after the last treatment for women of child-bearing potential.

Women must have a negative serum or urine pregnancy test within 24 hours prior to the start of transarterial chemoperfusion treatment.

Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.11 Men participate in the study must be surgically sterile or must agree to use adequate contraception (See Appendix C) prior to study entry and for the duration of study participation and after for a certain amount of time (as defined below) because the therapeutic agents used in this trial and the x-ray used during the transarterial treatment and diagnostic imaging are known to be teratogenic. The investigator shall review contraception methods and the time period that contraception must be followed. The duration of mandatory contraception is based on clearance of the investigational drug (5 half-lives after treatment completion). For males, an additional 90 days is required to complete turnover of drug-exposed sperm. Calculation of duration of mandatory contraception: The half-life of cisplatin is 20-30 minutes (Appendix E), half-life of metothrexate is 8-15 hours (Appendix F) and half-life of gemcitabine is 42-94 minutes (Appendix G). Thus, contraception for men is required for up to 14 weeks after the last treatment.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.1.13 Patients must have signed and dated an IRB approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

3.1.14 Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, imaging studies, and other requirements of the study.

3.1.15 This study permits the re-enrollment of a patient who has discontinued the study for a reason other than treatment failure or adverse event(s) of the study treatment. The patient must be re-consented and assigned a new subject number.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Recovery means resolution to at least Grade 1 toxicity if there was no baseline toxicity or less than or equal to the patient's baseline value.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with known brain metastases or leptomeningeal metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Patients with other extrapleural metastases are included in this study.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cisplatin, metothrexate, gemcitabine or other agents used during the study.

History of allergic reaction to intravenous iodinated contrast media is not contraindication to the study. Patients with history of mild allergic reaction to iodinated contrast media will be premedicated with 40 mg of prednisone p.o. 12 and 2 hrs before the transarterial chemoperfusion treatment to prevent allergic reaction. Patients with history of moderate and severe allergic reaction to iodinated contrast media or patients with history of mild allergic reaction to iodinated contrast media despite adequate premedication will undergo angiogram using carbon dioxide or a gadolinium based contrast agent.

3.2.5 Uncontrolled intercurrent illness including, but not limited to, presence of other malignancy, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Women who are pregnant or breastfeeding are excluded from the study because methotrexate and cisplatin are FDA pregnancy category D agents with positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans.

3.2.7 HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with cisplatin, methotrexate and gemcitabine during the study.

3.2.8 Prisoners or subjects who are involuntarily incarcerated.

3.2.9 Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

3.4 Patient Registration

Once clinical eligibility is confirmed, patients must sign an informed consent prior to registration indicating awareness of the investigation nature of the study and its inherent risks in keeping with the policies of the Moffitt Cancer Center and Federal regulations (Code of Federal Regulations Part 1X, Subpart B, Sections 50.20-50.27). The principal investigator in writing must approve request for an exemption to enroll a patient.

4. TREATMENT PLAN

4.1 Method of Assignment to Treatment

This is an open-label, single arm, phase 2 study. Patients with unresectable MPM who meet all criteria for enrollment will be offered to participate in the study. The eligible patients can voluntarily enroll in the study after reviewing the consent form and after detailed discussion of the procedural protocol and potential risks and benefits of this experimental treatment with the principal investigator or one of the co-investigator.

4.2 Study Design

This is an open-label, single arm, phase 2 study with a lead in safety cohort to evaluate the safety and efficacy of transarterial chemoperfusion treatment with

cisplatin, metothrexate and gemcitabine in patients with unresectable MPM. The patients receive 15 mg leucovorine po in every 12 hrs for a total of 4 doses starting 24 hrs after each chemoperfusion procedure. Chemoperfusion treatment will be administered in every 4 weeks. The treatment will be continued until the patient's death unless the treatment is terminated earlier due to reasons described in Section 4.12.1 *Removal of Patients From Study* and in Section 4.12.2 *Premature Study Termination.*

The study will be divided into the following phases:

- Screening Phase
- Treatment Phase
- Follow-up Phase

4.2.1 Screening Phase

Screening assessments must occur within 4 weeks of the chemoperfusion treatment for determination of a patient's overall eligibility. These assessments will include medical history, ECOG performance status, physical exam, full hematology and biochemistry laboratory, radiologic assessments of disease status, and an evaluation of vasculature compatibility for chemoperfusion.

4.2.2 Treatment Phase

Patients undergo angiogram and transarterial chemoperfusion treatment in every 4 weeks (3-6 weeks interval allowed) when cisplatin, methotrexate and gemcitabine will be administered into the thoracic aorta and/or the internal mammary artery on the side of the disease.

4.2.3 Follow-up Phase

Follow-up assessments will be performed at 4 weeks (3-6 weeks interval allowed) after each chemoperfusion treatment. Follow-up assessments must occur before the next chemoperfusion is performed. These assessments will include medical history, ECOG performance status, full hematology and biochemistry laboratory, radiologic assessments of disease status, and physical exam with special attention to the arterial access site. Other symptoms (severity and duration) such as dyspnea, chest pain, persistent cough, etc. will be monitored by using a questionnaire (see Appendix D). The questionnaire should be completed and returned to the principal investigator before each transarterial chemoperfusion treatment.

4.3 Rationale for Study Design

Transarterial chemoperfusion with mitomycin C, cisplatin and gemcitabine has been shown by Vogl et al. to significantly improve survival in patients with unresectable MPM [11]. We propose transarterial chemoperfusion with cisplatin, methotrexate and gemcitabine as a novel treatment option for patients with unresectable MPM. In our

protocol we replace mitomycin C with metothrexate because mitomycin C and cisplatin are both DNA crosslinker agents and it is potentially more advantageous to use a combination of drugs with different intracellular targets to increase the effectiveness of the multi agent chemotherapeutic regimen. In addition, folate antimetabolites like methotrexate and pemetrexed are regarded as the most active class of cytotoxic drugs against MPM [12-14] . Therefore, in our proposed drug combination each drug acts on different steps of the mitotic cycle as cisplatin is a DNA crosslinker, methotrexate is a folate antimetabolite and gemcitabine is a nucleoside analoge.

4.3.1 Rationale for a Lead in Safety Cohort

Although, there are data in the literature regarding the safety of intraarterial administration of cisplatin, methotrexate and gemcitabine (for details refer to section 4.3.2) there is no safety data regarding the intraarterial administration of cisplatin, methotrexate and gemcitabine in combination. Vogl et al. [11] used the combination of cisplatin (35 mg/m2 BSA), mitomycin C (8 mg/m2 BSA) and gemcitabine (1000 mg/m2 BSA) in patients with MPM injected intraarterially and demonstrated very favorable safety and tolerability profile. We are proposing to replace mitomycin with methotrexate and use the same concentrations for cisplatin (35 mg/m2 BSA) and gemcitabine (1000 mg/m2 BSA) as Vogl et al. did [11]. The new drug in our proposed combination is methothrexate. Therefore, in our lead in safety cohort we propose to use a 50% reduced dose of methotrexate (50 mg/m2) with cisplatin (35 mg/m2 BSA) and gemcitabine (1000 mg/m2 BSA) in 3 patients. Dose escalation will be contingent upon acceptable safety data obtained during the first three cycles of treatment (12 weeks). If no dose limiting toxicity observed, dose is escalated to methotrexate (100 mg/m2) with cisplatin (35 mg/m2 BSA) and gemcitabine (1000 mg/m2 BSA). The reduced dose level safety cohort will be expanded from 3 to 6 if one of the first 3 patients experiences dose limiting toxicity related to methotrexate. After the 12 weeks of dose limiting toxicity observation period for the final patient in the reduced dose safety cohort is complete, if less than one third of the patients enrolled in that cohort developed dose limiting toxicity, advancement to the regular dose level cohort can begin. If > 2 patients in the safety cohort experience dose limiting toxicity the methotrexate dose will be reduced to 25 mg/m2 and this will be used in the study.

4.3.2 Rationale for Phase 2 Study

Cisplatin, methotrexate and gemcitabine are commercially available chemotherapeutic agents with long history of clinical use and well established safety profiles. Although, cisplatin plus methotrexate plus gemcitabine drug combination has not been administered during the same treatment cycle in MPM, these drugs were used in sequential chemotherapy protocol in MPM when patients were treated with cisplatin (75 mg/m^2) and gemcitabine (1,200 mg/m^2) for four courses followed by mitoxantrone (10 mg/m^2), methotrexate (35 mg/m^2) and mitomycin (7 mg/m^2) for four courses and mild toxicity was

reported [25]. The combination of gemcitabine (usual dose around 1000 mg/m^2) with cisplatin (usual dose around 100 mg/m^2) was standard of care in the US for treatment of MPM before FDA approval of the use of pemetrexed-cisplatin combination in 2003 [26]. No unacceptable toxicity was reported in studies using cisplatin with gemcitabine in patients with MPM [27]. Combination of methotrexate (100 mg/m^2) and gemcitabine (800 mg/m^2) has recently been used to treat MPM and acceptable rate of hematologic toxicity was reported and non‐hematologic toxicity was mild [16]. Combination of gemcitabine with cisplatin and methotrexate with cisplatine are also widely used in the treatment of muscle invasive bladder cancer with a good safety profile [28]. Methotrexate (30 mg/m^2) with gemcitabine (800 mg/m^2) are used in patients with relapsing head and neck cancer with mild to moderate reported toxicity [29].

Vogl et al. [11] used the combination of cisplatin with mitomycin and gemcitabine for intraarterial chemoperfusion in patients with MPM and demonstrated very favorable safety and tolerability profile. We are proposing to replace mitomycin with methotrexate and use the same concentrations for cisplatin (35 mg/m^2 BSA) and gemcitabine (1000 mg/m^2 BSA) as Vogl et al. did [11]. We propose to use methotrexate in a relatively low concentration (100 mg/m^2 BSA) compared to treatment protocols when methotrexate was used at concentration of 1500 mg/m^2 BSA to treat MPM [13].

Intraarterial administration of these drugs is proven to be safe. Vogl et al [11] used intraarterial administration of cisplatin (35 mg/m^2 BSA) with mitomycin (8 mg/m^2 BSA) and gemcitabine (1000 mg/m^2 BSA) in patients with MPM and demonstrated very favorable safety and tolerability profile. High-dose intra-arterial cisplatin (150 mg/m^2 BSA) therapy was used for advanced squamous cell carcinoma of the head and neck with acceptable toxicity profile [30]. Intraarterial methotrexate (110 mg/m^2 BSA) with cisplatin (35 mg/m^2 BSA), mitomycin C (4.5 mg/m^2 BSA), bleomycin (15 mg/m^2 BSA), and 5-fluorouracil (1200 mg/m^2 BSA) was reported to treat penile cancer and grade 2 anorexia was the most frequent chemotherapy-related toxicity [31]. No toxicity was reported in the above mentioned studies which developed due to the intraarterial administration route.

In summary, all the chemotherapeutic agents used in this study have established safety profile.

4.3.3 Rationale for Treatment Interval

The 4-week treatment interval is selected for the chemoperfusion treatment protocol because this time frame is normally sufficient for the chemotherapeutics to achieve peak effect and also for the side effects of the previous chemotherapeutic treatment to have worn off, allowing the patient time to recover from the stress of the previous treatment. Efforts will be made to treat every patients in 4-week intervals, but the protocol allows treatment

intervals of 3-6 weeks to accommodate treatments for unforeseen circumstances which could prevent the planned 4-week treatment interval.

4.4 Rationale for Cisplatin Dosage

The recommended dose of cisplatin for transarterial chemoperfusion in this study is 35 mg/m^2 body surface area (BSA). Vogl et al [11] used this concentration of cisplatin in their MPM transarterial chemoperfusion study. This is a relatively low concentration of cisplatin compared to standard intravenous administration where the recommended dose of cisplatin is 75 mg/m^2 BSA to treat MPM. The concentration of the administered cisplatin solution will be 1 mg/ml as recommended by the manufacturer. Subjects may receive anti-emetics, e.g., ondansetron, dexamethasone, prior to cisplatin infusion per standard of care and investigator's practice. Dose reductions may be required for subjects with hepatic or renal impairment or history of hematologic or non-hematologic toxicity to cisplatin.

For complete information on cisplatin dosage and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions, please see Appendix E.

4.5 Rationale for Methotrexate Dosage

The recommended dose of methotrexate for transarterial chemoperfusion in this study is 100 mg/m^2 BSA. The anifolates like methotrexate and pemetrexed are regarded as the most effective class of cytotoxic drugs against MPM. Earlier publications reported that high-dose methotrexate (1500 mg/m^2) to be effective in the treatment of MPM, with a response rate of 37% [13]. However, high-dose methotrexate was associated with severe toxicity. Recent studies showed that 100 mg/m^2 BSA dose of methotrexate in combination with gemcitabine was effective in treatment of MPM [16].

The patients receive 15 mg leucovorin po in every 12 hrs for a total of 4 doses starting 24 hrs after the chemoperfusion procedure. Methotrexate level measurement will be performed if there is suspicion of methotrexate toxicity. In case of methotrexate toxicity the patient will be hospitalized and intravenous leucovorin will be administered.

For complete information on methotrexate dosage and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions, please see Appendix F.

4.6 Rationale for Gemcitabine Dosage

The recommended dose of gemcitabine for transarterial chemoperfusion in this study is 1000 mg/m^2 BSA. This is a usual therapeutic dose of gemcitabine to treat MPM [17]. Vogl et al [11] also used this concentration of gemcitabine in their MPM transarterial chemoperfusion study.

For complete information on gemcitabine dosage and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions, please see Appendix G.

4.7 Screening for Study Eligibility and Baseline Evaluation

All screening and baseline evaluations including imaging studies must be completed within 28 days prior to the first chemoperfusion treatment. The collected information will be reviewed against eligibility criteria to determine study eligibility. The investigator may use clinical judgment when determining the clinical significance of laboratory parameters and imaging findings throughout the study. The participating clinicians will be consulted before enrollment about a potential patient with abnormal laboratory values that are not considered clinically significant.

The following activities will be completed during the screening period within 28 days prior to the first chemoperfusion treatment.

4.7.1 Eligible Patients and Informed Consent

Any patient who appears to meet the eligibility criteria may be offered the opportunity to be evaluated for participation in this clinical trial. All such patients must sign and receive a copy of an informed consent form that was approved by the Institutional Review Board (IRB) and have the opportunity to ask the principal investigator any questions regarding the trial, and their rights and obligations as a trial participant before any protocol related evaluations can be performed. An original signed consent form will be retained in the patient's source documentation at the site, and a copy will be provided for the patient to take home.

4.7.2 Medical History

Medical history deemed clinically significant by the Investigator will be collected per body system with special attention to the diagnosis and treatment history of MPM. All on-going medical conditions and adverse events arising from treatment of those conditions present for ≥ 30 days are considered a part of the patient's medical history and must be recorded at baseline.

4.7.3 Physical Examination

A physical examination will cover the following:

• Vital signs: heart rate, respiratory rate, oxygen saturation by pulse oximetry, blood pressure taken after sitting for 5 minutes, and temperature (T)

• Height and weight
• Head, eyes, ears, nose, and throat
• Chest
• Heart
• Abdomen
• Extremities
• Genitourinary system
• Endocrine and immune systems
• Skin and appendages
• Neurological examination (level of consciousness, orientation, sensation, and motor function)

4.7.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Performance Status will be assessed and the following scores will assigned:
Score 0: Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction.)
Score 1: Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work.)
Score 2: Symptomatic, spends <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.)
Score 3: Symptomatic, spends >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.)
Score 4: Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair).

4.7.5 Allergies and Adverse Reaction

The patient's all known allergies and adverse reactions to medications must be recorded and added to the patient's medical record.

4.7.6 Review of Concomitant Medications

The patient's concurrent medications (medications taken within 28 days of screening and during the conduct of the study) including prescription and over-the-counter medications, herbs, vitamins, minerals, and prophylactic vaccines will be reviewed and documented.

4.7.7 Clinical Laboratory

The following clinical laboratory assessments will be completed:
• Hematology: white blood cell (WBC) count, platelet count, hematocrit, hemoglobin.
• Chemistry panel: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase,

total bilirubin, total protein, albumin, calcium, magnesium• Coagulation panel: Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized ratio for prothrombin time (INR)
• Pregnancy test: serum human choriogonadotropin (hCG) level measurement will be performed in females of child-bearing potential.

4.7.8 Electrocardiogram or Echocardiogram

Resting 12-lead electrocardiogram (ECG) or echocardiogram may be done by the discretion of the screening physician based on clinical history, physical and laboratory findings.

4.7.9 Imaging Studies

Contrast-enhanced CT scan of thorax will be performed if one has not been done within 28 days before screening. If a patient cannot have a contrast-enhanced CT scan (e.g., allergy to iodinated intravenous contrast dye) a magnetic resonance imaging (MRI) of the chest may be performed. CT with FDG-PET scan may be done.

4.7.10 Quality of Life Questionnaire

Quality of life will be assessed using the modified version of the Lung Cancer Symptom Scale for Mesothelioma questionnaire [18] (Appendix D).

4.8 Pre-procedure Care and Evaluation

Pre-procedure evaluation takes place on the day of each chemoperfusion treatment. The collected information will be reviewed against eligibility criteria to determine eligibility for the treatment. The primary clinician may use clinical judgment when determining the clinical significance of laboratory parameters and imaging findings. The participating clinicians will be consulted before treatment of a patient with abnormal laboratory values that are not considered clinically significant.

The following activities will be completed during the pre-procedure evaluation before each chemoperfusion treatment on the day of the treatment.

4.8.1 Medical History

Patients medical history will be updated with all medical events which has happened since the last visit and deemed clinically significant by the Investigator. All on-going medical conditions and adverse events arising from treatment of those conditions present for ≥ 30 days are considered a part of the patient's medical history and must be recorded.

4.8.2 Focused Physical Examination

The pre-procedure focused physical examination will cover the following:
• Vital signs: heart rate, respiratory rate, oxygen saturation by pulse oximetry, blood pressure taken after sitting for 5 minutes, and temperature (T)

• Height and weight
• Chest
• Heart
• Abdomen
• Extremities (special attention on peripheral pulses on the extermities which has been used for arterial access)
• Neurological examination (level of consciousness, orientation, sensation, and motor function)

4.8.3 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Performance Status will be assessed and the scores will assigned as described in detail in Section 4.7.4.

4.8.4 Allergies and Adverse Reaction

The patient's allergies and adverse reactions will be reviewed and updated with any new events in the patient's medical record.

4.8.5 Review of Concomitant Medications

The patient's medication list will be reviewed and updated in the patient's medical record.

4.8.6 Clinical Laboratory

The following clinical laboratory assessments will be completed within 14 days of the procedure:
• Hematology: white blood count (WBC) count, platelet count, hematocrit, hemoglobin.
• Chemistry panel: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase,
total bilirubin, total protein, albumin, calcium, magnesium,
• Coagulation panel: Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized ratio for prothrombin time (INR)
• Pregnancy test: urine human choriogonadotropin (hCG) level measurement will be performed in females of child-bearing potential.

4.8.7 Imaging Studies

Contrast-enhanced CT scan of thorax will be performed if one has not been done within 14 days of the treatment. If a patient cannot have a contrast-enhanced CT scan (e.g., allergy to iodinated intravenous contrast dye) a magnetic resonance imaging (MRI) may be performed. CT with FDG-PET scan may be done.

4.8.8 Quality of Life Questionnaire

Quality of life will be assessed using the modified version of the Lung Cancer Symptom Scale for Mesothelioma questionnaire [18] (Appendix D).

4.8.9 Intravenous Access

Intravenous access will be established either with a new peripheral venous stick or accessing the patient's long term venous access device (e.g. cental venous infusion port, PICC line, etc.). The venous access is used for administration of medications for moderate procedural sedations, intravenous fluids or other necessary medications during the chemoperfusion procedure.

4.8.10 Premedication

The following medications maybe given before the chemoperfusion treatment to alleviate the toxicity of the chemotherapeutic agents:
5% dextrose in 0.45% NaCl solution with 20 mEq KCl and 8 mEq MgSO4 for 1 hr before and 1 hr after chemoperfusion at 500 mL/hr rate.
Ondansetron 8 mg IV 30 min before chemoperfusion.
Fosaprepitant 150 mg IV 30 min before chemoperfusion.
Dexamethasone 20 mg IV 30 min before chemoperfusion.
Procholperazine 10 mg IV 30 min before chemoperfusion.
Mannitol 12.5 grams in 50 mL 0.9% NaCl solution before chemoperfusion.

4.9 Transarterial Chemoperfusion Procedure

The transarterial chemoperfusion treatment will be administered on an outpatient basis. The procedure will be performed in one of the interventional radiology procedure suites in the Moffitt Cancer which are equipped with all the necessary machines and tools to perform angiograms and other interventional radiology procedures. Performance of the procedure requires a procedural team that includes an interventional radiologist, an interventional radiology technologist and a procedural nurse.

4.9.1 Moderate Procedural Sedation

The procedure will be performed under moderate procedural sedation. Monitored anesthesia care may be provided by Anesthesiology in select patients if necessary based on the pre-procedural evaluation. If a patient wishes to proceed without sedation the procedure can be done using only local anesthesia at the arterial access site. Proceeding without sedation is the discretion of the primary clinician.

According to standard institutional protocol moderate procedural sedation will be administered by a registered procedural nurse under the direct supervision of the interventional radiologist who is performing the procedure. Vital signs, oxygen saturation by pulse oximetry, and response to verbal commands will be monitored and recorded by the registered nurse throughout the procedure

and the recovery period. The sedation flow sheet will be placed in the patient's medical record including the medications and dosages used.

4.9.2 Angiogram and Chemoperfusion

The arterial access site will be prepped and draped in standard sterile fashion. Local anesthesia (1% lidocaine) will be used at the puncture site to access the common femoral artery or the radial artery. The site and side of the arterial access will be determined by the interventional radiologist performing the procedure based on the patient's medical history, vascular anatomy, pre-procedural physical exam and the planned infusion site. Aortogram and selective angiograms will be performed to localize tumor feeding intercostal and/or internal mammary arteries.

Based on the pre-procedural imaging and the angiography findings the infusion catheter will be placed for the chemoperfusion within a tumor supplying intercostal artery or within the descending aorta slightly proximal to origin of the most cephalad tumor supplying intercostal artery, but below the origin of the left subclavian artery if multiple intercostal vessels are supplying the tumor. For tumors located predominantly anteriorly in the chest the infusion catheter will be placed into the ipsilateral internal mammary artery. For tumors supplied by both intercostal and internal mammary arteries chemoperfusion may be performed for the artery predominantly supplying the tumor or for multiple arteries per primary clinician discretion. When catheterization of the internal mammary artery is performed, intravenous administration of heparin is recommended. The level of anticoagulation will be determined by the interventional radiologist who is performing the procedure based the vascular anatomy and the patient's medical condition.

Drugs will be prepared individually for patients by the Chemotherapeutic Pharmacy of the Moffitt Cancer Center according to the manufacturers' recommendations and the drug doses will be calculated based on individual BSA of patients (cisplatin 35 mg/m2 BSA, methotrexate 100 mg/m2 BSA and gemcitabine 1000 mg/m2 BSA). The chemotherapeutic drugs will delivered freshly prepared from the Chemotherapeutic Pharmacy of the Moffitt Cancer Center to Interventional Radiology procedure suite in sterile syringes just before the start of the procedure. The intact packages will be stored at room temperature and protected from light until administration. The drugs will be administered in the following sequence: methotrexate followed by cisplatin, then gemcitabine.

After the chemoperfusion the catheters will be removed and will be discarded into a selective chemotherapeutic waste container per institutional protocol. The arteriotomy sites will be closed by an arterial closure device per primary clinician discreation.

After the procedure the patient will be transported into the Interventional Radiology post-procedural holding area or to the post-anesthesia care unit of the Moffitt Cancer Center for recovery.

4.10 Post-Procedural Supportive Care

Following the transarterial chemoperfusion treatment, the patient will remain under observation consistent with standard of care guidelines for aftercare in procedures involving femoral or radial arterial catheterization. The patient will be sent home when the physician determines that the patient is stable and that there is no risk of bleeding from the access site. At the time of discharge, patients will be instructed per institutional guidelines regarding after-care and provided with a 24-hour telephone number that they may use to contact the principal clinician or the interventional radiologist on call if they develop a problem or have questions about their treatment. Any concurrent medication or therapy deemed necessary, including post-procedural pain management, in the post-treatment period may be administered according to institutional standard of clinical care and by the approval of the primary clinician. The patients receive 15 mg leucovorin po in every 12 hrs for a total of 4 doses starting 24 hrs after the chemoperfusion procedure. Methotrexate level measurement will be performed if there is suspicion of methotrexate toxicity. In case of methotrexate toxicity the patient will be hospitalized and intravenous leucovorin will be administered.

4.11 Duration of Therapy

Transarterial chemoperfusion treatment will be administered in every 4 weeks (3-6 weeks interval allowed). The treatment will be continued until complete response or until the patient's death unless the treatment is terminated earlier due to reasons described below.

4.12 Removal of Patients from Study

Patients may be removed from the study at the discretion of the principal investigator for any of the following reasons:

- Progression of disease.
- Patient non-compliance: defined as any deviation from the protocol without prior agreement of the principal investigator.
- Patient's request to withdraw from the study or refusal of further therapy
- Unacceptable toxicity. Patients who cannot receive two out of the three individual drug component of the chemoperfusion treatment regimen for 49 days from the time of last treatment and patients requiring three dose reductions will be discontinued from the study (please also see Section 5).

- A patient may be removed from the study for any complication of treatment that the investigator feels is life threatening.
- If patient does not meet eligibility criteria (e.g. patient becomes pregnant)

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in the study protocol. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form.

In this study, disease control rate and overall survival are key endpoints of the study. Tumor responses initiated by chemoperfusion with cisplatin, methotrexate and gemcitabine may evolve after treatment discontinuation and the treatment may have effect on patient's survival. Therefore, post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required by the study protocol until death or the conclusion of the study.

4.13 Premature Study Termination

The Simon's two-stage design (see Section 11.1) requires 18 patients to be enrolled and evaluated in the first stage of the trial. If 4 or less of the patients respond to the therapy (CR or PR or SD), the treatment will be stopped. If 5 or more patients respond, 14 additional patients (a total of 32 patients per group) will be enrolled.

If conditions arising during the study that indicate that the study should be halted or terminated, this action may be taken after appropriate consultation among the clinical investigators involved in this study.

Conditions that may warrant termination of the study include, but are not limited to the following:
• The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
• Failure of the investigator to enroll subjects into the study at an acceptable rate.
• Failure of the investigator to comply with pertinent regulations of appropriate regulatory authorities.
• Submission of knowingly false information from the research facility to the appropriate regulatory authority.
• Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in compliance with the conditions

set forth in the International Conference on Harmonisation (ICH) E6,Guideline for Good Clinical Practice, Sections 4.12, 4.13, 5.20, and 5.21.

The Principal Investigator, the Protocol Monitoring Committee of Moffitt Cancer Center and the IRB have authority to suspend or terminate the study if the study has been associated with unexpected problems or serious harm to subjects or the study is not conducted in accordance with the IRB or the Moffitt Cancer Center research policy and regulatory requirements.

5. Drug Toxicities, Dose Modifications, Dosing Delays

5.1 General Considerations

- Any toxicity observed during the course of the study could be managed by reduction of dose of the study drugs or delaying the treatment if deemed appropriate by the Investigator based on the guidelines below.

- Where several toxicities with different grades or severity occur at the same time, the dose modification applied should be the greatest reduction applicable.

- Treatment may be delayed for up to 21 days to allow a patient sufficient time for recovery from study-related toxicity. A patient who cannot receive two out of the three individual drug component of the chemoperfusion treatment regimen for 49 days from the time of last treatment must be discontinued from the study.

- A patient requiring three dose reductions will be discontinued from the study. Any exceptions to discontinuation for a patient who in the judgment of the investigator is receiving clinical benefit and would need a further dose reduction must be discussed with the co-investigators and the multidisciplinary Mesothelioma Treatment Group of the Moffitt Cancer Center.

- Doses omitted during a chemoperfusion treatment will not be made up during the next treatment cycles.

5.2 Definition of Dose-Limiting Toxicity

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for Adverse Events (AE) and Serious Adverse Event (SAE) reporting. A dose-limiting toxicity (DLT) will be defined as Grade 3 and 4 toxicities which occur within 30 days after the chemoperfusion and are considered related to the treatment. The exceptions are the followings:

- Alopecia, vomiting, or diarrhea (unless not controlled by optimal anti-emetics or anti-diarrheals)
- Grade 1 or 2 neurotoxicity. The investigator and patient may decide to continue the treatment at a reduced dose of cisplatin (25 mg/m2 BSA) and full

dose of methotrexate (100 mg/m2 BSA) and gemcitabine (1000 mg/m2 BSA), with no delay required, as neurotoxicity may not resolve to baseline values.

- Grade 3 laboratory AEs that are asymptomatic and return to baseline or Grade 1 within 3 days, unless identified specifically as DLT by the investigator.
- Grade 3 fatigue
- Grade 3 systemic reactions (such as fever, headache, influenza like symptoms, myalgia, malaise, or nausea) that have returned to baseline or Grade 1 within 3 days of study inoculation
- Hospitalizations primarily intended to expedite diagnostic evaluations or for elective surgery will not be considered as SAEs for the purpose of ascertaining DLT.

Treatment should be delayed until resolution of DLT to at least Grade 1 toxicity if there was no baseline toxicity or less than or equal to the patient's baseline value before resuming treatment.

5.3 Hematological Toxicity

Dose adjustments at the start of a subsequent transarterial chemoperfusion therapy will be based on platelet and absolute neutrophil counts (ANC) measured within 2 days of the actual treatment. The ANC must be >1.5 x 10^9/L and platelet count must be >100 x 10^9/L before any chemoperfusion treatment. Dose delays will occur for up to 21 days if the ANC or platelet count has not sufficiently recovered by the time of the next cycle. Upon recovery, if treatment is resumed, it must be according to the dose modification guideline provided in the table below. Hematological toxicities not listed in the table, including non-hemolytic anemia do not require dose adjustments.

ANC x 10^9/L		**Platelet count x 10^9/L**	**Cisplatin dose (mg/m^2 BSA)**	**Methotrexate dose (mg/m^2 BSA)**	**Gemcitabine dose (mg/m^2 BSA)**
> 1.0	and	> 100	35	100	1000
0.5 – 1.0	or	50 - 100	35	75	750
< 0.5	or	< 50	delay dose	delay dose	delay dose

5.4 Renal Toxicity

Dose adjustments at the start of a subsequent transarterial chemoperfusion therapy will be based on creatinine clearance calculated from serum creatinine level which is measured within 2 days of the actual treatment. Creatinine clearance will be calculated using the Cockcroft and Gault formula [15] (Appendix B). The creatinine clearance must be >30 ml/min before any chemoperfusion treatment. Dose delays will occur for up to 21 days if creatinine clearance has not sufficiently recovered by the time of the next cycle. Upon recovery, if treatment is resumed, it must be

according to the dose modification guideline provided in the table below.

Creatinine clearance (ml/min)	Cisplatin dose (mg/m^2 BSA)	Methotrexate dose (mg/m^2 BSA)	Gemcitabine dose (mg/m^2 BSA)
> 50	35	100	1000
30 - 50	25	50	750
< 30	delay dose	delay dose	delay dose

5.5 Hepatic Toxicity

Dose adjustments at the start of a subsequent transarterial chemoperfusion therapy will be based on bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) levels measured within 2 days of the actual treatment. Bilirubin level must be < 3 x institutional institutional upper limit of normal (ULN), AST, ALT and ALP levels must be < 5 x ULN before any chemoperfusion treatment. Dose delays will occur for up to 21 days if the liver function test has not sufficiently recovered by the time of the next cycle. Upon recovery, if treatment is resumed, it must be according to the dose modification guideline provided in the table below.

Bilirubin (x ULN)		AST, ALT and ALP (x ULN)	Cisplatin dose (mg/m^2 BSA)	Methotrexate dose (mg/m^2 BSA)	Gemcitabine dose (mg/m^2 BSA)
< 2	and	< 3	35	100	1000
2 – 3	or	3 - 5	25	75	750
> 3	or	> 5	delay dose	delay dose	delay dose

5.6 Pericardial Effusion, Pleural Effusion, Ascites

Methotrexate exits slowly from third space compartments (e.g. pericardial effusion, pleural effusion or ascites). This results in a prolonged plasma half-life and could result in unexpected toxicity. Patients with third space fluid collections require especially careful monitoring for toxicity.

Patients with pleural effusion or ascites should undergo drainage of the fluid collection immediately before the transarterial chemoperfusion treatment. If the thoracentesis and/or paracentesis is not possible due to anatomic or other reason or the patient refuses the procedure, those patients will be treated with cisplatin and gemcitabine and methotrexate will not be administered during the chemoperfusion treatment. Patients with moderate to severe pericardial effusion will be treated with cisplatine and gemcitabine and methotrexate will not be administered during the chemoperfusion treatment.

5.7 Other Toxicities

More detailed information regarding drug specific toxicities please refer to the package inserts of cisplatin, methotrexate and gemcitabine in Appendix E, F and G.

6. PHARMACEUTICAL INFORMATION

All agents used in this study are commercially available.

6.1 Cisplatin

For complete product information on dosage and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions, see the package insert for cisplatin (Appendix E).

6.2 Methotrexate

For complete product information on dosage and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions, see the package insert for cisplatin (Appendix F).

6.3 Gemcitabine

For complete product information on dosage and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions, see the package insert for cisplatin (Appendix G).

7. STUDY CALENDAR

Baseline screening evaluations are to be conducted within 4 weeks prior to start of the transarterial chemoperfusion therapy. In the event that the patient's condition is deteriorating, evaluations should be repeated within 48 hours prior to initiation of the next transarterial chemoperfusion.

Transarterial chemoperfusion is performed in every 4 weeks until the patient's death unless the treatment is terminated earlier due to reasons described in Section 4.12. Post-treatment follow-up will be performed 4 weeks (3-6 weeks interval allowed) after the chemoperfusion treatment. Preferentially, the post-treatment follow-up and the upcoming chemoperfusion treatment performed on the same day.

	Screening Evaluation (0-4 weeks before first treatment)	**Chemoperfusion Treatment (every 4 weeks)[a]**	**Post-treatment follow-up (4 weeks after last treatment)[b]**	**Long term follow-up (every 2 months)**
Informed consent	X			
Demographics	X			
Medical history	X			
Review of Concomitant Medications	X	X	X	
Vital signs	X	X	X	
Height	X	X	X	
Weight	X	X	X	
Physical exam	X	X	X	
Performance status (ECOG)	X	X	X	
Clinical laboratory tests[c]	X	X	X	
Serum pregnancy test	X			
Urine pregnancy test		X		
Allergic event evaluation	X	X	X	
Adverse event evaluation	X	X	X	
Quality of life questionaire	X	X	X	
Radiologic evaluation[d]	X	X	X	
Transarterial chemoperfusion[a]		X		
Survival[e]				X

[a] Transarterial chemoperfusion performed in every 4 weeks (3-6 weeks interval allowed) with cisplatin (35 mg/m^2 BSA), methotrexate (100 mg/m^2 BSA), and gemcitabine (1000 mg/m^2 BSA), as described in Section 4.9 unless there is necessary treatment delay and/or dose reduction as described in Section 5. Transarterial chemoperfusion treatments will be administered until the patient's death unless the treatment

is terminated earlier due to reasons described Section 4.11.

[b] If transarterial chemoperfusion treatment is terminated earlier due to reasons described Section 4.12. the patient will have a clinic follow-up in 4 weeks (3-6 weeks interval allowed).

[c] Clinical laboratory tests include white blood cell count, platelet count, hematocrit, hemoglobin, sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, total protein, albumin, calcium, magnesium, Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized ratio for prothrombin time (INR).

[d]Radiologic evaluation using modified RECIST criteria performed at baseline during the screening evaluation and before each transarterial chemoperfusion treatment as described in Section 8.2.

[e]Overall survival will be followed every 2 months via in person or phone contact after subjects discontinue the study drug.

8. MEASUREMENT OF EFFECT

For the purposes of this study, patients are evaluated for response in every 4 weeks (3-6 weeks interval allowed) before they undergo the next transarterial chemoperfusion treatment. The evaluation includes focused medical history, quality of life questionnaire, physical exam, imaging study, laboratory tests amongst others. The complete list of studies included in the evaluation is detailed in Section 4.8 *Pre-procedure Care and Evaluation*.

8.1 Measurement of Tumor Response Using RECIST 1.1 Criteria

The primary objective of this study is to determine the disease control rate of transarterial chemoperfusion treatment with cisplatin, metothrexate and gemcitabine in patients with unresectable MPM. Tumor response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [19]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

8.1.1 Definitions

Evaluable for Objective Response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or

unequivocal progression of the lesions.

8.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions that are situated in a previously irradiated area are considered measurable in this protocol.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters.

If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Not acceptable for tumor evaluation in this study.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters

for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible

'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

8.1.4 Response Criteria for Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.1.5 Response Criteria for Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and

normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel or principal investigator.

8.1.6 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be

reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

8.1.7 Duration of Response

Duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

8.2 Measurement of Tumor Response Using Modified RECIST Criteria for Mesothelioma

The above mentioned RECIST 1.1 criteria a well-established tool of tumor response assessment. However, MPM most commonly grows as a rind around the pleural surface and the selection of measurement sites in MPM is difficult, and without further definition of the method of measurement, the RECIST 1.1 criteria could be applied differently by different investigators.

Byrne and Nowak developed a Modified RECIST criteria for mesothelioma [1] which is specifically designed to address the unique growth pattern of MPM and it is better suited for response assessment in this disease.

The modified RECIST criteria for mesothelioma [1] is using contrast enhanced CT scans of the chest. Where CT is contraindicated MRI may be used. At the level of the pleura, tumor thickness perpendicular to the chest wall, spine or mediastinum is measured in 2 positions at 3 separate levels on transverse cuts of CT scans. The sum of six measurements defines a pleural unidimensional measure. Transverse cuts, at least 1 cm apart and related to anatomical landmarks in the thorax, are chosen to allow reproducible assessment at later time points. If measureable tumor is present, transverse cuts in the upper thorax, above the level of division of the main bronchi are preferred. Nodal, subcutaneous, and other bidimensionally measurable lesions are measured unidimensionally as per the RECIST 1.1 criteria. Unidimensional measurements are added to obtain the total tumor measurement.

Modified RECIST criteria for pleural mesothelioma are as follows:

• Complete Response: Complete response (CR) is defined as the disappearance of all target
lesions with no evidence of tumor elsewhere.

• Partial Response: Partial response is defined as at least a 30% reduction in the total tumor
measurement.

• Stable Disease: Stable disease is defined as subjects who fulfilled the criteria for neither PR
nor PD.

• Progressive Disease: Progressive disease is defined as an increase of at least 20% in the total tumor measurement over the nadir measurement, or the appearance of one or more new
lesions.

8.3 Overall Survival

Overall survival is defined as the time between the date of treatment and the date of death due to any cause. A subject who has not died will be censored at the last known alive date. Overall survival will be followed continuously while subjects are on the study drug and every 2 months via inperson or phone contact after subjects discontinue the study drug.

8.4 Progression Free Survival

Progression free survival is defined as the time from the date of treatment to the date of the first documented tumor progression, as determined by the investigator (per

modified RECIST criteria as detailed in Section 8.2), or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.

8.5 Evaluation of Safety

8.5.1 Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for Adverse Events and Serious Adverse Event reporting. A copy of the CTCAE Version 4.03 can be downloaded from the NCI Cancer Therapy Evaluation Program home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.03.

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. CTCAE is a descriptive terminology for AE reporting. A grading (severity) scale is provided for each AE term. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

8.5.2 Serious Adverse Events

Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:
1) Death.
2) A life-threatening adverse drug experience.
3) Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

It is important to distinguish between serious criteria and severity grade of an AE. Severity is a measure of intensity (see Section 8.5.1) whereas seriousness is defined by the criteria as listed above in this Section. A Grade 3 severity AE is not necessarily considered an SAE whereas a Grade 2 AE resulting in a hospital admission would be considered an SAE.

8.5.3 Safety Data Collection

AEs will be collected throughout the treatment period from the time of the first transarterial chemoperfusion treatment until 30 days after the last chemoperfusion treatment.

At baseline evaluation, a medical history will be obtained to capture relevant underlying conditions. The baseline examination also includes physical examination, vital signs, ECOG performance status, medications, ECG, laboratory and imaging assessments as detailed in Section 4.7 and summarized in the Study Calendar in Section 7. The baseline evaluation should be performed within 28 days of the first chemoperfusion treatment. Similar to the baseline evaluation, patients will be evaluated before each chemoperfusion treatment in every 4 weeks as detailed in Section 4.8 and summarized in the Study Calendar in Section 7. Pre-procedure evaluation takes place on the day of each chemoperfusion treatment. Toxicity assessments will also be performed during the chemoperfusion treatment. Subjects who discontinue study treatment for reasons detailed in Section 4.12 must continue to be followed for collection of toxicity data for 30 days.

Incidences of AEs will be summarized by system organ class, preferred term, and severity (grading per CTCAE v. 4.03). Each patient will be counted only once within a system organ class or a preferred term by using the AEs with

the highest severity grade within each category. AEs will also be summarized by system organ class, preferred term, and relationship to treatment (drugs, procedure, device, or unrelated). AEs may be considered related to more than one of the causalities listed. AE onset will be shown relative (in number of days) to the day of the first study treatment

8.5.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: 'What health problems have you hadsince the previous visit/you were last asked?', or revealed by observation will be collected and recorded. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.5.5 Adverse Events Based on Examinations and Tests

The results from protocol mandated vital signs, laboratory tests and imaging results will be summarized in the clinical study report. Any laboratory value, vital sign that is clinically significant or meets the definition of an AE should be reported. Abnormal laboratory values, vital signs or test results that do not induce clinical signs/symptoms or require therapy, will not be considered clinically significant and will not be reported as AE. Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE.

8.5.6 Causality Collection

The principal investigator will assess causal relationship between investigational transarterial chemoperfusion treatment and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?' The principal investigator may discuss this question with co-investigators involved in this study.

8.5.7 Interpretation of Causality

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug:

• Time course of exposure to suspect drug.

Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

• Consistency with known drug profile.

Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

• Dechallenge experience.

Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
• No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
• Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Rechallenge is generally not recommended. It may be utilized only in questionable cases and only if patient safety is not jeopardized.
• Laboratory tests.
A specific laboratory investigation (if performed) has confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of the above mentioned factors exist. In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

8.6 Evaluation of Quality of Life

Patient-reported symptoms will be assessed using the modified version of the Lung Cancer Symptom Scale for Mesothelioma questionnaire [18](Appendix D).

This is a 7-question questionnaire, which covers the most common issues that can arise in patients with MPM, such as cough, chest pain, shortness of breath, etc. The questionnaire is available in English and Spanish.

The questionnaire will be completed prior to the first chemoperfusion treatment and in every 4 weeks before each additional chemoperfusion treatment. Subjects who discontinue study treatment for reasons detailed in Section 4.12 will be assessed using the questionnaire 4 weeks after the last chemoperfusion treatment. A patient is expected to complete the above questionnaires only when a translation is available in a language in which the patient is fluent.

9. ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Protocol and Regulatory Compliance

The Principal Investigator has primary responsibility for the study The Principal Investigator must conduct the study according to this protocol.

The study must be conducted by all Investigators in compliance with Good Clinical Practices (GCP) as defined as described in the U.S. FDA Code of Federal Regulations 21 CFR 312 (Investigational New Drug Application), 21 CFR 50 (Protection of Human Subjects), 21 CFR 54 (Financial Disclosure by Clinical Investigators), 21 CFR 56 (Institutional Review Boards) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines (Guideline to Good Clinical Practice).

The Principal Investigator of this study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol.

All protocols include a Data Safety Monitoring Plan (DSMP) and procedures for its implementation commensurate with the risk and complexity of the study. The DSMP must include a structured adverse event determination, monitoring and reporting system, including standardized forms and procedures for referring and/or treating subjects experiencing adverse events.

The Principal Investigator of this study will have primary responsibility for ensuring that the protocol is conducted as approved by the Scientific Review Committee of Moffitt Cancer Center and IRB. The Principal Investigator will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to a DSMP and/or to the Protocol Monitoring Committee (PMC) and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

9.2 Document Audits and Monitoring

Data will be captured in Oncore, Moffitt Cancer Center's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

The Protocol Monitoring Committee (PMC) monitors its assigned ongoing research protocols monthly for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC upon review of any agenda item may approve the study for continuation, require revisions, suspend or close a protocol.

Investigators of studies which are designed to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study.

9.3 Adverse Event Recording and Reporting

Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. A more detailed definition of AEs can be found in Section 8.5.1.

Adverse events should only be recorded by an investigator or by a health-care provider qualified by training and experience. Patients should be asked in an open-ended manner about the occurrence of AEs.

AEs will be collected throughout the treatment period from the time of the first transarterial chemoperfusion treatment and up to and including the 30-day follow-up period after the last chemoperfusion treatment. All ongoing and any new AE identified during the 30 calendar days follow up period after last chemoperfusion treatment must be followed to resolution.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A list of adverse events that have occurred or might occur can be found in Section 5 and Appendix E, F and G (Pharmaceutical Information). A copy of the CTCAE Version 4.03 can be downloaded from the NCI Cancer Therapy Evaluation Program home page (http://ctep.cancer.gov).

AEs will be listed by patient ID number. Deaths and other SAEs will be listed and summarized by patient ID number and treatment duration. Additionally, AEs leading to discontinuations will be listed separately. Incidence of AEs will be summarized by preferred term, maximum grade reported, and relationship to study treatment.

It is the Investigator's responsibility to report serious adverse events or pregnancy occurring during the treatment period or within 30 days following cessation of treatment, to the regulatory agencies and Institutional Review Board/ Independent

Ethics Committee as defined by policies and requirements (Table 1).

Table 1. Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Transarterial Chemoperfusion Treatment

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312) **NOTE:** Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64) An adverse event is considered serious if it results in **ANY** of the following outcomes: 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).
ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the IRB within the timeframes per IRB policies and requirements.

9.4 Protocol Amendments

Any changes to this protocol will be initiated by the investigators or by the Regulatory Sponsor (Moffitt cancer Center) as a protocol amendment. The Investigator must submit the amendment to the IRB, with a revised Informed Consent Document if applicable. The Investigator must receive written approval from the IRB before the amendment may take effect.

9.5 Regulatory Binder

To be in compliance with Good Clinical Practice, the Investigator must maintain accurate, complete, and organized documentation supporting the conduct of the study. This documentation includes, but is not limited to, the following: study personnel's qualifications and training, IRB approvals and communications, communications with the Regulatory Sponsor, Site Signature & Responsibility Log, laboratory accreditations and reference ranges, and Informed Consent Documents (copies of IRB approved versions, signed/dated originals, or copies for all enrolled patients).

9.6 Informed Consent

Prior to the performance of any protocol-specific procedures, informed consent must be obtained and documented by the use of a written Informed Consent Document approved by the IRB. The Informed Consent Document must be signed and dated by the patient or by the patient's legally authorized representative and by the person conducting the informed consent discussion. The Informed Consent Document must fulfill the requirements as contained in the U.S. Code of Federal Regulations (21 CFR 50.25), the ICH guidelines, and the Declaration of Helsinki. The Informed Consent Document must be written in a language understandable to the patient or to the representative.

A signed and dated copy of the Informed Consent Document must be given to the person signing the document. The original must be retained by the Investigator with the study documentation and be available for inspection by persons conducting an audit of the study.

Modifications to this template may be made by study site personnel to be in compliance with national, regional (e.g., state) or local laws and/or institutional requirements.

9.7 Institutional Review Board/Independent Ethics Committee

The protocol, Informed Consent Document, patient recruitment procedures (e.g., advertisements), information about payments and compensation available to patients, and any amendments must be approved by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) in compliance with current regulations of the U.S. FDA, ICH guidelines, and any country-specific regulations. Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates. The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

9.8 Patient Confidentiality

The Investigators must ensure that the patient's confidentiality is maintained. Patient medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Patients should be identified only by their initials and protocol-assigned patient ID number. For those patients whose surgical specimen is processed and read by the central pathology laboratory, the patient's billing information will be requested by this laboratory and will not be shared with the sponsor or any of its affiliates or representatives.

Study personnel should follow the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

All clinical information is confidential, but data generated for this study must be available for inspection on request to representatives of the U.S. FDA, other national or local regulatory or health authorities and the associated IRB.

All records must be kept in a secured area.

9.9 Curriculum Vitae and Medical Licenses

The Principal Investigator is responsible for ensuring that the study is being conducted by qualified personnel. Documentation of these qualifications must be maintained within the Regulatory Binder, and includes the following:

- **Curriculum Vitae (CV):** CVs for the Principal Investigator and all Sub-investigators listed in this study protocol must be signed and dated. These CVs must show affiliation with the institution conducting the study and be current within two years of the personnel initiating their participation in the study.

- **Medical Licenses:** Medical licenses (physicians, physician assistants, nurses) listed in this study must be valid according to the regulations of the Florida Board of Medicine and the regulations of the Moffitt Cancer Center, and copies are maintained in the Human Resources Office of the Moffitt Cancer Center during the entire period of the person's participation in the study.

9.10 Financial Disclosure

The Financial Disclosure process for Investigator Initiated studies outlined in Moffitt Policy MRI-S.CRO.73 will be followed. Financial Disclosure forms will not be utilized for this Investigator Initiated trial. The assigned regulatory specialist will work with corporate compliance to ensure proper documentation in Oncore of any significant financial interests that may exist.

10. DATA MANAGEMENT AND RECORD KEEPING

Data will be maintained by the Moffitt Cancer Center.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design and Sample Size Justification

From historical data [20] we will consider a rate of 23% for response rate (either complete response or partial response evaluated by modified RECIST for mesothelioma) as not warranting further study. We will use 45% for disease control rate as a promising result to pursue further study. Using Simon's two-stage minimax [21] design with 10% type I error rate and 10% type II error rate, 18 patients (including patient from the lead in safety cohort) will be enrolled and will be evaluated in the first stage of the trial. If 4 or less of the patients respond to the therapy (CR or PR or SD), the treatment will be stopped. If 5 or more patients respond, 14 additional patients (a total of 32 patients per group) will be enrolled. If a total number of responders (CR or PR or SD) are greater than or equal to 11, the null hypothesis will be rejected and the treatment is considered "promising" for further study. The actual type I error rate and power are 8.8% and 90.1%, respectively. The expected sample size under the null hypothesis (i.e., a disease control rate of 23%) is 23.62.

11.2 Accrual Rate

We expect that a total of 10 ~ 15 patients will accrued per year. Thus, it will take no more than 3 years to complete patient accrual.

11.3 Stratification Factors

No stratification factor is considered in this study.

11.4 Analysis of Primary and Secondary Endpoints

The primary endpoint of this study is to estimate the response rate (either partial or complete response). The one-sided and two-sided 95% confidence intervals by Atkinson and Brown [22] will be reported, which accounts for the nature of two-stage design. The secondary endpoints include OS and PFS, which are estimated by the Kaplan-Meier method [23]. Point-wise 95% confidence intervals for survival curves and cumulative incidence curves were computed using log-log transformation. The association of these time-to-events data with other covariates will be examined by the Cox proportional hazards regression model [24]. For all subjects, descriptive statistics (median, range for continuous variables and frequency and proportion for categorical variables) is utilized to summarize patients' demographic and clinical variables.

All statistical analyses and summaries will be performed by a statistician using SAS statistical software (version 9.3).

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

Cockcroft - Gault Formula

For serum creatinine concentration in mg/dL:

$$\text{CrCl} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ (\text{if female}),\ \text{or} \times \mathbf{1.0}\ (\text{if male})}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}\ (\text{mL/min})$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ (\text{if female}),\ \text{or} \times \mathbf{1.0}\ (\text{if male})}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ (\mu mol/L)}\ (\text{mL/min})$$

[a] age in years, weight (wt) in kilograms.
Source: Cockcroft and Gault 1976.

APPENDIX C

Guidance on Contraception

Investigators are expected to communicate the importance of pregnancy prevention because of the increased potential for an adverse reproductive outcome. The investigator shall describe the length of time that strict precautions against pregnancy must be observed and provide guidance on the use of appropriate methods for sexually active subjects and their partners. Women and men who are not capable of reproduction or choose to be abstinent shall be exempt from following the pregnancy prevention requirements specified below. All subjects shall be counseled on pregnancy prevention and follow pregnancy testing requirements as specified in the protocol.

1. Duration of Mandatory Contraception

The duration of mandatory contraception is based on clearance of the investigational drug (5 half-lives after treatment completion). For males, an additional 90 days is required to complete turnover of drug-exposed sperm. For women, an additional 30 days is required to complete an ovulatory cycle.

2. Calculation of Duration of Mandatory Contraception

Males: (Duration of treatment) + (5 half-lives of the investigational drug) + (90 days)

Females: (Duration of treatment) + (5 half-lives of the investigational drug) + (30 days)

3. Contraceptive Methods

3.1 Highly Effective Methods of Contraception

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. Women of child bearing potential (WOCBP) and female partners of male subjects who are WOCBP (unless the male is azoospermic), are expected to use one of the highly effective methods of contraception listed below:

1) Male condoms with spermicide
2) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena
3) IUDs, such as ParaGard
4) Tubal ligation
5) Vasectomy

Studies that administer drugs known to be teratogenic or drugs that have not undergone requisite preclinical testing for teratogenicity require two forms of contraception for both WOCBP and female partners of male subjects who are WOCBP (unless the male is azoospermic). One method must be highly effective and the second method may also be highly effective or selected from the list of other contraceptive methods in Section B. WOCBP are exempt from this requirement if a commitment to abstinence is made.

3.2 Other Contraceptive Methods

1) Diaphragm with spermicide
2) Cervical cap with spermicide
3) Vaginal sponge
4) Male condom without spermicide
5) Progestin only pills
6) Female condom (A male and a female condom must not be used together.)

3.3 Hormone Based Methods of Contraception

The treating physician, who must consider a recommendation from the relevant clinical pharmacologist, must agree that the use of a hormone-based contraceptive is safe and efficacious for WOCBP. A drug-drug interaction study should have been completed, if appropriate. Or there must be compelling evidence to substantiate that the investigational product(s) or concomitant medications will not adversely affect hormone exposures such that efficacy might be compromised or present additional risk.
Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving drug.

3.4 Abstinence

Abstinence is an acceptable form of contraception for all study drugs. It is not necessary to use a second method of contraception when abstinence is elected. Subjects who choose abstinence must continue to have pregnancy tests, as specified. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego abstinence.

3.5 Methods of Contraception with Insufficent Data to Support Effectiveness

No method
Withdrawal
Rhythm
Spermicide alone

APPENDIX D

Mesothelioma Symptom Scale Questionnaire

Directions: Please rate each of your symptom on the scales circling one number in each scale which best describe the severity of your symptom in question during the LAST 24 HOURS.

1. How much coughing do you have?

0	1	2	3	4	5	6	7	8	9	10
None										Constant cough

2. How much chest pain do you have?

0	1	2	3	4	5	6	7	8	9	10
None										Pain as bad as it could be

3. How much shortness of breath do you have?

0	1	2	3	4	5	6	7	8	9	10
None										As much as it could be

4. How much fatigue do you have?

0	1	2	3	4	5	6	7	8	9	10
None										As much as it could be

5. How good is your appetite?

0	1	2	3	4	5	6	7	8	9	10
Very good										As bad as it could be

6. How much has mesothelioma affected your usual activities?

0	1	2	3	4	5	6	7	8	9	10
Not at all										Unable to perform usual activities

7. How would you rate your quality of life today?

0	1	2	3	4	5	6	7	8	9	10
Very high										Extremely low