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Cover Page for Protocol

Sponsor Name	Ferring Ventures Limited
Official Title of the Study	A Phase 3, Open-Label, Randomized, Parallel Group Study to Evaluate the Efficacy and Safety of Intrapleural Administration of Adenovirus-Delivered Interferon Alpha-2b (rAd-IFN) in Combination with Celecoxib and Gemcitabine in Patients with Malignant Pleural Mesothelioma
NCT Number	NCT03710876
Date of Document	11 December 2023

CLINICAL STUDY PROTOCOL

A Phase 3, Open-Label, Randomized, Parallel Group Study to Evaluate the Efficacy and Safety of Intrapleural Administration of Adenovirus-Delivered Interferon Alpha-2b (rAd-IFN) in Combination with Celecoxib and Gemcitabine in Patients with Malignant Pleural Mesothelioma

Study Drugs: Nadofaragene firadenovec (Recombinant adenovirus vector containing the human interferon alpha-2b gene: rAd-IFN), celecoxib, and gemcitabine

Protocol Number: rAd-IFN-MM-301

EudraCT Number: 2017-003169-82

IND Number: 13854

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Version 1.0: 26 February 2018
Version 2.0: 12 June 2018
Version 3.0: 10 September 2018
Version 4.0: 14 August 2019
Version 5.0: 20 May 2020
Version 6.0: 28 April 2021
Version 7.0: 13 July 2023
Version 8.0: 11 December 2023

SIGNATURE PAGE

STUDY TITLE: A Phase 3, Open-Label, Randomized, Parallel Group Study to Evaluate the Efficacy and Safety of Intrapleural Administration of Adenovirus-Delivered Interferon Alpha-2b (rAd-IFN) in Combination with Celecoxib and Gemcitabine in Patients with Malignant Pleural Mesothelioma

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature PPD Digitally signed by PPD Date

PPD
Consultant Medical Advisor
Trizell, Ltd.

PPD Digitally signed by PPD Date: 2023.12.12 15:47:32 Z

PPD
Consultant Statistician
Peter Treasure Statistical Services, Ltd.

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Trizell to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Trizell and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Trizell, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

_____

_____

_____

Investigational Site/Address

SYNOPSIS

TITLE: A Phase 3, Open-Label, Randomized, Parallel Group Study to Evaluate the Efficacy and Safety of Intrapleural Administration of Adenovirus-Delivered Interferon Alpha-2b (rAd-IFN) in Combination with Celecoxib and Gemcitabine in Patients with Malignant Pleural Mesothelioma

PROTOCOL NUMBER: rAd-IFN-MM-301

STUDY DRUGS: Nadofaragene firadenovec (Recombinant adenovirus vector containing the human interferon alpha-2b gene: rAd-IFN), celecoxib, and gemcitabine

PHASE: 3

INDICATION: Malignant pleural mesothelioma (MPM)

OBJECTIVES:

The primary objective of this study is to compare the overall survival (OS) associated with rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen.

The secondary objectives of this study are:

- To compare between rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen, with respect to:
  - Survival rate at 12 months and every 6 months thereafter;
  - Progression-free survival (PFS);
  - Best response (complete response, partial response, or stable disease); and
  - Safety of rAd-IFN; and
- To evaluate rAd-IFN, when administered with celecoxib and gemcitabine, in a sub-set of patients with MPM who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen, with respect to viral shedding and biodistribution.

The exploratory objectives of this study are:

- To compare between rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen, with respect to:
  - Health-related Quality-of-Life,
  - The relationship between immunological status and response to treatment, and
  - Biocorrelates of response to treatment.

POPULATION:

The study population is patients with MPM and confirmed epithelioid or biphasic histology (if biphasic, histology must be predominantly [≥50%] epithelioid) who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen.

STUDY DESIGN AND DURATION:

The study is an open-label, randomized, parallel group study conducted in patients with MPM and confirmed epithelioid or biphasic histology (if biphasic, histology must be predominantly [≥50%] epithelioid) who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen.

Screening assessments must be completed within 28 days prior to Study Day 1, and eligible patients will be randomized to either:

1. Treatment group: rAd-IFN (Study Day 1) + celecoxib (Study Days 1 to 14) + gemcitabine (Study Days 14 and 21 [i.e., Days 1 and 8 of the first gemcitabine treatment cycle], gemcitabine will be administered on a 21-day cycle, unless the cycle is modified due to toxicity/delay, and repeated every 3 weeks until disease progression/early termination [ET]); or
2. Control group: celecoxib (Study Days 1 to 14) + gemcitabine (Study Days 14 and 21 [i.e., Days 1 and 8 of the first gemcitabine treatment cycle], gemcitabine will be administered on a 21-day cycle, unless the cycle is modified due to toxicity/delay, and repeated every 3 weeks until disease progression/ET).

An extension to the Screening Period will be permitted on a case-by-case basis following discussion between the Investigator, the Medical Monitor, and/or the Sponsor. The reason(s) for the extension is to be clearly documented.

The target interval between randomization and Study Day 1 should be up to 7 days and no greater than 14 days. Any extension beyond 14 days will be considered on a case-by-case basis, following discussion between the Investigator, Medical Monitor, and Sponsor.

Treatment Phase

Patients randomized to receive rAd-IFN (treatment group) will have an intrapleural catheter (IPC) or similar device either previously in place or inserted for the study, permitting drug administration to an accessible pleural space. The rAd-IFN will be diluted to a volume of 25 mL using sterile

normal saline and will be administered directly to the pleural space via the IPC or similar device. The IPC or similar device will then be flushed with up to 20 mL of sterile normal saline.

Patients will receive gemcitabine until disease progression/ET. All adverse events will be captured from the time of the main study's informed consent through 30 days after the last dose of study treatment (rAd-IFN, celecoxib, and gemcitabine). All treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) will be followed until resolution or stabilization.

Clinical Follow-Up Phase

Following disease progression/ET, patients in the rAd-IFN treatment group will be followed every 6 months (±14 days) for survival and safety for up to 5 years after receiving the first dose of rAd-IFN, assuming consent has not been withdrawn. All previously recorded TEAEs and SAEs will be followed until resolution or stabilization. Patients in the control group will not continue in the clinical Follow-up phase and study participation will conclude after end of study treatment.

Discontinuation of Screening and Enrollment Into the Study

The study opened to recruitment in January 2019 and was scheduled to complete recruitment by May 2021, with a target of approximately 300 patients. As of April 2021, a total of 53 patients have been randomized to treatment, of whom 30 have discontinued the study. After careful consideration and a thorough evaluation of available options, Trizell has decided to discontinue screening and enrollment into the study, while continuing to treat and collect study data from randomized patients as per the Schedule of Procedures.

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DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Patients randomized to the treatment group will receive rAd-IFN (3×10^{11} viral particles) on Study Day 1, diluted to a total volume of 25 mL using sterile normal saline and administered into the pleural space via an IPC or similar device. The IPC or similar device will then be flushed with up to 20 mL of sterile normal saline.

All study patients (treatment and control) will receive:

- Celecoxib administered at a dose of 400 mg twice daily orally on Study Days 1 to 14; and
- Gemcitabine starting on Study Day 14, using the following treatment regimen: 1250 mg/m^2 administered intravenously on Days 1 and 8 of a 21-day gemcitabine cycle, unless the cycle is modified due to toxicity/delay, and continued every 3 weeks until disease progression/ET.

ENDPOINTS:

The primary endpoint is OS, defined as time to death (from any cause) from randomization.

Secondary endpoints include efficacy and safety endpoints.

The secondary efficacy endpoints are:

- To evaluate survival rate at 12 months, defined as the number of deaths (from any cause) at 12 months from randomization, and every 6 months thereafter;
- To evaluate PFS, defined as the time from randomization to the time when the modified Response Evaluation Criteria in Solid Tumors 1.1 criteria for disease progression are first met, or when death from any cause occurs; and
- To evaluate best response, defined as the best response after randomization (complete response, partial response, or stable disease).

The secondary safety endpoints are:

- To evaluate the number of patients with Common Terminology Criteria for Adverse Events Grade 3 or 4, and
- To evaluate post-treatment levels of rAd-IFN-related viral DNA in biological samples collected up to 28 days after Study Day 1 in a sub-set of patients.

The exploratory efficacy endpoints are:

- Change in total score and individual components of the EQ-5D-5L and Lung Cancer Symptom Scale-mesothelioma (patient and observer) from baseline (randomization) to each successive cycle of gemcitabine,
- Correlation between the presence of adenovirus type 5 neutralizing antibodies prior to treatment and survival (death from any cause),
- Correlation between pre- and post-treatment levels of serum mesothelin and treatment outcomes, and
- Correlation between pre- and post-treatment levels of serum fibulin-3 and treatment outcomes.

SAFETY VARIABLES:

Safety assessments will include the assessment of adverse events including adverse events of special interest, as well as physical examinations, vital sign measurements, clinical laboratory assessments, and electrocardiographic data through electrocardiogram.

STATISTICAL ANALYSES:

The primary analysis of the primary endpoint is a comparison of the OS curves between the 2 treatment groups using a log-rank test. A Cox proportional hazards model with treatment as an explanatory variable will be used to assess the magnitude of the treatment difference in OS. The hazard ratio and the associated 95% confidence interval obtained from the Cox proportional hazards model will be presented.

The median OS and the 95% confidence interval for each treatment group will be estimated using the Kaplan-Meier method and summarized by treatment group. Plots of the Kaplan-Meier curve of OS will be presented by treatment group.

Secondary analyses of the primary endpoint will include a comparison of the survival rates at various time points since randomization.

Secondary time-to-event endpoints will be analyzed in the same manner as the primary efficacy endpoint.

Categorical efficacy endpoints will be summarized and compared between groups using Fisher's exact test.

The nature, incidence, severity, relatedness, expectedness, seriousness, and outcome of TEAEs will be summarized by treatment group for safety analyses.

SAMPLE SIZE DETERMINATION:

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It is anticipated that approximately 44 events (equivalent to 89% of the planned 50 enrolled patients) will be observed 24 months after the last patient is randomized. The final analysis of the study will be conducted after the forty-fourth event (death) or 30 months after the last patient is randomized, whichever occurs first.

DATA AND SAFETY MONITORING BOARD:

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to monitor safety, efficacy, and study integrity. All aspects of the DSMB's scope of review and procedures will be detailed in a DSMB charter.

SITES: Up to 45 sites globally

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
Ad5	Adenovirus type 5
Ad.muIFN-β	Adenoviral vector containing the mouse interferon beta gene
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice daily
CD	Cluster of differentiation
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
COX	Cyclooxygenase
CRA	Clinical Research Associate
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EPD	Extended pleurectomy/decortication
EPP	Extrapleural pneumonectomy
ET	Early termination
FAP	Familial adenomatous polyposis
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IFN-α2b	Interferon alpha-2b
IFN-β	Interferon beta
IFN-γ	Interferon gamma
IL	Interleukin
INR	International normalized ratio
IPC	Intrapleural catheter
IRB	Institutional Review Board

Abbreviation	Definition
IRT	Interactive Response Technology
LCSS-Meso	Lung Cancer Symptom Scale-mesothelioma
MOS	Median overall survival
MPM	Malignant pleural mesothelioma
nAb	Neutralizing antibody
NMIBC	Non-muscle invasive bladder cancer
NSAID	Nonsteroidal anti-inflammatory drug
OS	Overall survival
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PGE2	Prostaglandin E2
QoL	Quality-of-Life
rAd-IFN	Recombinant adenovirus vector containing the human interferon alpha-2b gene
rAd-IFN-β	Recombinant adenovirus vector containing the interferon beta gene
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Syn3	A clinical polyamide surfactant excipient
TEAE	Treatment-emergent adverse event
Th1	T helper type 1
TPL	Tripartite leader
ULN	Upper limit of normal
US	United States
vp	Viral particles
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

Malignant pleural mesothelioma (MPM) is an aggressive tumor of the serosal surface of the thoracic cavity. Asbestos is the principal carcinogen associated with MPM, causing up to 80% of cases, although other agents, such as simian virus 40, may also be implicated in the disease etiology. Estimates of the annual incidence of MPM range from 8 to 29 cases per million people in the population.[1] The annual incidences in Europe and the United States (US) are 18 and 15 cases per million people in the population, respectively.[2] There are approximately 3000 and 5000 new cases per year in the US and Europe, respectively. Analysis of mesothelioma mortality recorded by the World Health Organization (WHO) between 1994 and 2008 yielded an age-adjusted mortality rate of 4.9 per million, a mean age of death of 70 years, and a male to female ratio of 3.6:1.[3]

Malignant pleural mesothelioma typically presents with shortness of breath, unexplained pleural effusion, pleural or chest pain, weight loss, and fatigue and is usually diagnosed through video-assisted thoracoscopic surgery and tumor biopsy. There are 3 major histological tumor sub-types: epithelioid, sarcomatoid, and biphasic; the proportion of each is approximately 60%, 20%, and 20%, respectively.[4] Where feasible, patients with MPM are initially treated by surgical resection of the tumor, using either extrapleural pneumonectomy (EPP) (en bloc removal of parietal and visceral pleura, involved lung, mediastinal lymph nodes, diaphragm, and pericardium) or extended pleurectomy/decortication (EPD) (removal of visceral and parietal pleura, mediastinal pleura, pericardium, and diaphragm). Both procedures leave residual tumor and are considered equally effective in "maximal cytoreduction." An analysis of 663 consecutive patients treated with EPP or EPD showed no statistical difference in survival by procedure at any stage; 5-year overall survival (OS) was 12%.[5]

Platinum plus multi-targeted anti-folate regimens are standard first-line therapy worldwide for patients with advanced or unresectable MPM and have a good performance status. The EMPHACIS trial of pemetrexed plus cisplatin, versus cisplatin alone, in chemotherapy-naïve patients with MPM who were not eligible for surgery demonstrated statistically significant improvements in response rate (41.3% versus 16.7%) and median overall survival (MOS) (12.1 versus 9.3 months) in the combination-treated patients.[6] A similar study of raltitrexed plus cisplatin, versus cisplatin alone, also showed improved response rates (23.6% versus 13.6%) and MOS (11.4 versus 8.8 months) in patients receiving combination therapy. In relapsed or refractory disease, typically a gemcitabine or vinorelbine-based regimen is used in patients with good performance status; however, there are no published Phase 3 clinical trials that have shown improvements in OS associated with second-line therapies.[7] Therefore, there remains a significant unmet need for new treatments in patients with relapsed MPM.

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adenovirus viral vector itself also elicits additional "danger signals," further potentiating anti-tumor immune responses.[14] This multi-modal approach alters the tumor microenvironment, kills tumor cells, and stimulates the innate and adaptive immune systems.

1.1 Overview of Nonclinical Studies

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1.2 Overview of Clinical Studies

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anti-tumor humoral immune responses in 7 out of 8 patients; clinical responses characterized by

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1.2.1 Celecoxib

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animals. The mechanism of action of celecoxib is believed to be related to inhibition of cyclooxygenase (COX)-2, which is expressed at high levels in inflamed tissues, where it is induced by mediators of inflammation. It also plays physiological roles in a limited number of tissues, including the female reproductive tract, the kidney, and possibly the vascular endothelium. Celecoxib is indicated in adults for the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. In some regions, it is also indicated for the management of acute pain in adults and for the treatment of primary dysmenorrhea, as well as for juvenile rheumatoid arthritis in patients 2 years and older. In addition to its approved uses in inflammatory pain conditions, celecoxib has also been shown to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), when administered at a dose of 400 mg BID as an adjunct to usual care (e.g., endoscopic surveillance and surgery).[20]

Cyclooxygenase-2 is known to be overexpressed in various malignancies, including pancreatic, gastric, prostate, lung, colon, breast, liver, brain, and esophageal cancer. The mechanisms by which COX-2 inhibition results in anti-tumor activity include direct inhibition of tumor cell growth, blockade of angiogenesis, suppression of apoptosis, and decreased carcinogenic metabolite production.[21] In addition to the observed anti-tumor effects of COX-2 inhibition, prostaglandins derived from arachidonic acid through the COX enzymes have very potent immunosuppressive properties, particularly prostaglandin E2 (PGE2). Prostaglandin E2 has been shown to inhibit T-cell proliferation and interferon gamma (IFN-γ) and interleukin (IL)-2 production, while enhancing IL-4 and IL-10 production, thereby promoting a T helper type 2 response over a Th1 anti-tumor response. Furthermore, PGE2 has been shown to prevent the maturation and ability of dendritic cells to present antigen and to produce IL-12 and IFN-γ.[22]

Human mesothelioma tumors have been shown to overexpress COX-2, and high levels of COX-2 protein have been demonstrated to be a prognostic factor indicating poor outcome in this tumor, suggesting that COX-2 may contribute to the pathogenesis of malignant mesothelioma.[23,24] Blockade of COX-1 and/or COX-2 has some direct anti-proliferative effects on human mesothelioma cell lines and has been reported to restore depressed lymphokine-activated killer cell activity *ex vivo*.[25]

The potential interaction between immunotherapy and COX-2 inhibition has been evaluated in a mouse model of MPM. In these experiments, mice were injected with MPM cells in the flank region. When flank tumors were established, treatment with a combination of COX-2 inhibition and Ad-IFN resulted in complete eradication of tumors.

Celecoxib 400 mg BID has been studied in patients with FAP. In a study of celecoxib administered for 6 months to patients with FAP, administration of a dose of 400 mg BID was well tolerated, and there were no significant differences in the incidence of any adverse event between the celecoxib groups (100 mg BID and 400 mg BID) and the placebo group.[20]

Based on the potential role of COX-2 in the pathogenesis and prognosis of MPM and the encouraging nonclinical data supporting the beneficial effects of COX-2 inhibition combined with immunotherapy, celecoxib was included in the second clinical study of rAd-IFN in patients with MPM. In this study, patients received celecoxib orally at a dose of 400 mg BID for a period of 14 days, starting 3 days before the first dose of rAd-IFN. The outcomes of this study indicated that administration of rAd-IFN appeared to have an acceptable tolerability profile when given in combination with celecoxib 400 mg BID and followed by treatment with chemotherapy. Efficacy outcomes also appeared encouraging, with an MOS in the entire study population of 13 months.

1.2.1.1 Rationale for celecoxib dosing

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1.2.2 Gemcitabine

Gemcitabine is used across a range of solid tumors as a single agent or in combination with other anti-neoplastic agents. In addition, a number of nonclinical studies have indicated that gemcitabine has immuno-modulatory properties that make it an attractive agent to combine with IFN-α2b, which itself stimulates immune-mediated anti-tumor effects:

1. B-cell proliferation and antibody production in response to tumor antigens is inhibited by gemcitabine, a phenomenon that may skew anti-tumor immunity towards beneficial T-cell responses;[26,27]
2. The frequency of CD11b+GR1+ myeloid-derived suppressor cells is reduced by gemcitabine; these cells have been shown to induce tumor-associated antigen-specific CD8+ T-cell tolerance;[28]
3. Through its effects on apoptosis of established tumors, gemcitabine may enhance the dendritic cell dependent cross-presentation of tumor antigens to T-cells;[29] and
4. The range of tumor antigens eliciting cytotoxic T-lymphocyte responses *in vivo* is expanded by gemcitabine and it promotes infiltration of tumor-specific T-cells.[30]

The effects of co-administration of rAd-IFN and gemcitabine (plus cisplatin) have been studied in a mouse model of MPM. In this model, the combination of rAd-IFN and gemcitabine (plus

cisplatin) had a statistically better response than chemotherapy alone or rAd-IFN alone ($p<0.05$). All 6 mice in the combination therapy group were cured.[31]

In the second study of rAd-IFN in 40 patients with MPM, 15 patients received second-line gemcitabine (±platinum). In this cohort of second-line patients, MOS was 10 months (95% confidence interval, 4 to 21), which compares favorably with placebo response rates observed in the second-line treatment setting.[32,33] Furthermore, approximately 20% of second-line patients receiving gemcitabine-based chemotherapy were alive at 24 months, suggesting a prolonged immunologic phenomenon. While patients who received pemetrexed as a second-line therapy also demonstrated encouraging MOS (26 months; 95% confidence interval, 3 to ∞), the number of patients was small (n=7), and these patients had previously responded to pemetrexed as first-line therapy, and therefore had good response characteristics.

Although there are no approved treatments for MPM in the second-line setting, the National Comprehensive Cancer Network Clinical Practice Guidelines for MPM recommend gemcitabine as an appropriate second-line treatment.[34]

1.2.2.1 Rationale for gemcitabine dosing

Based on the known immune-modulatory properties of gemcitabine and its activity when combined with rAd-IFN in a mouse model of MPM, observed clinical outcomes in patients treated with rAd-IFN followed by gemcitabine as second-line therapy, and national guidelines supporting its use, gemcitabine has been selected as suitable second-line therapy for all patients participating in the proposed study. Given that the key comparison in the study is between patients who receive and who do not receive rAd-IFN, it is considered appropriate for all enrolled patients to receive gemcitabine. Thus, the study will not draw conclusions on the effectiveness of gemcitabine alone in the second-line setting.

1.3 Rationale for rAd-IFN Dosing

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the cycle is modified due to toxicity/delay. Biocorrelates of response to intrapleural rAd-IFN will also be evaluated.

1.4 Risk/Benefit

1.4.1 Potential Risks of rAd-IFN

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1.4.1.1 Viral shedding

In the context of providing a comprehensive risk assessment, additional monitoring will be performed during this study, notably to assess viral shedding in an initial cohort of patients prior to exposing a larger number of patients to rAd-IFN.

The 28-day sampling duration for viral shedding is based on data with a similar vector containing the IFN-β gene, where vector shedding was observed on skin at 24 days and longer in the pleural fluid of some patients. It is anticipated that some shedding may occur at and/or around the IPC or similar device site; however, available data indicate that no shedding in other biological materials is expected. The study containment processes are intended to prevent horizontal transmission from

the site of administration. The sample size for the Viral Shedding Cohort will be approximately 10 patients. Samples will be analyzed by polymerase chain reaction.

1.4.1.2 Inclusion of patients with pre-existing adenovirus neutralizing antibody titers

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[redacted]

1.4.2 Potential Benefits of rAd-IFN

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[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

1.4.3 Potential Risks and Benefits of Celecoxib

The risk/benefit balance favors inclusion of celecoxib at a dose of 400 mg BID for 14 days in the proposed Phase 3 clinical study. There is a sound scientific rationale supporting the role of COX-2 in MPM pathogenesis, and preclinical evidence from 2 mouse models supports the potential synergy of IFN-based gene therapy when administered with COX-2 inhibition. CCI

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[redacted]

In accordance with the labelled contraindications to celecoxib use, patients who i) have experienced asthma, acute rhinitis, nasal polyps, angioneurotic edema, urticaria, or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs, including COX-2 inhibitors; ii) have a history of ulcer disease or gastrointestinal bleeding; iii) have significant renal or hepatic impairment; iv) have New York Heart Association class III or IV congestive heart failure; v) have a history of myocardial infarction in the past 12 months or unstable angina; vi) have uncontrolled or poorly controlled hypertension requiring 3 or more anti-hypertensive drugs; or vii) have known hypersensitivity to celecoxib or sulfonamides will be excluded from the study, thus further reducing the likelihood of patients experiencing adverse effects relating to celecoxib treatment.

1.4.4 Potential Risks and Benefits of Gemcitabine

The risk/benefit balance favors inclusion of gemcitabine at a dose of 1250 mg/m^2 on Days 1 and 8 of a repeating 21-day cycle in the proposed Phase 3 clinical study. Data from a mouse model of MPM indicate that addition of gemcitabine to a treatment regimen of rAd-IFN and celecoxib results in a very pronounced suppression of tumor growth. In a clinical trial of rAd-IFN in MPM, patients who received second line treatment with gemcitabine showed encouraging outcomes with respect to MOS, comparing favorably to historical controls and other second line trials.

In accordance with the labelled contraindications to gemcitabine use, patients with known hypersensitivity to gemcitabine or who are breastfeeding will be excluded from the study. Patients with significantly impaired renal function, impaired hepatic function, or stage IV extrathoracic metastatic disease will also be excluded, reflecting special warnings and precautions for gemcitabine. Patients will undergo regular safety monitoring on Days 1 and 8 of each gemcitabine treatment cycle, allowing for the detection of adverse effects of treatment. Additionally, the dose of gemcitabine can be modified based on the results of safety laboratory results or observed

toxicity. Gemcitabine will be permanently discontinued in patients who develop posterior reversible encephalopathy syndrome, capillary leak syndrome, or hemolytic uremic syndrome.

1.5 Coronavirus Disease 2019

In March 2020, the Coronavirus Disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was characterized as a pandemic by the WHO. The COVID-19 pandemic continues to impact clinical studies worldwide due to quarantines, clinical site closures, travel limitations, diversion of resources, and/or general interruptions in study-specific procedures. Any impacts on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the Clinical Study Report.

If any patient is suspected of contracting COVID-19 or has a confirmed diagnosis of COVID-19, this information should be communicated to Medpace immediately. This information must be documented and recorded as an adverse event with the relevant concomitant medications prescribed clearly documented in the patient's source notes.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the OS associated with rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To compare between rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen, with respect to:
  - Survival rate at 12 months and every 6 months thereafter;
  - Progression-free survival (PFS);
  - Best response (complete response, partial response, or stable disease); and
  - Safety of rAd-IFN; and
- To evaluate rAd-IFN, when administered with celecoxib and gemcitabine, in a sub-set of patients with MPM who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen, with respect to viral shedding and biodistribution.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To compare between rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen, with respect to:
  - Health-related Quality-of-Life (QoL),
  - The relationship between immunological status and response to treatment, and
  - Biocorrelates of response to treatment.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

3.1.1 Overview

The study is an open-label, randomized, parallel group study conducted in patients with MPM and confirmed epithelioid or biphasic histology (if biphasic, histology must be predominantly [≥50%] epithelioid) who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen.

Screening assessments must be completed within 28 days prior to Study Day 1, and eligible patients will be randomized to either:

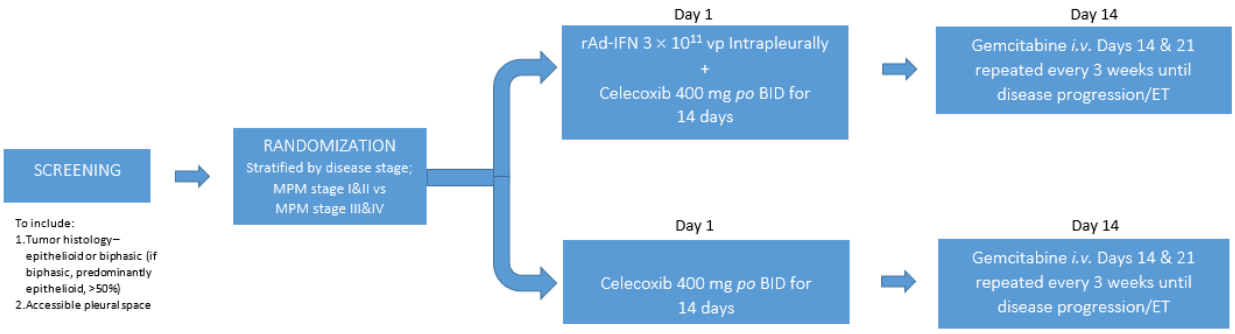
1. Treatment group: rAd-IFN (Study Day 1) + celecoxib (Study Days 1 to 14) + gemcitabine (Study Days 14 and 21 [i.e., Days 1 and 8 of the first gemcitabine treatment cycle], gemcitabine will be administered on a 21-day cycle, unless the cycle is modified due to toxicity/delay, and repeated every 3 weeks until disease progression/early termination [ET]); or
2. Control group: celecoxib (Study Days 1 to 14) + gemcitabine (Study Days 14 and 21 [i.e., Days 1 and 8 of the first gemcitabine treatment cycle], gemcitabine will be administered on a 21-day cycle, unless the cycle is modified due to toxicity/delay, and repeated every 3 weeks until disease progression/ET).

An extension to the Screening Period will be permitted on a case-by-case basis following discussion between the Investigator, the Medical Monitor, and/or the Sponsor. The reason(s) for the extension is to be clearly documented.

The target interval between randomization and Study Day 1 should be up to 7 days and no greater than 14 days. Any extension beyond 14 days will be considered on a case-by-case basis, following discussion between the Investigator, Medical Monitor, and Sponsor.

The design of the study is summarized in Figure 1.

Figure 1. Study Schematic



BID = twice daily; ET = early termination; i.v. = intravenous; MPM = malignant pleural mesothelioma; po = oral; rAd-IFN = recombinant adenovirus interferon alpha-2b; vp = viral particles.

Treatment Phase

Patients randomized to receive rAd-IFN (treatment group) will have an IPC or similar device either previously in place or inserted for the study, permitting drug administration to an accessible pleural

space. The rAd-IFN will be diluted to a volume of 25 mL using sterile normal saline and will be administered directly to the pleural space via the IPC or similar device. The IPC or similar device will then be flushed with up to 20 mL of sterile normal saline.

Patients will receive gemcitabine until disease progression/ET. All adverse events will be captured from the time of the main study's informed consent through 30 days after the last dose of study treatment (rAd-IFN, celecoxib, and gemcitabine). All TEAEs and SAEs will be followed until resolution or stabilization.

Clinical Follow-Up Phase

Following disease progression/ET, patients in the rAd-IFN treatment group will be followed every 6 months (±14 days) for survival and safety for up to 5 years after receiving the first dose of rAd-IFN, assuming consent has not been withdrawn. All previously recorded TEAEs and SAEs will be followed until resolution or stabilization. Patients in the control group will not continue in the clinical Follow-up phase and study participation will conclude after end of study treatment.

The study will be conducted in up to 45 sites globally.

3.1.2 Viral Shedding Cohort

A sub-set of patients randomized to the rAd-IFN treatment group will be asked to participate in the Viral Shedding Cohort to assess rAd-IFN viral vector shedding. Patients in the Viral Shedding Cohort will be required to sign an additional section of the main study informed consent form (ICF) prior to performing any viral shedding-related procedures. The Viral Shedding Cohort will include the first 10 patients randomized to the rAd-IFN treatment group who consent to participation. The evaluations will include collection of blood (for biodistribution), saliva, urine, pleural access site swab, and pleural fluid sample as indicated in the Schedule of Procedures (Table 1). The pleural fluid sample will be collected using the IPC or similar device (if the IPC or similar device is still in place). See Appendix G for pleural fluid sample collection procedure.

3.1.3 Study Duration and End of Study

The study will consist of the following periods:

- Screening Period of up to 28 days;

  An extension to the Screening Period will be permitted on a case-by-case basis following discussion between the Investigator, the Medical Monitor, and/or the Sponsor.

- 14-day treatment period with rAd-IFN (Study Day 1) + celecoxib (Study Days 1 to 14) in treatment group and celecoxib (Study Days 1 to 14) in control group;

- 21-day gemcitabine treatment cycles, unless the cycle is modified due to toxicity/delay, repeated every 3 weeks until disease progression/ET; and

- Clinical Follow-Up Visits every 6 months (±14 days) for up to 5 years:
  - Patients in the rAd-IFN treatment group will be followed for survival and safety after receiving the first dose of rAd-IFN; and
  - Patients in the control group will not continue with clinical Follow-up Visits and study participation concludes after the end of study treatment.

  Note: Under previous Protocol versions all patients were to be followed for survival and safety every 3 months, including patients who have withdrawn prior to commencing Study Day 1 treatment.

Patients will discontinue study treatment at the time of disease progression or ET (i.e., development of an unacceptable toxicity, withdrawal of consent, or termination of the study). A patient's participation in the study will conclude after the completion of clinical Follow-up Visits (rAd-IFN treatment group), end of study treatment (control group), or if the withdrawal criteria are met (see Section 4.3). The end of the study (study completion) is defined as the last visit of the last patient.

The final analysis will be conducted after the forty-fourth event (death) or at least 30 months after the last patient is randomized, whichever occurs first. The long-term safety follow-up data will be collected.

3.1.4 Discontinuation of Screening and Enrollment Into the Study

3.2 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study to monitor safety, efficacy, and study integrity. All aspects of the DSMB's scope of review and procedures will be detailed in a DSMB charter.

3.3 Stopping Rules

The DSMB may recommend that the study stop recruitment if any emergent safety issue is identified that changes the benefit/risk balance to study patients (see Section 9.2.4 for additional details).

3.4 Study Indication

The indication for this study is MPM.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Aged 18 years or older at the time of consent;
2. Able to give informed consent;
3. Has a confirmed histological diagnosis of MPM with histological type epithelioid or biphasic (if biphasic, histology must be predominantly [≥50%] epithelioid). Histological diagnosis of MPM will be confirmed centrally using specimens or slides from tumor specimens obtained at the time of initial presentation or a subsequent procedure. Central confirmation of diagnosis with immunohistochemistry will be performed, and independent central confirmation will be required for study entry;
4. Measurable disease, per modified Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 (see Section 7) for pleural mesothelioma;[42]
5. Has received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, which may have been chemotherapeutic and/or immunotherapeutic treatment regimens for MPM which included at least 1 anti-folate and platinum combination regimen;
    - Adjuvant or neoadjuvant therapy represent 1 line of therapy each;
    - Patients who have undergone primary surgical resection and/or radiation therapy to the pulmonary site are eligible to participate. For clarity, surgical resection and/or radiation therapy to the pulmonary site are not exclusionary and are not considered a line of therapy;
    - Treatment that is split between pre-surgical resection and post-surgical resection and is the same regimen will be counted as 1 regimen. Patients meeting this condition should be discussed with the Medical Monitor prior to including the patient in the study;
6. Has a pleural space accessible for IPC or similar device insertion. Patients with a previously inserted IPC or similar device may be enrolled, and the pre-existing IPC or similar device can be used for vector administration as long as it is functional and has no evidence of local infection;
7. Life expectancy ≥12 weeks in the judgement of the Investigator;
8. Eastern Cooperative Oncology Group (ECOG) status of 1 or 0;
9. Female and male patients:
    - Female patients of childbearing potential must have a negative pregnancy test upon entry into this study and agree to use a highly effective method of contraception from Screening until 1 month after the last dose of gemcitabine;
        - Highly effective methods of contraception that result in a low failure rate (i.e., <1% per year) when used consistently and correctly include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or

implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence;

- True abstinence, when in line with the preferred and usual lifestyle of the patient, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of study participation and for 1 month after the last dose of gemcitabine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation method) and withdrawal are not acceptable methods of contraception; and

- Female patients of non-childbearing potential must be either postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile upon entry into the study;
- Male patients must be either surgically sterile or agree to use a double-barrier contraception method from Screening until 6 months after the last dose of gemcitabine;
  - Where available and in accordance with local practice, male patients must be advised to seek further advice regarding cryoconservation of sperm prior to gemcitabine treatment due to the possibility of infertility after therapy with gemcitabine; and

10. Adequate laboratory values at Screening:
    - Hemoglobin ≥9 g/dL;
    - White blood cell count ≥3500/µL;
    - Absolute neutrophil count ≥1500/µL;
    - Platelet count ≥100,000/µL;
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) below the upper limit of normal (ULN). It is expected that patients receiving anticoagulation therapy will not have INR and aPTT results that fall within normal limits. It is not intended to exclude these patients and, therefore, medical discretion is permitted for patients who have clinically acceptable results in regards to their current concomitant anticoagulant therapy;
    - Aspartate aminotransferase (AST) ≤3 × ULN;
    - Alanine aminotransferase (ALT) ≤3 × ULN;
    - Total bilirubin ≤2 × ULN;
    - Estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease study equation [see Appendix B]) ≥50 mL/min/1.73 m^2; and
    - Serum albumin ≥2.5 g/dL.

4.2 Exclusion Criteria

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

1. Is "treatment-naïve" (i.e., has not received at least 1 anti-folate and platinum combination regimen);
2. Has previously received 3 or more lines of systemic chemotherapeutic or immunotherapeutic treatment. Treatment that is split between pre-surgical resection and post-surgical resection and is the same regimen will be counted as 1 regimen. Patients meeting this condition should be discussed with the Medical Monitor prior to including the patient in the study;
3. Has previously received treatment with gemcitabine;
4. Has stage IV extrathoracic metastatic disease;
5. Inadequate pulmonary function of clinical significance as per Investigator review;
6. Clinically significant pericardial effusion (i.e., as judged by the Investigator and/or requiring drainage) detected by computed tomography (CT) scan at Screening. Standard of care CT scans completed within 2 weeks prior to Screening may be used in place of the Screening CT scan on a case-by-case basis as agreed with the Medical Monitor;
7. Prior therapy(ies), if applicable, must be completed according to the criteria below prior to vector administration:
    - Cytotoxic chemotherapy, at least 21 days from last dose;
    - Non-cytotoxic chemotherapy (e.g., small molecule inhibitor), at least 14 days from last dose;
    - Monoclonal antibody, at least 30 days from last dose;
    - Non-antibody immunotherapy (e.g., tumor vaccine), at least 42 days from last dose;
    - Radiotherapy, at least 14 days from last local site radiotherapy;
    - Hematopoietic growth factor, at least 14 days from last dose; or
    - Study drug, 30 days or 5 half-lives, whichever is longer, from last dose;
8. Patient previously treated with IFNs (e.g., for chronic active hepatitis);
9. Suspected/known hypersensitivity to IFN-α2b or rAd-IFN (including any of its excipients);
10. Known hypersensitivity to celecoxib (including any of its excipients) or sulfonamides;
11. Known hypersensitivity to gemcitabine (including any of its excipients);
12. Impaired cardiac function or clinically significant cardiac disease including the following:
    - New York Heart Association class III or IV congestive heart failure;
    - Myocardial infarction within the last 12 months; and
    - Patients known to have impaired left ventricular ejection fraction per institutional standards and of clinical significance as per Investigator review;
13. Women who are pregnant or breastfeeding;

14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, depression, or psychiatric illness/social situations within the last 12 months;
15. Patients with active, known, or suspected auto-immune disease or a syndrome that requires systemic or immunosuppressive agents (oral prednisolone or equivalent at a dose of ≤10 mg per day is permitted);

    Note: patients with vitiligo, residual hypothyroidism due to auto-immune disease only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
16. History of asthma, acute rhinitis, nasal polyps, angioneurotic edema, urticaria, or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs, including COX-2 inhibitors;
17. History of ulcer disease or gastrointestinal bleeding;
18. Uncontrolled or poorly controlled hypertension (i.e., blood pressure >160/100 mmHg) requiring 3 or more anti-hypertensive drugs;
19. Heart rate corrected QT interval using Fridericia's formula >470 ms on resting 12-lead electrocardiogram (ECG);
20. Patients receiving lithium;
21. Any significant disease which, in the opinion of the Investigator, would place the patient at increased risk of harm if he/she participated in the study;
22. History of a prior malignancy for which treatment was completed <2 years prior to Screening or for which the patient has continued evidence of disease, or concurrent malignancy that is clinically unstable and requires tumor-directed treatment;
23. Has a congenital or acquired immunodeficiency, including patients with known history of infection with human immunodeficiency virus;
24. Has both serum albumin 2.5 to 3.5 g/dL and total bilirubin >1.5 × ULN;
25. History of clinically significant inflammatory bowel disease requiring systemic (parenteral) immunosuppressive therapy within 5 years prior to Screening; or
26. History of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

4.3 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient;

- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study, after commencing Study Day 1 treatment and prior to disease progression, due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the ET Visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF). Where applicable, patients in the rAd-IFN treatment group who have withdrawn from study treatment, not including those who have withdrawn prior to commencing Study Day 1 treatment, will be asked if they would agree to continue to be followed for survival and safety every 6 months (±14 days) for up to 5 years.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS AND INTRAPLEURAL CATHETER OR SIMILAR DEVICE PROCEDURES

5.1 Nadofaragene Firadenovec (rAd-IFN)

CCI

5.1.1 Formulation, Packaging, and Handling

CCI

CCI

5.1.2 Dosage and Administration

CCI

5.1.2.1 Intrapleural catheter or similar device placement

Patients with a previously inserted IPC or similar device may be enrolled, and the pre-existing IPC or similar device can be used for vector administration as long as it is functional and has no evidence of local infection.

For patients allocated to the rAd-IFN treatment group that do not have an existing IPC or similar device in situ, an IPC or similar device will be inserted under local anesthesia as an outpatient visit. Sedation and analgesia may be administered as needed for the patient's comfort.

If this is not technically feasible, an IPC or similar device may be inserted via thoracoscopy under general anesthesia. Some cases may require interventional radiology for the placement of a tunneled or non-tunneled catheter (depending on each individual case).

Patients with minimally accessible pleural space as a result of pleurodesis or prior surgery may require video-assisted thoracoscopic placement of the IPC or similar device.

In each circumstance (i.e., patients with a previously inserted or a newly inserted IPC or similar device), the correct position of the IPC or similar device will be confirmed by the Investigator or an appropriately qualified designee, in accordance with local institutional practice.

After IPC or similar device insertion (if not already in situ) and prior to vector instillation, patients will be monitored carefully for dyspnea, chest pain, infection, and rapid symptomatic re-accumulation of the malignant pleural effusion.

5.1.2.2 rAd-IFN administration via intrapleural catheter or similar device

rAd-IFN administration will be performed under sterile conditions and will include the following steps:

1. Maximally drain the pleural space prior to rAd-IFN infusion;

   Note: If the Investigator determines the pleural space cannot be drained sufficiently (i.e., to accommodate up to 45 mL of fluid [25 mL of rAd-IFN and up to 20 mL saline flush]), the patient will be withdrawn from the study.
2. Clamp the IPC or similar device after drainage is complete;
3. Attach syringe with rAd-IFN to the stop-cock;
4. Infuse rAd-IFN over 2 to 5 minutes, as tolerated by the patient;
5. Flush the IPC or similar device with up to 20 mL of sterile normal saline;
6. Clamp the IPC or similar device; and
7. Re-dress site as per standard of care.

It is recommended that the pleural space is not drained within the first 24 hours post-rAd-IFN administration, unless deemed necessary by the Investigator.

5.1.3 Intrapleural Catheter or Similar Device Removal Post-rAd-IFN Administration

At the discretion of the Investigator, the IPC or similar device may be removed at any time during the 6-hour post-rAd-IFN administration observation period or at the Study Day 2 Visit for patients in the rAd-IFN treatment group. The Investigator may keep the IPC or similar device in situ beyond the Study Day 2 Visit if required for clinical purposes.

5.1.4 Patient Preparation and Monitoring

Immediately before (within 10 minutes prior to the start time of rAd-IFN administration), during, and immediately after (within 10 minutes after the start time of rAd-IFN administration) rAd-IFN administration,

- Patients should be monitored using pulse oximetry,
- Oxygen via nasal cannula should be administered at approximately 2 L/min as required, and
- Cardiac telemetry may also be used to monitor patients as per the Principal Investigator's discretion.

These safety procedures should be continued post-rAd-IFN administration as per the Principal Investigator's or designee's discretion.

An intravenous cannula should be placed prior to rAd-IFN administration, and normal saline (or equivalent as per local institutional standards) should be administered slowly.

Analgesia may be administered as required, in accordance with local institutional standards.

Post-rAd-IFN administration,

- Body temperature will be monitored every hour (±10 minutes) for 6 hours; and
- Blood pressure, respiratory rate, pulse rate, and oxygen saturation will be measured and recorded every 15 minutes (±5 minutes) for the first 2 hours; every 30 minutes (±10 minutes) for the next 2 hours; then, every hour (±10 minutes) for the remainder of the inpatient monitoring period up to 6 hours post-rAd-IFN administration (unless further surveillance is required as per the Principal Investigator's discretion).

After 6 hours of observation, the patient can go home if vital signs and oxygen saturation are within acceptable limits, as per local institutional practice and guidelines, following assessment by the Investigator or an appropriately qualified designee. After leaving the facility, the patient may use acetaminophen or equivalent (as per local institutional standards) for the management of pyrexia, should it occur. rAd-IFN treatment group patients will return to the site to be reviewed approximately 24 hours after rAd-IFN administration (see Section 6.3.2).

In the event the patient experiences CRS, see Appendix E for details on CRS grading. Local guidelines for the management and treatment of CRS should be followed. In the absence of any such appropriate guidelines, see Appendix E for details on the therapeutic strategy for the management of CRS.

5.2 Celecoxib

All patients will take oral celecoxib 400 mg BID on Study Days 1 to 14; no celecoxib should be taken after Study Day 14. The first dose of celecoxib will be administered 1 to 2 hours prior to rAd-IFN administration (rAd-IFN treatment group) or on Study Day 1 (control group). The patient will be provided with the remainder of the 14-day treatment to be taken at home. The patient will be provided with a celecoxib diary and instructed that the next dose should be taken approximately 12 hours post-rAd-IFN administration (rAd-IFN treatment group) or approximately 12 hours after the first celecoxib dose (control group) and 400 mg orally BID, at approximately 12-hour intervals, thereafter. If the patient receives the first dose of celecoxib late on Study Day 1, such that the patient is only able to take 1 dose of celecoxib on Study Day 1, the patient must not take a celecoxib dose on Study Day 15, regardless of whether or not the patient has taken all planned celecoxib doses. If BID dosing does not occur on Study Day 1 for this reason, it will not be considered a protocol deviation.

If, during treatment with celecoxib, patients experience Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher deterioration in renal or hepatic function, appropriate measures should be taken, and celecoxib therapy should be discontinued. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. It should be noted that celecoxib may mask fever and other signs of inflammation. If the patient vomits after taking celecoxib, the patient should not replace that dose; instead, the patient should wait until the next scheduled time point to take their next scheduled celecoxib dose.

Storage and administration should be done in compliance with the instructions provided by the manufacturer.

5.3 Gemcitabine

Gemcitabine will be administered for all patients starting on Study Day 14 (gemcitabine Cycle 1 Day 1) with intravenous administration of 1250 mg/m^2 on Days 1 and 8 of a 21-day gemcitabine cycle, unless the cycle is modified due to toxicity/delay, and continued every 3 weeks until disease progression/ET.

The regimen will be administered in compliance with local clinical practice and manufacturer guidelines. Dose banding may be permitted for gemcitabine in accordance with local policy.

Gemcitabine will be permanently discontinued in patients who develop posterior reversible encephalopathy syndrome, capillary leak syndrome, or hemolytic uremic syndrome at any time in the study, and supportive measures will be implemented. Supportive measures will include blood pressure control and anti-seizure therapy for posterior reversible encephalopathy. If pulmonary effects, such as pulmonary edema, interstitial pneumonitis, or adult respiratory distress syndrome, develop at any time during the study, the Investigator should discuss with the Sponsor and consider discontinuing gemcitabine. Treatment with gemcitabine should be discontinued if there is unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity. See Appendix F for further details regarding suggested dose modification strategies for gemcitabine.

See Section 5.6 for details regarding gemcitabine treatment delay.

The use of myeloid growth factors is not prohibited; however, their use within the first 30 days after rAd-IFN administration must be discussed with the Medical Monitor and Sponsor.

Gemcitabine (1 g powder for solution) for infusion contains sodium. This should be taken into consideration by patients on a controlled sodium diet.

Storage, handling, and preparation will be done in compliance with local practice and manufacturer guidelines.

5.4 Storage and Accountability

The rAd-IFN concentrate should be stored frozen (below -60°C [-76°F]) and thawed under ambient temperature and light at the time of preparation.

An accurate and current accounting of the receipt, storage, and administration of all study drugs for each patient will be maintained on an ongoing basis by a member of the study site staff on the Investigational Product Accountability Record. Chain of custody will be documented at all stages. The study monitor will verify these documents throughout the course of the study.

5.4.1 rAd-IFN Biosafety Precautions

Adenoviruses are classified as Risk Group 2 out of the 4 Risk Group categories (European Union Directive 2000/54/EC; National Institutes of Health Recombinant DNA Guidelines 2016; WHO Laboratory Safety Manual 3rd Ed, 2004).[45,46,47] Risk Group 2 biological agents are usually associated with human disease that is rarely serious and for which preventive or therapeutic interventions are often available.[46] Although viral vectors, such as adenoviruses, may be replication deficient, there is always a risk of replication-competent viruses arising from spontaneous recombinant events. Because of this, it is recommended that vectors are handled at the same biosafety level as the parent virus from which they are derived. In the case of adenoviruses, and specifically rAd-IFN, this is Risk Group 2.[47]

All biosafety precautions and procedures required by the Institutional Biosafety Committee and/or local regulatory authorities must be observed.

Biosafety procedures and policies already established at the sites are sufficient for the management of rAd-IFN; however, the rAd-IFN Clinical Biosafety Precautions described in the current Investigator's Brochure[48] provide an overview of safety practices, safety equipment, and facility requirements that are advised during the handling, preparation, and administration of rAd-IFN and in the event of spillage.

See Section 3.3 of the Investigator's Brochure for further details related to rAd-IFN Biosafety Precautions.

5.5 Treatment Groups

Patients will be randomized to either:

- Treatment group: rAd-IFN (Study Day 1) + celecoxib (Study Days 1 to 14) + gemcitabine (Study Days 14 and 21 [i.e., Days 1 and 8 of the first gemcitabine treatment cycle], gemcitabine will be administered on a 21-day cycle, unless the cycle is modified due to toxicity/delay, and repeated every 3 weeks until disease progression/ET); or
- Control group: celecoxib (Study Days 1 to 14) + gemcitabine (Study Days 14 and 21 [i.e., Days 1 and 8 of the first gemcitabine treatment cycle], gemcitabine will be administered on a 21-day cycle, unless the cycle is modified due to toxicity/delay, and repeated every 3 weeks until disease progression/ET).

5.5.1 Treatment Compliance

rAd-IFN will be administered via the intrapleural route by the Principal Investigator or designee and recorded in the source documents and eCRF.

The first dose of celecoxib will be administered orally 1 to 2 hours prior to rAd-IFN administration (rAd-IFN treatment group) or on Study Day 1 (control group) and provided to the patient by hospital staff while in the hospital. The patient will be provided with the remainder of the 14-day treatment to be taken at home. The patient will be provided with a celecoxib diary and instructed that the next dose should be taken approximately 12 hours post-rAd-IFN administration (rAd-IFN treatment group) or approximately 12 hours after the first celecoxib dose (control group) and 400 mg orally BID, at approximately 12-hour intervals, thereafter. If the patient receives the first dose of celecoxib late on Study Day 1, such that the patient is only able to take 1 dose of celecoxib on Study Day 1, the patient must not take a celecoxib dose on Study Day 15, regardless of whether or not the patient has taken all planned celecoxib doses. If BID dosing does not occur on Study Day 1 for this reason, it will not be considered a protocol deviation. The dosing diary and unused celecoxib capsules will be returned to the site staff at the next visit to check for compliance.

Gemcitabine will be administered for all patients intravenously by site staff on a standard 3-week cycle regimen as per local clinical practice and manufacturer guidelines. This will be recorded in the source documents and eCRF. See Section 5.6 for details regarding gemcitabine treatment delay.

5.5.2 Treatment of Overdose

In the event of an overdose of rAd-IFN, gemcitabine, or celecoxib, the Investigator should contact the Medical Monitor immediately and monitor the patient for possible adverse events/SAEs.

5.6 Dose Modification and Treatment Delay

5.6.1 rAd-IFN

No dose modifications of rAd-IFN will be allowed during the study.

5.6.2 Celecoxib

Patients who develop gastrointestinal side effects considered by the Investigator to be attributable to celecoxib may be given a proton pump inhibitor or other suitable symptomatic relief at the discretion of the Investigator.

Dose modifications to celecoxib will be considered on an individual basis after discussion between the Investigator and Medical Monitor.

If, during treatment with celecoxib, patients experience CTCAE Grade 3 or higher deterioration in renal or hepatic function, appropriate measures should be taken, and celecoxib therapy should be discontinued. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

See Appendix F for further details regarding suggested dose modification strategies for celecoxib.

5.6.3 Gemcitabine

Gemcitabine dose level reductions required due to toxicity should be made following the guidelines in Appendix F.

Recommended dose modifications of gemcitabine due to hematological toxicities and adjustments related to other toxicities are also provided in Appendix F.

The following rules will be applied if any of the following gemcitabine doses are missed in the 21-day gemcitabine cycle:

- Day 1 of any cycle can be delayed by a maximum of 7 days to accommodate a maximum of 21 days between the Day 1 dose and the previous cycle's Day 8 dose;
- Day 8 of any cycle can be delayed by a maximum of 7 days to accommodate a maximum of 14 days between the Day 1 dose and the Day 8 dose of the same cycle; and
- If Day 8 of any cycle is delayed, then the Day 1 dose for the next cycle must occur at least 14 days and up to a maximum of 21 days after the previous cycle's Day 8 dose.

If the maximum delay between a scheduled dose and the next dose is greater than what is described above, then this would be considered a missed dose.

If the time required for recovery from gemcitabine toxicity is more than 21 days, consideration should be given to permanently discontinue the patient from study treatment, unless the patient is demonstrating benefit overall; in which case, the possibility of remaining on study treatment should be discussed between the Investigator, Medical Monitor, and Sponsor after review of the associated risks and benefits.

Gemcitabine will be permanently discontinued in patients who develop posterior reversible encephalopathy syndrome, capillary leak syndrome, or hemolytic uremic syndrome at any time in the study, and supportive measures will be implemented. Supportive measures will include blood pressure control and anti-seizure therapy for posterior reversible encephalopathy. If pulmonary effects, such as pulmonary edema, interstitial pneumonitis, or adult respiratory distress syndrome, develop at any time during the study, the Investigator should discuss with the Sponsor and consider discontinuing gemcitabine. Treatment with gemcitabine should be discontinued if there is unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity.

Any changes in dose or regimen should be recorded in the source documents and eCRF.

5.7 Randomization and Blinding

This is an open-label study. Eligible patients will be randomized to 1 of the 2 treatment groups.

Selection bias will be minimized by randomizing patients via an Interactive Response Technology (IRT) system. The IRT will stratify patients based on disease stage – stage I/II versus stage III/IV (without extrathoracic metastasis). Randomization via the IRT will ensure equal representation of disease stages in each treatment group such that there is not preferential allocation of patients with better prognosis to one treatment group or the other. Each study site will not know the randomized allocation for a patient until they have committed that patient for randomization.

While this is an open-label study, bias due to study personnel knowing the treatment allocation will be reduced by restricting that knowledge on a need-to-know basis. The schedule of assessment of tumor response is identical for both treatment groups.

Bias due to informative censoring of OS will be minimized by performing active follow-up to pre-specified data cut-offs and censoring survival at that cut-off. Every effort will be made to trace patients. Patients will be informed of the importance of being followed up for survival, and where applicable, patients will be asked to confirm if they will agree to survival follow-up even if they withdraw from other study activities.

Appropriate adjustments to the statistical analyses will be made for other factors that may affect response to treatment (e.g., age, gender, tumor histology, response to first-line treatment).

5.8 Breaking the Blind

This is an open-label study. Investigators, study staff, and patients will be aware of drug assignment.

5.9 Prior and Concomitant Medications and/or Procedures

5.9.1 Excluded Medications and/or Procedures

The following medications and products will be prohibited during the study:

- Other anticancer therapy, including cytotoxic, antibody, retinoid, or hormonal treatment;
- Other investigational therapeutic agents; and
- Lithium.

5.9.2 Restricted Medications and/or Procedures

During the period of celecoxib administration, the following medications and products will be restricted:

- Celecoxib should not be taken, other than as indicated in the protocol; and
- Other COX-2 inhibitors, standard doses of acetylsalicylic acid, and NSAIDs should not be taken. Patients who are receiving low doses of acetylsalicylic acid for cardiovascular prophylaxis may continue treatment during the period of celecoxib administration.

During the period of celecoxib administration and for 72 hours afterwards, the following medications and products will be restricted:

- Patients should not receive concomitant potent inhibitors of cytochrome P450 (CYP)2C9 (i.e., fluconazole) (see Appendix D);
- Caution should be taken in patients receiving concomitant substrates of CYP2D6, including tamoxifen, beta blockers, anti-depressants, and anti-psychotics (see Appendix D);
- Blood pressure should be monitored in patients receiving angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers;
- Renal function should be monitored in patients receiving angiotensin-converting enzyme inhibitors and angiotensin receptor blockers;
- Patients receiving concomitant furosemide and thiazide diuretics should be monitored to assure diuretic efficacy including antihypertensive effects; and
- Patients receiving digoxin should have serum digoxin levels monitored.

During the period of gemcitabine treatment, yellow fever vaccine and other live attenuated vaccines are not recommended.

The use of myeloid growth factors is not prohibited in the event of gemcitabine-related toxicity; however, their use within the first 30 days after rAd-IFN administration must be discussed with the Medical Monitor and Sponsor.

5.9.2.1 rAd-IFN and COVID-19 vaccination

Although the combination of rAd-IFN and newly approved COVID-19 vaccines has not been studied, the use of an approved COVID-19 vaccine is likely to have a positive benefit/risk ratio in this vulnerable patient population and is recommended.

The use of any newly approved COVID-19 vaccine will be determined on an individual basis according to the Investigator's medical judgment, their interpretation of the published information available for the vaccine, and in agreement with current regulatory guidelines and local institutional practices.

A temporary, non-specific inflammatory response may be induced by exposure to any adenovirus vector. As a general rule, the use of any vaccine should be separated from rAd-IFN treatment by 2 weeks, if possible. If a COVID-19 vaccine is administered during the study, it should be recorded as a concomitant medication in the patient's eCRF.

Therefore, the following actions apply if vaccinating a study patient for COVID-19 and/or if a study patient becomes infected with SARS-CoV-2:

- Administer only approved vaccines. Experimental and/or non-approved COVID-19 vaccinations should not be administered.

5.9.2.2 Celecoxib and COVID-19 vaccination

The reference safety information for celecoxib warns that its use may mask fever and other signs of inflammation and the current product information for celecoxib makes no mention of any interaction or potential interaction with vaccines.[49,50]

It is the opinion of the Sponsor that the use of celecoxib by patients in this study poses no additional risk in the context of any COVID-19 vaccination currently in use and that the benefits of receiving such vaccine are fully maintained.

5.9.2.3 Gemcitabine and COVID-19 vaccination

The reference safety information for gemcitabine warns that its use can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia. As such, patients receiving gemcitabine should be monitored prior to each dose for platelet, leukocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected. However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation. The use of live attenuated vaccines is not recommended in patients treated with gemcitabine.[51,52] The COVID-19 vaccinations currently in use are not live attenuated vaccines and it is unlikely that any future formulations will be of that type.

Current guidance from the Macmillan Cancer Support Organisation states that the COVID-19 vaccines that are currently available can be given to people who are receiving cancer treatment. While it is possible that COVID-19 vaccines may be slightly less effective for patients receiving chemotherapy or other cancer treatments, it is still expected that the vaccine will give useful protection against the virus. In addition, experts on cancer immunotherapy have recommended that patients who are receiving immunotherapy or who are receiving (or have received) targeted therapies, including antibody treatments, as part of their therapy should receive the COVID-19 vaccines. Although the vaccines can be given before, during, or after cancer treatment, if a patient has been recommended to start a treatment that affects the immune system (i.e., chemotherapy, immunotherapy), receiving a COVID-19 vaccine before the start of treatment may improve its effectiveness.[53] The benefits of receiving a COVID-19 vaccine for patients in the study outweigh any potential additional risk posed by the use of gemcitabine.

5.9.3 Allowed Medications and/or Procedures

The following medications and procedures will be allowed:

- Patients receiving warfarin should be monitored closely for symptoms or signs of bleeding during the period of celecoxib administration and for 72 hours afterwards;
- No precautions are required with respect to co-administration of CYP1A2 substrates with celecoxib;

- Supportive care measures including low dose corticosteroids up to 10 mg daily, if clinically indicated, and symptomatic treatment for any treatment-related toxicity;
- Oral prednisolone or equivalent at a dose of ≤10 mg per day for patients with active, known, or suspected auto-immune disease or a syndrome that requires systemic or immunosuppressive agents;
- Prophylactic use of standard anti-emetics;
- Intermittent use of dexamethasone is permitted as an anti-emetic;
- Blood and platelet transfusions, as needed per the judgment of the Investigator; and
- Palliative radiation therapy will be permitted for pain or severe symptom control. It should be noted that toxicity has been reported when radiation therapy is administered together with or within 7 days of gemcitabine treatment. Radiation will be limited to non-target lesions only and will be documented in the eCRF.

5.9.4 Documentation of Prior and Concomitant Medication Use

Medications used within 28 days of Screening will be recorded. All concomitant medications will be recorded on the eCRF as indicated in Appendix A.

6 STUDY PROCEDURES

A study visit schedule in tabular format is provided in Appendix A.

Disease assessments will be performed as indicated in the Schedule of Procedures (Table 1).

6.1 Informed Consent

Informed consent will be obtained prior to performance of any study-related procedures.

An optional pre-Screening ICF will be available for patients choosing to submit their archival tumor tissue for histological assessment prior to consenting to the study. The pre-Screening ICF will not include consent for any other study-related procedures.

Patients may choose to forego the optional pre-Screening ICF and only sign the main study ICF. All patients will need to sign the main study ICF in order to proceed with any other study-related procedures. The main study ICF will allow patients to complete Screening procedures in parallel with submitting their archival tumor tissue.

The main study ICF will also contain a section for patients to confirm their consent to participate in the Viral Shedding Cohort. The Viral Shedding Cohort is an optional cohort for those patients who are randomized to the rAd-IFN treatment group. Not all patients who consent to the Viral Shedding Cohort will be included in this cohort as it will depend on their treatment randomization and whether any slots remain in this cohort. Medpace will confirm availability of slots for those patients randomized to the rAd-IFN treatment group.

See Section 11.3 for details on informed consent.

6.2 Screening (Study Days -28 to 0)

The following assessments will be performed at Screening:

- Obtain informed consent;
- Obtain informed consent specifically allowing viral shedding-related procedures (Viral Shedding Cohort only);
- Record demographics information;
- Review medical history (including history of prior exposure to checkpoint inhibitors);
- Perform physical examination;
- Record vital signs including weight and height;
- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation) and local serum pregnancy test (for female patients of childbearing potential only);

  Note: Laboratory assessments must be performed within 28 days prior to Study Day 1. Estimated glomerular filtration rate will be calculated using the Modification of Diet in Renal Disease study equation at Screening only (see Appendix B).

- Collect urine sample for urinalysis;

  Note: Laboratory assessments must be performed within 28 days prior to Study Day 1.

- Perform ECG (resting);
- Submit archival tumor block or 3 to 5 unstained slides from archival tumor block for central pathology review if patient did not sign pre-Screening ICF and archival tumor sample has not already been submitted (confirmation of tumor histology is required for inclusion criterion number 3);
- Perform radiographic assessment of tumor by CT scan of the chest, abdomen, and pelvis (see Section 7.2 and Appendix C);

  Note: CT scan must be performed within 28 days prior to Study Day 1. The CT scan performed during Screening will be used as the patient's baseline modified RECIST 1.1 assessment. Standard of care CT scans completed within 2 weeks prior to Screening may be used in place of the Screening CT scan on a case-by-case basis as agreed with the Medical Monitor.
- Assess pleural space for ability to site an IPC or similar device for patients who do not have a pre-existing IPC or similar device;
- Record the ECOG performance status;
- Assess QoL using EQ-5D-5L and Lung Cancer Symptom Scale-mesothelioma (LCSS-Meso) (patient and observer) questionnaires;
- Record adverse events and concomitant medications; and
- Submit all CT scans to central archive.

During the Screening Period, after tumor histology results are received, and the patient is confirmed to be eligible for the study, the following should be completed in preparation for Study Day 1:

- Randomize via IRT, and

  Note: The target interval between randomization and Study Day 1 should be up to 7 days and no greater than 14 days. Any extension beyond 14 days will be considered on a case-by-case basis, following discussion between the Investigator, Medical Monitor, and Sponsor.
- Schedule IPC or similar device placement (rAd-IFN treatment group only), if required.

  Note: An IPC or similar device must be inserted on or before Study Day 1 for patients who do not have a pre-existing IPC or similar device.

An extension to the Screening Period will be permitted on a case-by-case basis following discussion between the Investigator, the Medical Monitor, and/or the Sponsor. The reason(s) for the extension is to be clearly documented.

6.3 Treatment Period

6.3.1 Study Day 1

Study Day 1 will be a maximum of 28 days after the start of Screening unless an extension is approved by the Sponsor or Medical Monitor.

The following assessments will be performed for all patients before starting study treatment on Study Day 1 or within 24 hours before starting study treatment (i.e., the following Study Day 1 assessments may be split over 2 days):

- Record vital signs;
- Perform physical examination;
- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation), serum mesothelin and fibulin-3 measurement, and local serum pregnancy test (for female patients of childbearing potential only);
- Collect blood sample for Ad5 nAbs (samples collected and stored for later analysis, antibody status not required for study enrollment);
- Collect urine sample for urinalysis;
- Perform ECG (resting);
- Record adverse events and concomitant medications; and
- Insert IPC or similar device if not previously inserted (rAd-IFN treatment group only).

  Note: For all rAd-IFN treatment group patients (i.e., patients with a previously inserted or a newly inserted IPC or similar device), the correct position of the IPC or similar device will be confirmed by the Investigator or an appropriately qualified designee, in accordance with local institutional practice.

The following procedure must be performed on Study Day 1:

- Administer the first dose of celecoxib (400 mg) orally.

  Note: The first dose of celecoxib will be administered 1 to 2 hours prior to rAd-IFN administration for the rAd-IFN treatment group.

rAd-IFN will be administered via the intrapleural route by the Principal Investigator or designee according to Section 5.1.2 and recorded in the source documents and eCRF (rAd-IFN treatment group only). It is recommended that the pleural space is not drained within the first 24 hours post-rAd-IFN administration, unless deemed necessary by the Investigator.

See Section 5.1.4 for instructions to prepare the patient and to monitor the patient before, during, and after rAd-IFN administration.

At the discretion of the Investigator, the IPC or similar device may be removed at any time during the 6-hour post-rAd-IFN administration observation period or at the Study Day 2 Visit. The Investigator may keep the IPC or similar device in situ beyond the Study Day 2 Visit if required for clinical purposes.

The following assessments will be performed on Study Day 1 for all patients (post-rAd-IFN administration for the rAd-IFN treatment group):

- Provide patient with the remainder of celecoxib for at home dosing and instruct patient that dosing should be 400 mg orally BID, at approximately 12-hour intervals;

  Note: If the patient receives the first dose of celecoxib late on Study Day 1, such that the patient is only able to take 1 dose of celecoxib on Study Day 1, the patient must not take a celecoxib

dose on Study Day 15, regardless of whether or not the patient has taken all planned celecoxib doses. If BID dosing does not occur on Study Day 1 for this reason, it will not be considered a protocol deviation. If the patient vomits after taking celecoxib, the patient should not replace that dose; instead, the patient should wait until the next scheduled time point to take their next scheduled celecoxib dose.

- Provide patient with a celecoxib diary and instruct patient that the next dose should be taken approximately 12 hours post-rAd-IFN administration (rAd-IFN treatment group) or approximately 12 hours after the first celecoxib dose (control group); and
- Record adverse events and concomitant medications.

For patients in the rAd-IFN treatment group participating in the Viral Shedding Cohort, the following assessments will also be performed:

- Collect urine sample for viral shedding 2 to 3 hours post-rAd-IFN administration;
- Collect saliva and pleural access site swab for viral shedding 2 to 3 hours post-rAd-IFN administration; and
- Collect blood sample for biodistribution 2 to 3 hours post-rAd-IFN administration.

6.3.2 Study Day 2 (rAd-IFN Treatment Group Only)

For patients randomized to the rAd-IFN treatment group only, the following assessments will be performed on Study Day 2 (approximately 24 hours after rAd-IFN administration):

- Record vital signs;
- Perform physical examination;
- Review diary/complete capsule count to calculate compliance and accountability; and

  Note: Retrain patients with <100% compliance (unless the only reason compliance is <100% is a result of the patient taking the first dose of celecoxib late on Study Day 1, such that the patient is only able to take 1 dose of celecoxib on Study Day 1).
- Record adverse events and concomitant medications.

For patients in the rAd-IFN treatment group participating in the Viral Shedding Cohort, the following assessments will also be performed:

- Collect urine sample for viral shedding approximately 24 hours post-rAd-IFN administration;
- Collect saliva and pleural access site swab for viral shedding approximately 24 hours post-rAd-IFN administration;
- Collect pleural fluid sample using the IPC or similar device (if the IPC or similar device is still in place) approximately 24 hours post-rAd-IFN administration. See Appendix G for collection procedure; and
- Collect blood sample for biodistribution approximately 24 hours post-rAd-IFN administration.

6.3.3 Study Day 7

The following assessments will be performed on Study Day 7 (±1 day) for all patients:

- Record vital signs;
- Perform physical examination;
- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation);
- Collect urine sample for urinalysis;
- Review diary/complete capsule count to calculate compliance and accountability; and

  Note: Retrain patients with <100% compliance (unless the only reason compliance is <100% is a result of the patient taking the first dose of celecoxib late on Study Day 1, such that the patient is only able to take 1 dose of celecoxib on Study Day 1).
- Record adverse events and concomitant medications.

For patients in the rAd-IFN treatment group participating in the Viral Shedding Cohort, the following assessments will also be performed:

- Collect urine sample for viral shedding;
- Collect saliva and pleural access site swab for viral shedding;
- Collect pleural fluid sample using the IPC or similar device (if the IPC or similar device is still in place). See Appendix G for collection procedure; and
- Collect blood sample for biodistribution.

6.3.4 Study Days 14 to 28 (Gemcitabine Cycle 1)

6.3.4.1 Study Day 14 (Gemcitabine Cycle 1 Day 1)

The following assessments will be performed on gemcitabine Cycle 1 Day 1 (±1 day) for all patients:

- Record vital signs including weight;
- Perform physical examination;
- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation) and local serum pregnancy test (for female patients of childbearing potential only);
- Collect urine sample for urinalysis;
- Perform ECG (resting);
- Administer gemcitabine 1250 mg/m^2 intravenously;
- Assess QoL using EQ-5D-5L and LCSS-Meso (patient and observer) questionnaires;

- Review diary/complete capsule count to calculate compliance and accountability; and

  Note: Retrain patients with <100% compliance (unless the only reason compliance is <100% is a result of the patient taking the first dose of celecoxib late on Study Day 1, such that the patient is only able to take 1 dose of celecoxib on Study Day 1).

- Record adverse events and concomitant medications.

For patients in the rAd-IFN treatment group participating in the Viral Shedding Cohort, the following assessments will also be performed:

- Collect urine sample for viral shedding;
- Collect saliva and pleural access site swab for viral shedding;
- Collect pleural fluid sample using the IPC or similar device (if the IPC or similar device is still in place). See Appendix G for collection procedure; and
- Collect blood sample for biodistribution.

6.3.4.2 Study Day 21 (Gemcitabine Cycle 1 Day 8)

The following assessments will be performed on gemcitabine Cycle 1 Day 8 (±1 day) for all patients:

- Record vital signs including weight;
- Perform physical examination;
- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation);
- Collect urine sample for urinalysis;
- Administer gemcitabine 1250 mg/m^2 intravenously;
- Review diary/complete capsule count to calculate compliance and accountability; and
- Record adverse events and concomitant medications.

For patients in the rAd-IFN treatment group participating in the Viral Shedding Cohort, the following assessments will also be performed:

- Collect urine sample for viral shedding;
- Collect saliva and pleural access site swab for viral shedding;
- Collect pleural fluid sample using the IPC or similar device (if the IPC or similar device is still in place). See Appendix G for collection procedure; and
- Collect blood sample for biodistribution.

6.3.4.3 Study Day 28 (Gemcitabine Cycle 1 Day 15)

The following assessments will be performed on gemcitabine Cycle 1 Day 15 (±3 days) for all patients:

- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation);
- Collect urine sample for urinalysis; and
- Record adverse events and concomitant medications.

For patients in the rAd-IFN treatment group participating in the Viral Shedding Cohort, the following assessments will also be performed:

- Collect urine sample for viral shedding;
- Collect saliva and pleural access site swab for viral shedding;
- Collect pleural fluid sample using the IPC or similar device (if the IPC or similar device is still in place). See Appendix G for collection procedure; and
- Collect blood sample for biodistribution.

6.3.5 Gemcitabine Cycle 2, 3, 4, and Beyond

6.3.5.1 Gemcitabine Cycle 2, 3, 4, and Beyond Day 1

The following assessments will be performed on gemcitabine Cycle 2, 3, 4, and Beyond Day 1 (±3 days) for all patients:

- Record vital signs including weight;
- Perform physical examination;
- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation) and local serum pregnancy test (for female patients of childbearing potential only);
- Collect urine sample for urinalysis;
- Collect blood sample for serum mesothelin and fibulin-3 measurement;
- Perform ECG (resting);
- Perform radiographic assessment of tumor by CT scan of the chest, abdomen, and pelvis on gemcitabine Cycle 3 Day 1 (±3 days) only (see Section 7.2 and Appendix C);
- Administer gemcitabine 1250 mg/m^2 intravenously;
- Assess QoL using EQ-5D-5L and LCSS-Meso (patient and observer) questionnaires;

- Record adverse events and concomitant medications; and
- Submit all CT scans to central archive.

  Note: All CT scans will be submitted for central archiving on an ongoing basis throughout the study. Any CT scans completed for standard of care purposes after disease progression/ET will not be collected for the central archive.

6.3.5.2 Gemcitabine Cycle 2, 3, 4, and Beyond Day 8

The following assessments will be performed on gemcitabine Cycle 2, 3, 4, and Beyond Day 8 (±3 days) for all patients:

- Record vital signs including weight;
- Perform physical examination;
- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation);
- Collect urine sample for urinalysis;
- Administer gemcitabine 1250 mg/m^2 intravenously; and
- Record adverse events and concomitant medications.

6.4 Post-Randomization CT Scans

The following assessments will be performed for all patients:

- Perform radiographic assessment of tumor by CT scan of the chest, abdomen, and pelvis (see Section 7.2 and Appendix C); and

  Note: The first CT scan after randomization will be performed at gemcitabine Cycle 3 Day 1 (±3 days).

  Subsequent CT scans will be performed every 9 weeks (±3 days) until disease progression/ET. The CT scan schedule of every 9 weeks (±3 days) from gemcitabine Cycle 3 Day 1 will be maintained regardless of gemcitabine dose delays or interruptions.

- Submit all CT scans to central archive.

  Note: All CT scans will be submitted for central archiving on an ongoing basis throughout the study. Any CT scans completed for standard of care purposes after disease progression/ET will not be collected for the central archive.

6.5 End of Treatment (Disease Progression) Visit

The following assessments will be performed at the End of Treatment (Disease Progression) Visit (±3 days) for all patients:

- Record vital signs;
- Perform physical examination;

- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation) and local serum pregnancy test (for female patients of childbearing potential only);
- Collect urine sample for urinalysis;
- Perform ECG (resting);
- Record adverse events and concomitant medications; and
- Submit all CT scans to central archive.

  Note: All CT scans will be submitted for central archiving on an ongoing basis throughout the study. Any CT scans completed for standard of care purposes after disease progression/ET will not be collected for the central archive.

6.6 Clinical Follow-Up Visits

Following the End of Treatment (Disease Progression) Visit or ET, patients in the rAd-IFN treatment group will continue to have clinical Follow-up Visits every 6 months (±14 days) for survival and safety for up to 5 years after receiving the first dose of rAd-IFN, assuming consent has not been withdrawn. Cause and date of death will be recorded where possible. Concomitant medications specific for mesothelioma treatment will be recorded. All previously recorded TEAEs and SAEs will be followed until resolution or stabilization. Clinical Follow-up Visits can be performed face-to-face, through physician contact, or by telephone. Patients in the control group will not continue with clinical Follow-up Visits and study participation concludes after end of study treatment.

6.7 Early Termination

For patients who are withdrawn from study treatment after commencing Study Day 1 treatment and prior to disease progression, the following procedures will be performed at an ET Visit:

- Record vital signs;
- Perform physical examination;
- Collect blood sample for routine laboratory assessments (hematology, clinical chemistry, and coagulation) and local serum pregnancy test (for female patients of childbearing potential only);
- Collect urine sample for urinalysis;
- Perform ECG (resting);
- Record adverse events and concomitant medications; and
- Submit all CT scans to central archive.

  Note: All CT scans will be submitted for central archiving on an ongoing basis throughout the study. Any CT scans completed for standard of care purposes after disease progression/ET will not be collected for the central archive.

For patients who have withdrawn consent to the study after commencing Study Day 1 treatment and prior to disease progression, all attempts should be made to complete the above procedures.

For patients who have withdrawn prior to commencing Study Day 1 treatment, the above procedures do not need to be completed.

Where applicable, patients in the rAd-IFN treatment group who have withdrawn from study treatment, not including those who have withdrawn prior to commencing Study Day 1 treatment, will be asked if they would agree to continue to be followed for survival and safety every 6 months (±14 days) for up to 5 years.

7 EFFICACY ASSESSMENTS

The primary endpoint is OS, defined as time to death (from any cause) from randomization.

The secondary efficacy endpoints are:

- To evaluate survival rate at 12 months, defined as the number of deaths (from any cause) at 12 months from randomization, and every 6 months thereafter;
- To evaluate PFS, defined as the time from randomization to the time when the modified RECIST 1.1 criteria for disease progression are first met, or when death from any cause occurs; and
- To evaluate best response, defined as the best response after randomization (complete response, partial response, or stable disease).

The exploratory efficacy endpoints are:

- Change in total score and individual components of the EQ-5D-5L and LCSS-Meso (patient and observer) from baseline (randomization) to each successive cycle of gemcitabine,
- Correlation between the presence of Ad5 nAbs prior to treatment and survival (death from any cause),
- Correlation between pre- and post-treatment levels of serum mesothelin and treatment outcomes, and
- Correlation between pre- and post-treatment levels of serum fibulin-3 and treatment outcomes.

7.1 Archival Tumor or Biopsy at Screening

Archival tumor samples will be requested at Screening from all patients enrolled in the study. The diagnostic pathology block or tumor tissue obtained at the time of the patient's initial diagnosis and/or at the time of subsequent procedures is acceptable. If a tumor block is not available, 3 to 5 unstained paraffin-embedded tumor tissue containing slides may be provided. Fresh tumor biopsies will not be taken as part of this study.

The archival tissue or unstained slides will be reviewed by a central pathologist to confirm histological diagnosis. The Sponsor or its designee will return all blocks/tissue samples to the originating site upon completion of the associated analyses. **Confirmation of tumor histology is required prior to inclusion into the study.**

The archival tumor samples will also be assessed for programmed death-ligand 1 (PD-L1) expression by a central pathologist, and the data will be retained for exploratory analysis. Programmed death-ligand 1 expression is not required prior to inclusion into the study.

A Laboratory Manual detailing the tumor sample collection, preparation, storage, and shipping process will be provided.

7.2 Tumor Assessments

Tumor assessments will be performed locally in accordance with modified RECIST 1.1 based on diagnostic CT examinations performed of the chest, abdomen, and pelvis (see Appendix C).[42] Contrast-enhanced examinations are preferred when possible. Standard of care CT scans completed within 2 weeks prior to Screening may be used in place of the Screening CT scan on a

case-by-case basis as agreed with the Medical Monitor. All CT scans will be submitted for central archiving on an ongoing basis throughout the study. Any CT scans completed for standard of care purposes after disease progression/ET will not be collected for the central archive.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of the main study's informed consent through 30 days after the last dose of study treatment (rAd-IFN, celecoxib, and gemcitabine). All TEAEs will be followed until resolution or stabilization. Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning with Screening, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF. Disease progression should not be reported as an adverse event/SAE; however, when a patient dies from disease progression, the event will be captured as an outcome on an eCRF for deaths due to disease progression.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the adverse event eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at Screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study, or are present at Screening and significantly worsen during the study, should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For rAd-IFN, the reference safety information is included in Section 6.9 of the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, severe, life-threatening, or death and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity

The severity of all adverse events should be graded according to the CTCAE Version 4.03, with the exception of CRS. See Appendix E for details on CRS grading. The CTCAE can be found at http://ctep.cancer.gov/reporting/ctc.html. For those adverse events not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of signs/symptoms, but easily tolerated and no interference with patient's daily activities.
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with patient's usual activities, but still acceptable.
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the patient's daily activities, unacceptable.
- Life-threatening (CTCAE Grade 4): Life-threatening or disabling adverse event.
- Death (CTCAE Grade 5): Death-related adverse event.

Causality Assessment

The relationship of an adverse event to the administration of each study drug (rAd-IFN, celecoxib, and gemcitabine) is to be assessed according to the following definitions:

No (unrelated, not related, no relation) The time course between the administration of each study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of each study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship, and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or nonclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.1.4 Adverse Events of Special Interest

Adverse events of special interest (AESIs) must be recorded in the eCRF. An AESI will be recorded within the first 30 days of rAd-IFN treatment for patients who are randomized to rAd-IFN treatment and received the rAd-IFN dose. Adverse events of special interest will be followed up to resolution.

For this study, AESIs include:

- Laboratory results, signs, and symptoms associated with CRS;
- Laboratory results, signs, and symptoms associated with transaminitis (defined as ALT >3.0 × ULN and/or AST >3.0 × ULN); and
- Infection at IPC or similar device site.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
    - Note: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
    - Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
    - Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.
    - Note: Disease progression should not be reported as an adverse event/SAE; however, when a patient dies from disease progression, the event will be captured as an outcome on an eCRF for deaths due to disease progression.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

Serious adverse events will be captured from the time of the main study's informed consent through 30 days after the last dose of study treatment (rAd-IFN, celecoxib, and gemcitabine). All SAEs must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs will be followed until resolution or stabilization.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is saved, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (telephone number listed below) and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
e-mail: medpace-safetynotification@medpace.com

Medpace SAE reporting line Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
e-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 30 days of the last dose of study drug (rAd-IFN, celecoxib, and gemcitabine), the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and ET study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor will report all relevant information about all suspected unexpected serious adverse reactions (fatal, life-threatening, or other) to the respective health authority, Principal Investigators, ethics committees, and other local authorities as per local guidelines within the expected reporting timeframes.

8.6 Safety Assessments

The secondary safety endpoints are:

- To evaluate the number of patients with CTCAE Grade 3 or 4, and
- To evaluate post-treatment levels of rAd-IFN-related viral DNA in biological samples collected up to 28 days after Study Day 1 in a sub-set of patients.

Safety assessments will also include the assessment of adverse events including AESIs, as well as physical examinations, vital sign measurements, clinical laboratory assessments, and electrocardiographic data through ECG.

8.7 Clinical Laboratory Evaluations

Blood for chemistry, hematology, and coagulation panels will be obtained as indicated in Appendix A and sent to the site's clinical laboratory per institutional guidelines for analysis. See Appendix B for a complete list of analytes. Estimated glomerular filtration rate will be calculated using the Modification of Diet in Renal Disease study equation at Screening only (see Appendix B).

Urine will be obtained as indicated in Appendix A and sent to each site's clinical laboratory per institutional guidelines for complete urinalysis. See Appendix B for a complete list of analytes.

A local laboratory serum pregnancy test will be performed for female patients of childbearing potential only prior to their participation in the study (Screening and Study Day 1), on Day 1 of all gemcitabine cycles, and at the End of Treatment (Disease Progression)/ET Visit.

Laboratory results will be collected for the clinical study database.

8.8 Vital Signs

Vital sign measurements will be taken after at least a 5-minute rest in a sitting or supine position. Measurements will include blood pressure, respiratory rate, pulse rate, and body temperature.

Weight and height will be measured at Screening (see Appendix A). Weight will also be measured on Day 1 and Day 8 of all gemcitabine cycles and can be used to calculate the gemcitabine dose for that visit.

8.9 Electrocardiograms

Standard ECGs will be performed. Patients will rest for 5 minutes prior to each ECG reading (see Appendix A).

8.10 Physical Examinations

The physical examination appropriate to the physical condition of the patient will be performed by either the Investigator or a Sub-Investigator who is a physician (see Appendix A).

8.11 Viral Shedding Evaluation

A sub-set of patients randomized to the rAd-IFN treatment group will be selected to participate in the Viral Shedding Cohort to assess rAd-IFN viral vector shedding. The Viral Shedding Cohort will include the first 10 patients randomized to the rAd-IFN treatment group who consent to participation. The viral shedding evaluation will include collection of saliva, urine, pleural access site swab, and blood samples for biodistribution, taken at designated time points 2 to 3 hours post-rAd-IFN administration (Study Day 1); approximately 24 hours post-rAd-IFN administration (Study Day 2); and on Study Days 7, 14, 21, and 28. A pleural fluid sample will be collected using the IPC or similar device (if the IPC or similar device is still in place) approximately 24 hours post-rAd-IFN administration (Study Day 2) and on Study Days 7, 14, 21, and 28. See Appendix G for pleural fluid sample collection procedure.

8.12 Patient Preparation and Monitoring (rAd-IFN Treatment Group Only)

Immediately before (within 10 minutes prior to the start time of rAd-IFN administration), during, and immediately after (within 10 minutes after the start time of rAd-IFN administration) rAd-IFN administration,

- Patients should be monitored using pulse oximetry,
- Oxygen via nasal cannula should be administered at approximately 2 L/min as required, and
- Cardiac telemetry may also be used to monitor patients as per the Principal Investigator's discretion.

These safety procedures should be continued post-rAd-IFN administration as per the Principal Investigator's or designee's discretion.

An intravenous cannula should be placed prior to rAd-IFN administration, and normal saline (or equivalent as per local institutional standards) should be administered slowly.

Analgesia may be administered as required, in accordance with local institutional standards.

Post-rAd-IFN administration,

- Body temperature will be monitored every hour (±10 minutes) for 6 hours; and
- Blood pressure, respiratory rate, pulse rate, and oxygen saturation will be measured and recorded every 15 minutes (±5 minutes) for the first 2 hours; every 30 minutes (±10 minutes) for the next 2 hours; then, every hour (±10 minutes) for the remainder of the inpatient monitoring period up to 6 hours post-rAd-IFN administration (unless further surveillance is required as per the Principal Investigator's discretion).

After 6 hours of observation, the patient can go home if vital signs and oxygen saturation are within acceptable limits, as per local institutional practice and guidelines, following assessment by the Investigator or an appropriately qualified designee. After leaving the facility, the patient may use acetaminophen or equivalent (as per local institutional standards) for the management of pyrexia,

should it occur. rAd-IFN treatment group patients will return to the site to be reviewed approximately 24 hours after rAd-IFN administration (see Section 6.3.2).

In the event the patient experiences CRS, see Appendix E for details on CRS grading. Local guidelines for the management and treatment of CRS should be followed. In the absence of any such appropriate guidelines, see Appendix E for details on the therapeutic strategy for the management of CRS.

9 STATISTICS

9.1 Analysis Populations

The study population is patients with MPM and confirmed epithelioid or biphasic histology (if biphasic, histology must be predominantly [≥50%] epithelioid) who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen.

The Full Analysis Set comprises all patients appropriately randomized into the study who have received at least 1 dose of study drug (rAd-IFN, celecoxib, or gemcitabine).

The Safety Analysis Set comprises all patients who have received at least 1 dose of study drug (rAd-IFN, celecoxib, or gemcitabine).

9.2 Statistical Methods

A Statistical Analysis Plan (SAP) will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the Clinical Study Report.

9.2.1 Analysis of Efficacy

9.2.1.1 Primary efficacy analysis

The primary analysis of the primary endpoint is a comparison of the OS curves between the 2 treatment groups using a log-rank test. A Cox proportional hazards model with treatment as an explanatory variable will be used to assess the magnitude of the treatment difference in OS. The hazard ratio and the associated 95% confidence interval obtained from the Cox proportional hazards model will be presented.

The median OS and the 95% confidence interval for each treatment group will be estimated using the Kaplan-Meier method and summarized by treatment group. Plots of the Kaplan-Meier curve of OS will be presented by treatment group.

Secondary analyses of the primary endpoint will include a comparison of the survival rates at various time points since randomization.

9.2.1.2 Secondary efficacy analysis

Secondary time-to-event endpoints will be analyzed in the same manner as the primary efficacy endpoint.

Categorical efficacy endpoints will be summarized and compared between groups using Fisher's exact test.

9.2.2 Analysis of Safety

The nature, incidence, severity, relatedness, expectedness, seriousness, and outcome of TEAEs will be summarized by treatment group.

9.2.3 Analysis Timing

9.2.3.1 Interim analysis

No interim analysis is planned due to the premature termination of enrollment for the study.

9.2.3.2 Final analysis

The final analysis will be conducted after the forty-fourth event (death) or at least 30 months after the last patient is randomized, whichever occurs first. The long-term safety follow-up data will be collected.

9.2.4 Data and Safety Monitoring Board

An independent DSMB will be convened for this study to monitor safety, efficacy, and study integrity. The DSMB will consist of individuals, experts in relevant fields, including but not limited to mesothelioma, drug safety, and biostatistics. It will convene on a regular basis and will review all safety and study conduct information to determine whether the study should continue unchanged or whether protocol modifications are required to ensure patient safety and study integrity.

All aspects of the DSMB's scope of review and procedures will be detailed in a DSMB charter, to be finalized before the first patient is randomized.

9.2.5 Sample Size Determination

The planned sample size is approximately 50 patients. The sample size is not based on statistical considerations. Patient recruitment into the study has been significantly slower than expected due to several technical study challenges. Therefore, Trizell has decided to discontinue screening and enrollment into the study after a total of approximately 50 patients have been randomized to treatment.

It is anticipated that approximately 44 events (equivalent to 89% of the approximately 50 enrolled patients) will be observed 24 months after the last patient is randomized. The final analysis of the study will be conducted after the forty-fourth event (death) or 30 months after the last patient is randomized, whichever occurs first.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities for medical history and adverse events, and
- WHO Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Ethics and Regulatory Review

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

International regulations and International Council for Harmonisation (ICH) guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor or other approval has been granted, as applicable, according to national regulations.

It is the responsibility of the Sponsor or their designee (i.e., Medpace) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start at the respective sites once the respective ethics committee's written approval has been obtained, and the respective applicable national regulatory authority(ies) has been notified and its approval has been obtained as required per national requirements for clinical trials and for genetically modified organisms.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

An optional pre-Screening ICF will be available for patients choosing to submit their archival tumor tissue for histological assessment prior to consenting to the study. The pre-Screening ICF will not include consent for any other study-related procedures. If the patient chooses to consent, the consent form should be signed and personally dated by the patient prior to submission of his/her archival tumor tissue for histological assessment.

Patients may choose to forego the optional pre-Screening ICF and only sign the main study ICF. All patients will need to sign the main study ICF in order to proceed with any other study-related

procedures. The main study ICF will allow patients to complete Screening procedures in parallel with submitting their archival tumor tissue.

The main study ICF will also contain a section for patients to confirm their consent to participate in the Viral Shedding Cohort. The Viral Shedding Cohort is an optional cohort for those patients who are randomized to the rAd-IFN treatment group. Not all patients who consent to the Viral Shedding Cohort will be included in this cohort as it will depend on their treatment randomization and whether any slots remain in this cohort. Medpace will confirm availability of slots for those patients randomized to the rAd-IFN treatment group.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRBs/IECs and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, Directive 2001/20/EC and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the Sponsor or their designee, applicable regulatory authorities, and the IRB/IEC, as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Each Investigator (including Principal and any Sub-Investigators) directly involved in the treatment or evaluation of study patients is required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its US obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.9 Financing and Insurance

The financing and insurance for this study are outlined in the Clinical Study Agreement.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the relevant competent authority(ies) and/or IRB/IEC, as applicable, unless immediate implementation of the change is necessary for patient safety, in compliance with local requirements. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days (or other local requirement as applicable).

12.2 Address List

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12.2.6 Gemcitabine and Celecoxib Supplier (Where Supplied Centrally)

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Catalent Philadelphia
Receipt, storage, and distribution:
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13 REFERENCES

1. Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. Ann Cardiothorac Surg. 2012 Nov;1(4):491-6.
2. Robinson BW, Lake RA. Advances in malignant mesothelioma. N Engl J Med. 2005 Oct;353(15):1591-603.
3. Delgermaa V, Takahashi K, Park EK, Le GV, Hara T, Sorahan T. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. Bull World Health Organ. 2011 Oct;89(10):716-24.
4. Inai K. Pathology of mesothelioma. Environ Health Prev Med. 2008 Mar;13(2):60-4.
5. Flores RM, Pass HI, Seshan VE, Dycoco J, Zakowski M, Carbone M, Bains MS, Rusch VW. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg. 2008 Mar;135(3):620-6.
6. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003 Jul;15;21(14):2636-44.
7. Abdel-Rahman O, Kelany M. Systemic therapy options for malignant pleural mesothelioma beyond first-line therapy: a systematic review. Expert Rev Respir Med. 2015 Oct;9(5):533-49.
8. Sterman DH, Recio A, Carroll RG, Gillespie CT, Haas A, Vachani A, Kapoor V, Sun J, Hodinka R, Brown JL, Corbley MJ, Parr M, Ho M, Pastan I, Machuzak M, Benedict W, Zhang XQ, Lord EM, Litzky LA, Heitjan DF, June CH, Kaiser LR, Vonderheide RH, Albelda SM, Kanther M. A phase I clinical trial of single-dose intrapleural IFN-beta gene transfer for malignant pleural mesothelioma and metastatic pleural effusions: high rate of antitumor immune responses. Clin Cancer Res. 2007 Aug;13(15 Pt 1):4456-66.
9. Sterman DH, Recio A, Haas AR, Vachani A, Katz SI, Gillespie CT, Cheng G, Sun J, Moon E, Pereira L, Wang X, Heitjan DF, Litzky L, June CH, Vonderheide RH, Carroll RG, Albelda SM. A phase I trial of repeated intrapleural adenoviral-mediated interferon-beta gene transfer for mesothelioma and metastatic pleural effusions. Mol Ther. 2010 Apr;18(4):852-60.
10. Sterman DH, Haas A, Moon E, Recio A, Schwed D, Vachani A, Katz SI, Gillespie CT, Cheng G, Sun J, Papasavvas E, Montaner LJ, Heitjan DF, Litzky L, Friedberg J, Culligan M, June CH, Carroll RG, Albelda SM. A trial of intrapleural adenoviral-mediated Interferon-α2b gene transfer for malignant pleural mesothelioma. Am J Respir Crit Care Med. 2011 Dec;184(12):1395-9.
11. Sterman DH, Alley E, Stevenson JP, Friedberg J, Metzger S, Recio A, Moon EK, Haas AR, Vachani A, Katz SI, Sun J, Heitjan DF, Hwang WT, Litzky L, Yearley JH, Tan KS, Papasavvas E, Kennedy P, Montaner LJ, Cengel KA, Simone CB, Culligan M, Langer CJ, Albelda SM. Pilot and Feasibility Trial Evaluating Immuno-Gene Therapy of Malignant Mesothelioma Using Intrapleural Delivery of Adenovirus-IFNα Combined with Chemotherapy. Clin Cancer Res. 2016 Aug;22(15):3791-800.
12. Ferrantini M, Capone I, Belardelli F. Interferon-alpha and cancer: mechanisms of action and new perspectives of clinical use. Biochimie. 2007 Jun-Jul;89(6-7):884-93.

13. Aricò E, Belardelli F. Interferon-α as antiviral and antitumor vaccine adjuvants: mechanisms of action and response signature. J Interferon Cytokine Res. 2012 Jun;32(6):235-47.
14. Majhen D, Calderon H, Chandra N, Fajardo CA, Rajan A, Alemany R, Custers J. Adenovirus-based vaccines for fighting infectious diseases and cancer: progress in the field. Hum Gene Ther. 2014 Apr;25(4):301-17.
15. Manning LS, Davis MR, Bielefeldt-Ohmann H, et al. Evaluation of immunogenicity of murine mesothelioma cells by immunization. Eur Resp Rev.1993;3:234-7.
16. Davis MR, Manning LS, Whitaker D, Garlepp MJ, Robinson BW. Establishment of a murine model of malignant mesothelioma. Int J Cancer. 1992 Dec;52(6):881-6.
17. Odaka M, Sterman D, Wiewrodt R, Zhang Y, Kiefer M, Amin KM, Gao GP, Wilson JM, Barsoum J, Kaiser LR, Albelda SM. Eradication of intraperitoneal and distant tumor by adenovirus-mediated interferon-beta gene therapy due to induction of systemic immunity. Cancer Res. 2001 Aug;61(16):6201-12.
18. Rosso R, Rimoldi R, Salvati F, De Palma M, Cinquegrana A, Nicolò G, Ardizzoni A, Fusco U, Capaccio A, Centofanti R, et al. Intrapleural natural beta interferon in the treatment of malignant pleural effusions. Oncology. 1988;45(3):253-6.
19. Taniguchi T, Takaoka A. The interferon-alpha/beta system in antiviral responses: a multimodal machinery of gene regulation by the IRF family of transcription factors. Curr Opin Immunol. 2002 Feb;14(1):111-6.
20. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su LK, Levin B, Godio L, Patterson S, Rodriguez-Bigas MA, Jester SL, King KL, Schumacher M, Abbruzzese J, DuBois RN, Hittelman WN, Zimmerman S, Sherman JW, Kelloff G. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med. 2000 Jun;342(26):1946-52.
21. Taketo MM. Cyclooxygenase-2 inhibitors in tumorigenesis (part I and II). J Natl Cancer Inst. 1998 Nov;90(20):1609-20.
22. Haas DW, Geraghty DE, Andersen J. Immunogenetics of CD4 lymphocyte count recovery during antiretroviral therapy: An AIDS Clinical Trials Group study. J Infect Dis. 2006;194(8):1098-107.
23. Marrogi A, Pass HI, Khan M. Human mesothelioma samples overexpress both cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (NOS2): in vitro antiproliferative effects of a COX-2 inhibitor. Cancer Res. 2000;60(14):3696-700.
24. Edwards JG, Faux SP, Plummer SM, Abrams KR, Walker RA, Waller DA, O'Byrne KJ. Cyclooxygenase-2 expression is a novel prognostic factor in malignant mesothelioma. Clin Cancer Res. 2002 Jun;8(6):1857-62.
25. Fitzpatrick DR, Peroni DJ, Bielefeldt-Ohmann H. The role of growth factors and cytokines in the tumorigenesis and immunobiology of malignant mesothelioma. Am J Respir Cell Mol Biol. 1995;12(5):455-60.
26. Nowak AK, Robinson BW, Lake RA. Gemcitabine exerts a selective effect on the humoral immune response: implications for combination chemo-immunotherapy. Cancer Res. 2002;62(8):2353-8.

27. Qin XF, Reichlin A, Luo Y, Roeder RG, Nussenzweig MC. OCA-B integrates B cell antigen receptor-, CD40L- and IL 4-mediated signals for the germinal center pathway of B cell development. EMBO J. 1998;17(17):5066-75.
28. Suzuki E, Kapoor V, Jassar AS, Kaiser LR, Albelda SM. Gemcitabine selectively eliminates splenic Gr-1+/CD11b+ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune activity. Clin Cancer Res. 2005;11(18):6713-21.
29. Nowak AK, Lake RA, Marzo AL, Scott B, Heath WR, Collins EJ, Frelinger JA, Robinson BW. Induction of tumor cell apoptosis in vivo increases tumor antigen cross-presentation, cross-priming rather than cross-tolerizing host tumor-specific CD8 T cells. J Immunol. 2003;170(10):4905-13.
30. Jackaman C, Majewski D, Fox SA, Nowak AK, Nelson DJ. Chemotherapy broadens the range of tumor antigens seen by cytotoxic CD8(+) T cells in vivo. Cancer Immunol Immunother. 2012;61(12):2343-56.
31. Fridlender ZG, Sun J, Singhal S. Chemotherapy delivered after viral immunogene therapy augments antitumor efficacy via multiple immune-mediated mechanisms. Mol Ther. 2010;18(11):1947-59.
32. Di Maio M. Quality of life: an important element of treatment value. Lancet Oncol. 2017;18(12):1557-8.
33. Krug S, Gress TM, Michl P, Rinke A. The Role of Cytotoxic Chemotherapy in Advanced Pancreatic Neuroendocrine Tumors. Digestion. 2017;96(2):67-75.
34. National Comprehensive Cancer Network Guidelines®: Malignant Pleural Mesothelioma, Version 1.2017.
35. Navai N, Benedict WF, Zhang G, Abraham A, Ainslie N, Shah JB, Grossman HB, Kamat AM, Dinney CP. Phase 1b Trial to Evaluate Tissue Response to a Second Dose of Intravesical Recombinant Adenoviral Interferon α2b Formulated in Syn3 for Failures of Bacillus Calmette-Guerin (BCG) Therapy in Nonmuscle Invasive Bladder Cancer. Ann Surg Oncol. 2016;23(12):4110-14.
36. Aggarwal C, Haas AR, Metzger S, Aguilar LK, Aguilar-Cordova E, Manzanera AG, Gómez-Hernández G, Katz SI, Alley EW, Evans TL, Bauml JM, Cohen RB, Langer CJ, Albelda SM, Sterman DH. Phase I study of intrapleural gene-mediated cytotoxic immunotherapy in patients with malignant pleural effusion. Mol Ther. 2018 May:26(5):1198-1205.
37. Krug LM, Kindler HL, Calvert H, Manegold C, Tsao AS, Fennell D, Öhman R, Plummer R, Eberhardt WE, Fukuoka K, Gaafar RM, Lafitte JJ, Hillerdal G, Chu Q, Buikhuisen WA, Lubiniecki GM, Sun X, Smith M, Baas P. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Oncol. 2015 Apr:16(4):447-56.
38. Stebbing J, Powles T, McPherson K, Shamash J, Wells P, Sheaff MT, Slater S, Rudd RM, Fennell D, Steele JP. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer. 2009 Jan;63:94-97.
39. Zucali PA, Perrino M, Lorenzi E, et al. Vinorelbine in pemetrexed-pretreated patients with malignant pleural mesothelioma. Lung Cancer. 2014 Jun;84:265-270.

40. Ceresoli GL, Zucali PA, De Vincenzo F, et al. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. Lung Cancer. 2011 Apr;72(1):73-7.
41. Zucali PA, Simmonelli M, Michetti G, Tiseo M, Ceresoli GL, Collovà E, Follador A, Lo Dico M, Moretti A, De Vincenzo F, et al. Second-line chemotherapy in malignant pleural mesothelioma: Results of a retrospective multicenter survey. Lung Cancer. 2012 Mar;75(3):360-7.
42. Armato SG, Nowak AK. Revised modified Response Evaluation Criteria in Solid Tumors for assessment of response in malignant pleural mesothelioma (version 1.1). J Thorac Oncol. 2018 Jul;13(7):1012-1021.
43. Kaufman RJ. Identification of the components necessary for adenovirus translational control and their utilization in cDNA expression vectors. Proc Natl Acad Sci USA. 1985;82:689-93.
44. Graham FL, Prevec L. Methods of construction of adenovirus vectors. Mol Biotechnol. 1995 Jun;3:207-20.
45. European Union Directive 2000/54/EC – biological agents at work, 2000.
46. National Institutes of Health guidelines for research involving recombinant or synthetic nucleic acid molecules (NIH guidelines), NIH Guidelines, 2016.
47. World Health Organization Laboratory safety manual 3rd Ed, 2004.
48. rAd-IFN Investigator's Brochure, Version 1.0. Trizell, Ltd. Chinnor, Oxon. February 2018.
49. Datapharm. Electronic medicines compendium. Celecoxib 200 mg capsules. https://www.medicines.org.uk/emc/product/2116/smpc. Accessed 27 April 2021.
50. National Institutes of Health. US National Library of Medicine. DailyMed. CELECOXIB capsule. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e811c3a-5653-4617-b958-380802cc443a. Accessed 28 April 2021.
51. Dataphram. Electronic medicines compendium. Gemcitabine 1000 mg powder for soution for infusion. https://www.medicines.org.uk/emc/product/3119/smpc. Accessed 27 April 2021.
52. National Institutes of Health. US National Library of Medicine. DailyMed. GEMCITABINE injection, powder, lyophilized, for solution. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d16907e7-a8c8-4039-ace4-cf4e24ba68c0. Accessed 28 April 2021.
53. Macmillan Cancer Support Organisation. Coronavirus vaccine for people living with cancer. https://www.macmillan.org.uk/coronavirus/vaccine. Accessed 28 April 2021.

APPENDIX A: SCHEDULE OF PROCEDURES

Table 1. Schedule of Procedures

Study Visit Day	Screening	Day 1[1]	Day 2	Day 7	Day 14	Day 21	Day 28			EOT (Disease Progression)/ ET Visit	Clinical Follow-Up Visit[2]
Gemcitabine Cycle[3]					C1, D1	C1, D8	C1, D15	C2, 3, 4, etc., D1	C2, 3, 4, etc., D8		
Visit Window (Days)	-28 to 0[4]			±1	±1	±1	±3	±3	±3	±3	±14
Informed consent[5]	X										
Demographics	X										
Medical history	X										
Physical examination	X	X	X[6]	X	X	X		X	X	X	
Vital signs[7]	X	X	X[6]	X	X	X		X	X	X	
Clinical chemistry, hematology, coagulation, and urinalysis	X[8]	X		X	X	X	X	X	X	X	
Pregnancy test (serum)[9]	X	X			X			X		X	
ECG (resting)	X	X			X			X		X	
Confirmation of tumor histology, including PD-L1 expression[10]	X										
CT scan of chest, abdomen, and pelvis (radiographic tumor assessment)	X[11]							X[12]			
Assessment of pleural space for ability to site an IPC or similar device	X										
ECOG performance status	X										
Randomization[13]	X										
Serum mesothelin and fibulin-3		X						X			
Adenovirus type 5 neutralizing antibodies		X									
Viral shedding and biodistribution (Viral Shedding Cohort only)[14]		X	X[6]	X	X	X	X				
Insert IPC or similar device[6]	X[15]										
rAd-IFN administration[6,16]		X									
IPC or similar device removal[6]		X[17]									
Celecoxib[18]		← X →									
Gemcitabine[19]					X	X		X	X		
QoL assessment (EQ-5D-5L and LCSS-Meso [patient and observer])	X				X			X			

Table 1. Schedule of Procedures (Continued)

Study Visit Day	Screening	Day 1[1]	Day 2	Day 7	Day 14	Day 21	Day 28			EOT (Disease Progression)/ ET Visit	Clinical Follow-Up Visit[2]
Gemcitabine Cycle[3]					C1, D1	C1, D8	C1, D15	C2, 3, 4, etc., D1	C2, 3, 4, etc., D8		
Visit Window (Days)	-28 to 0[4]			±1	±1	±1	±3	±3	±3	±3	±14
Review diary/complete capsule count to calculate compliance and accountability			X[6,20]	X[20]	X[20]	X					
Adverse events[21]	X	X	X[6]	X	X	X	X	X	X	X	X[22]
Concomitant medications	X	X	X[6]	X	X	X	X	X	X	X	X[23]
Submit all CT scans to central archive[24]	X							X		X	
Survival[25]											X

Note: Informed consent will be obtained prior to performance of any study-related procedures. An optional pre-Screening ICF will be available for patients choosing to submit their archival tumor tissue for histological assessment prior to consenting to the study. The pre-Screening ICF will not include consent for any other study-related procedures. Patients may choose to forego the optional pre-Screening ICF and only sign the main study ICF. All patients will need to sign the main study ICF in order to proceed with any other study-related procedures. The main study ICF will allow patients to complete Screening procedures in parallel with submitting their archival tumor tissue.
Assessments that are scheduled to be performed on treatment days may be completed on non-treatment days as long as the assessment is completed within the visit window.

1. The following assessments will be performed for all patients before starting study treatment on Study Day 1 or within 24 hours before starting study treatment (i.e., the following Study Day 1 assessments may be split over 2 days): vital signs; physical examination; clinical chemistry, hematology, coagulation, and urinalysis; serum mesothelin and fibulin-3 measurement; adenovirus type 5 neutralizing antibodies; pregnancy test; ECG (resting); adverse events; concomitant medications; and IPC or similar device insertion (if not previously inserted [rAd-IFN treatment group only]). The first dose of celecoxib (400 mg) will be administered orally 1 to 2 hours prior to rAd-IFN administration (rAd-IFN treatment group) or on Study Day 1 (control group). rAd-IFN will be administered via the intrapleural route by the Principal Investigator or designee and recorded in the source documents and eCRF. The following assessments will be performed on Study Day 1 for all patients (post-rAd-IFN administration for the rAd-IFN treatment group): celecoxib dosing (at home), provide celecoxib diary, viral shedding and biodistribution (for Viral Shedding Cohort only), adverse events, and concomitant medications. Study Day 1 will be a maximum of 28 days after the start of Screening unless an extension is approved by the Sponsor or Medical Monitor.
2. Following the EOT (Disease Progression) Visit or ET, patients in the rAd-IFN treatment group will continue to have clinical Follow-up Visits every 6 months (±14 days) for survival and safety for up to 5 years after receiving the first dose of rAd-IFN, assuming consent has not been withdrawn. Cause and date of death will be recorded where possible. Clinical Follow-up Visits can be performed face-to-face, through physician contact, or by telephone.
3. Patients will receive gemcitabine on a 21-day cycle, unless the cycle is modified due to toxicity/delay, that will continue every 3 weeks until disease progression/ET.
4. An extension to the Screening Period will be permitted on a case-by-case basis following discussion between the Investigator, the Medical Monitor, and/or the Sponsor. The reason(s) for the extension is to be clearly documented.
5. The main study ICF will also contain a section for patients to confirm their consent to participate in the Viral Shedding Cohort. The Viral Shedding Cohort is an optional cohort for those patients who are randomized to the rAd-IFN treatment group. Not all patients who consent to the Viral Shedding Cohort will be included in this cohort as it will depend on their treatment randomization and whether any slots remain in this cohort. Medpace will confirm availability of slots for those patients randomized to the rAd-IFN treatment group.
6. rAd-IFN treatment group only.
7. Vital sign measurements will be taken after at least a 5-minute rest in a sitting or supine position. Measurements will include blood pressure, respiratory rate, pulse rate, and body temperature. Weight and height will be measured at Screening. Weight will also be measured on Day 1 and Day 8 of all gemcitabine cycles and can be used to calculate the gemcitabine dose for that visit.
8. Assessment must be performed within 28 days prior to Study Day 1. Estimated glomerular filtration rate will be calculated using the Modification of Diet in Renal Disease study equation at Screening only.

9. Local serum pregnancy test for female patients of childbearing potential only. Confirmation of negative pregnancy test must be obtained within 24 hours prior to dosing with rAd-IFN.
10. Tumor histology will be confirmed centrally using specimens or slides from tumor specimens obtained at the time of initial presentation or a subsequent procedure. Fresh tumor biopsies will not be taken as part of this study. Confirmation of tumor histology is required prior to inclusion into the study. Information on PD-L1 tumor expression should be collected but is not required prior to inclusion into the study.
11. CT scan must be performed within 28 days prior to Study Day 1. The CT scan performed during Screening will be used as the patient's baseline modified Response Evaluation Criteria in Solid Tumors 1.1 assessment. Standard of care CT scans completed within 2 weeks prior to Screening may be used in place of the Screening CT scan on a case-by-case basis as agreed with the Medical Monitor.
12. The first CT scan after randomization will be performed at gemcitabine Cycle 3 Day 1 (±3 days). Subsequent CT scans will be performed every 9 weeks (±3 days) until disease progression/ET. The CT scan schedule of every 9 weeks (±3 days) from gemcitabine Cycle 3 Day 1 will be maintained regardless of gemcitabine dose delays or interruptions.
13. During the Screening Period, after tumor histology results are received, and the patient is confirmed to be eligible for the study, randomization via IRT will take place. The target interval between randomization and Study Day 1 should be up to 7 days and no greater than 14 days. Any extension beyond 14 days will be considered on a case-by-case basis, following discussion between the Investigator, Medical Monitor, and Sponsor.
    For patients randomized to the rAd-IFN treatment group who do not have a pre-existing IPC or similar device, schedule IPC or similar device placement for either on or before Study Day 1.
14. For patients in the rAd-IFN treatment group participating in the Viral Shedding Cohort only. Viral shedding evaluations will include collection of saliva, urine, pleural access site swab, and blood samples for biodistribution, taken at designated time points 2 to 3 hours post-rAd-IFN administration (Study Day 1); approximately 24 hours post-rAd-IFN administration (Study Day 2); and on Study Days 7, 14, 21, and 28. A pleural fluid sample will be collected using the IPC or similar device (if the IPC or similar device is still in place) approximately 24 hours post-rAd-IFN administration (Study Day 2) and on Study Days 7, 14, 21, and 28.
15. For patients in the rAd-IFN treatment group who do not have a pre-existing IPC or similar device, an IPC or similar device must be inserted on or before Study Day 1, prior to rAd-IFN administration. For all rAd-IFN treatment group patients (i.e., patients with a previously inserted or a newly inserted IPC or similar device), the correct position of the IPC or similar device will be confirmed by the Investigator or an appropriately qualified designee, in accordance with local institutional practice.
16. rAd-IFN will be administered as described in Section 5.1.2. It is recommended that the pleural space is not drained within the first 24 hours post-rAd-IFN administration, unless deemed necessary by the Investigator.
    See Section 5.1.4 for instructions to prepare the patient and to monitor the patient before, during, and after rAd-IFN administration.
17. At the discretion of the Investigator, the IPC or similar device may be removed at any time during the 6-hour post-rAd-IFN administration observation period or at the Study Day 2 Visit. The Investigator may keep the IPC or similar device in situ beyond the Study Day 2 Visit if required for clinical purposes.
18. All patients will take oral celecoxib 400 mg BID on Study Days 1 to 14; no celecoxib should be taken after Study Day 14. The first dose of celecoxib will be administered 1 to 2 hours prior to rAd-IFN administration (rAd-IFN treatment group) or on Study Day 1 (control group). The patient will be provided with the remainder of the 14-day treatment to be taken at home. The patient will be provided with a celecoxib diary and instructed that the next dose should be taken approximately 12 hours post-rAd-IFN administration (rAd-IFN treatment group) or approximately 12 hours after the first celecoxib dose (control group) and 400 mg orally BID, at approximately 12-hour intervals, thereafter. If the patient receives the first dose of celecoxib late on Study Day 1, such that the patient is only able to take 1 dose of celecoxib on Study Day 1, the patient must not take a celecoxib dose on Study Day 15, regardless of whether or not the patient has taken all planned celecoxib doses. If BID dosing does not occur on Study Day 1 for this reason, it will not be considered a protocol deviation. If the patient vomits after taking celecoxib, the patient should not replace that dose; instead, the patient should wait until the next scheduled time point to take their next scheduled celecoxib dose.
19. 1250 mg/m^2 administered intravenously on Days 1 and 8 of a 21-day gemcitabine cycle, unless the cycle is modified due to toxicity/delay. See Section 5.6 for details regarding gemcitabine treatment delay.
20. Retrain patients with <100% compliance (unless the only reason compliance is <100% is a result of the patient taking the first dose of celecoxib late on Study Day 1, such that the patient is only able to take 1 dose of celecoxib on Study Day 1).
21. All adverse events will be monitored and documented from the time of the main study's informed consent through 30 days after the last dose of study treatment (rAd-IFN, celecoxib, and gemcitabine).
22. All previously recorded treatment-emergent adverse events and SAEs will be followed until resolution or stabilization.
23. Concomitant medications specific for mesothelioma treatment.

24. All CT scans will be submitted for central archiving on an ongoing basis throughout the study. Any CT scans completed for standard of care purposes after disease progression/ET will not be collected for the central archive.
25. Where applicable, patients in the rAd-IFN treatment group who have withdrawn from study treatment, not including those who have withdrawn prior to commencing Study Day 1 treatment, will be asked if they would agree to continue to be followed for survival and safety every 6 months (±14 days) for up to 5 years.

BID = twice daily; C = cycle; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; ET = early termination; ICF = informed consent form; IPC = intrapleural catheter; IRT = Interactive Response Technology; LCSS-Meso = Lung Cancer Symptom Scale-mesothelioma; PD-L1 = programmed death-ligand 1; QoL = Quality-of-Life; rAd-IFN = recombinant adenovirus vector containing the human interferon alpha-2b gene; SAE = serious adverse event.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen (or local equivalent)	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate [1, 2]
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lipase
Magnesium	Potassium
Sodium	Total bilirubin
Total protein	Total cholesterol
Triglycerides	Uric acid (or local equivalent)

1. Estimated glomerular filtration rate will be calculated using the Modification of Diet in Renal Disease study equation, i.e., Estimated glomerular filtration rate (mL/min/1.73 m^2) = $175 \times (\text{serum creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742$ if female) $\times (1.212$ if African American), where serum creatinine is reported in μmol/L.
2. Estimated glomerular filtration rate will be calculated at Screening only.

Hematology

Absolute neutrophil count	Hematocrit
Hemoglobin	Platelets
Red blood cell count	Reticulocyte
White blood cell count and differential [1]	

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy is performed only as needed based on initial positive test results.

Pregnancy Test

Serum pregnancy tests will be performed for female patients of childbearing potential only.

APPENDIX C: MODIFIED RECIST 1.1 CRITERIA ADAPTED TO THE GROWTH PATTERN OF MALIGNANT PLEURAL MESOTHELIOMA

The baseline computed tomography (CT) scan of chest, abdomen, and pelvis performed during Screening will be used to determine restaging of the disease. Only those patients with no evidence of malignant pleural mesothelioma outside of the thoracic cavity will be eligible for the study. The baseline CT scan performed during Screening and all other CT scans performed for the patient during the study will be required to be submitted to a central archive. Details are provided in the Imaging Manual. If patients have clinical symptoms of metastatic disease (e.g., bone pain), this should be evaluated before the patient is enrolled in the study.

This study seeks to evaluate therapy response by measuring tumor response to therapy in patients with malignant pleural mesothelioma (with no extrathoracic disease). Imaging evaluations will employ the modified Response Evaluation Criteria in Solid Tumors guideline (version 1.1), which is tailored to this disease. All patients enrolled in this study will be evaluated for therapy response approximately every 9 weeks, with measurements of target lesions performed locally. Changes in longest radial diameter for pleural lesions, longest diameter for thoracic non-pleural, thoracic non-nodal measurements, and shortest diameter in the case of malignant thoracic lymph nodes will be assessed for target lesions identified at baseline for each re-imaging time point over the course of the study.

General Guidelines for Measurement of Disease Response

Timing of disease measurement: Baseline imaging (i.e., CT scan of the chest, abdomen, and pelvis) must be performed within 28 days prior to Study Day 1. The CT scan performed during Screening will be used as the patient's baseline modified Response Evaluation Criteria in Solid Tumors 1.1 assessment. Standard of care CT scans completed within 2 weeks prior to Screening may be used in place of the Screening CT scan on a case-by-case basis as agreed with the Medical Monitor. The purpose of baseline imaging is to exclude ineligible patients with extrathoracic disease and identify measurable sites of disease that will be followed over time for evidence of response. The first CT scan after randomization will be performed at gemcitabine Cycle 3 Day 1 (±3 days). Subsequent CT scans will be performed every 9 weeks (±3 days) until disease progression/early termination. The CT scan schedule of every 9 weeks (±3 days) from gemcitabine Cycle 3 Day 1 will be maintained regardless of gemcitabine dose delays or interruptions.

Identifying sites of measurable disease: Measurable disease is defined by the presence of at least 1 measurable lesion. In addition to identifying the sites of disease, the evaluator must decide if the disease is measurable. In choosing sites of measurable disease, it is vital to choose sites that allow for reproducible measurement since slight variations in lesion measurement can introduce unwanted variability in response assessment. This is of particular importance in the case of pleural disease.

Measurement technique: All measurements will be recorded in metric notation using millimeters by use of a ruler or calipers. Radial measurements of the pleural thickness will be made with measurement trajectories perpendicular to the surface of the pleura using the same orientation of measurement for all subsequent follow-up scans. In order to ensure reproducibility for subsequent measurements, it is advised that a screenshot of the measurements be retained.

Modalities used for measurement: CT scan is the mandated modality for tumor imaging assessments in this study. The measurability of lesions on a CT scan provided in this Clinical Study Protocol is based on the assumption that the CT slice thickness is ≤5 mm.

Computed tomography imaging protocol recommendations: The modality of choice for imaging evaluation in this study is diagnostic CT scan performed on multidetector CT and obtained with intravenous contrast enhancement when possible. The same imaging technique will be used to acquire CT images at baseline and for imaging acquired on therapy for tumor response assessment. Images of the chest should be acquired at full inspiration with coverage of the entire chest and include the abdomen and pelvis. Axial, coronal, and sagittal reconstructions with 1 mm slice thickness are recommended, and the maximum allowable slice thickness is 5 mm.

Definitions of Disease Measurements

The following are definitions relevant to therapy response assessment in this study. Measurable disease is necessary for sites of disease to qualify as target lesions.

Measurable disease (pleural): Measurable disease in the pleural space is defined as a lesion with a minimum pleural thickness of 7 mm. This measurement of pleural thickness is measured radially, perpendicular to the curvature of the pleural surface. Care should be taken to accurately discriminate between pleural tumor and adjacent pleural plaque, complex pleural fluid, atelectatic lung, and chest wall soft tissues. Target lesions should be chosen at locations with anatomical landmarks that allow for reproducible measurement longitudinally. This sometimes may mean that the target lesion chosen is not the largest lesion available. In general, it is preferable to choose lesions away from pleural fluid and not in proximity to the diaphragm, since the curvature of the diaphragm can be variable based on the degree of inspiration. In addition, the curvature of the pleura at the lung apex can result in measurement error. The preferred site of pleural measurement is as follows:

- Superior to the level of the left atrium (to minimize inspiratory effort and pleural curvature), and
- Below the level of the aortic arch (to minimize the impact of pleural curvature).

All tumor measurements must be recorded in millimeters. In the case of bilateral disease, the pleura of both hemithoraces are considered 1 organ.

Measurable disease (thoracic non-pleural, thoracic non-nodal): Thoracic non-nodal lesions outside of the pleural space must measure at least 10 mm in the longest dimension to be considered measurable for assignment as target lesions. All tumor measurements must be recorded in millimeters.

Measurable disease (thoracic nodal): To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis. At baseline and in follow-up examinations, only the short axis will be measured and followed.

New lesions: New lesions represent new sites of malignant involvement. If a new site of disease is in question but not certain to be malignant, then this lesion should be considered a “finding” rather than a “new lesion” since the later term automatically implies progressive disease (PD). If a “finding” is later discovered to represent a site of disease, it should be re-categorized as a “new lesion” dating from the time it first manifested. An enlarging lymph node should not be considered a “new lesion” if it is <15 mm in the short axis. If the newly enlarged lymph node has been

biopsy-proven to be malignant, the newly enlarged lymph node is considered a "new lesion" even if the short axis is <15 mm.

Non-measurable disease: Sites of malignant disease that are smaller than the threshold to be considered measurable (i.e., pleural disease <7 mm in radial thickness; thoracic nodal disease ≥10 mm but <15 mm in the short axis; or thoracic non-nodal, thoracic non-pleural disease <10 mm in the long axis) are considered non-measurable disease and can be followed as non-target lesions. Also included in this category are lesions at sites of disease that are measurable in size but are in excess of the allowed number of target lesions at that site.

Evaluable for therapy response assessment: Only patients with measurable disease present at baseline who have received at least 1 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.

Assessment of Baseline Imaging

All baseline evaluations should be performed as close as possible to the beginning of treatment and never more than 28 days prior to Study Day 1, unless there is prior agreement with the Medical Monitor as stated in this protocol. At baseline, prior to the start of therapy, sites of measurable disease must be determined and target lesions as well as non-target lesions must be defined. These are the lesions that will be assessed, longitudinally, over the course of therapy to determine tumor response to therapy. At baseline, the determination will be made as to whether the patient has measurable disease and can be a candidate for this study. Tumor lesions will be assigned as follows.

Target lesions: If the patient has exclusively pleural disease, all measurable pleural lesions up to 6 lesions can be included as target lesions using the following rule: no more than 2 lesions measured per slice and image slices should be chosen at least 1 cm apart. Pleural lesions should be chosen in locations with anatomical landmarks that are reproducible for longitudinal assessments to maintain accuracy in assessment of therapy response.

In patients with a mix of pleural and thoracic non-pleural disease, all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total can be included as target lesions. For measurable target lesions that are both pleural and thoracic non-pleural, the pleura (inclusive of both hemithoraces) are considered 1 organ. Target lesions should be chosen so that they are representative of all of the organs involved to convey the changes in overall tumor burden. As with pleural disease, lesions should be chosen in locations with anatomical landmarks that are reproducible for longitudinal assessments.

Non-target lesions: Disease that is evaluable but does not meet the criteria for measurable disease, or exceeds the allowed number of target lesions for a specified organ, can be assigned as a non-target lesion. These lesions will be assessed for presence, absence, and significant change in burden over time. Although, patients with only non-target lesions will not be enrolled in the study.

Assessment of Tumor Response to Therapy

In order to determine the tumor response to therapy, the diameters of the target lesions are summed at each time point beginning with the baseline imaging. At each subsequent post-therapy time point, the new post-therapy sum is compared to the baseline sum, and the percent change is calculated. This percent change is used to assign an objective response for that time point.

Target lesions: At each post-therapy time point, the target lesions that are identified at baseline will be measured using millimeter measurements. The same measurement technique and imaging modality will be made for these serial measurements.

- Pleural lesions that remain detectable but are too small to measure are indicated as "too small," and a default measurement of 2 mm is assigned to that lesion for that time point. If the lesion can be measured, it should be measured, and the measurement should be recorded. Lesions that disappear completely are termed "disappeared."
- Thoracic non-pleural, thoracic non-nodal lesions that are detectable but are too small to measure are indicated as "too small," and a default measurement of 5 mm is assigned to that lesion for that time point. If the lesion can be measured, it should be measured, and the measurement should be recorded. Lesions that disappear completely are termed "disappeared."
- For thoracic lymph nodes, a decrease in size such that the short axis measurement is <10 mm is considered "disappeared."

Non-target lesions: All baseline evaluations of non-target lesions will be recorded separate from the time point sum. These lesions are not measured but rather are qualitatively assessed at each time point with a determination made as to whether they are stable, significantly progressed, significantly regressed, or disappeared.

- For thoracic non-pleural lesions, these non-target lesions may be individually identified.
- For pleural lesions, if these non-target lesions represent a few discrete lesions beyond those measured as target lesions, they may be individually identified as non-target lesions. In cases where there is extensive pleural nodularity or pleural tumor cannot be discriminated from adjacent diaphragm or complex pleural effusion, specific descriptors characterizing this disease should be used such as "circumferential pleural thickening" or "tumor indistinguishable from diaphragm."
- For thoracic nodal lesions considered to be malignant, lymph nodes ≥10 mm in the short axis but <15 mm may be considered non-target lesions.

Assignment of objective time point response: target lesions

Progressive disease: The criteria for an assessment of PD are met if either of the following are true:

- The time point sum of target lesion diameters increased by at least 20% taking as reference the smallest time point sum in the course of the study (including the baseline, if that is the smallest sum on study), which must be at least a 5 mm increase in sum when compared to the baseline sum; or
- New lesions are present.

Stable disease (SD): The criteria for an assessment of SD are met if the following is true:

- The criteria for complete response (CR), partial response (PR), or PD are not met (i.e., <20% increase or <30% decrease in time point sum, or >20% increase in time point sum but the increase is not at least 5 mm, taking as reference the smallest time point sum in the course of the study [including the baseline, if that is the smallest sum on study]).

Partial response: The criteria for an assessment of PR are met if the following are true:

- There is a >30% decrease in the time point sum of the target lesion diameters taking as reference the baseline sums, and
- Criteria for PR are met on 2 sequential re-imaging assessments performed >4 weeks apart.

Complete response: The criteria for an assessment of CR are met if the following are true:

- There is complete disappearance of the target lesion (if thoracic non-nodal),
- There is regression of thoracic nodal disease such that all malignant thoracic lymph nodes have a short axis <10 mm, and
- Criteria for CR are met on 2 sequential re-imaging assessments performed >4 weeks apart.

Assignment of time point response: non-target lesions

In the majority of cases, the overall time point response will be determined by the assessment of the changes in the target lesion sums. However, there may be rare cases of marked enlargement of a non-target lesion that is considered unequivocal progression and will result in an assessment of PD.

Progressive disease: The criteria for PD are fulfilled if the following are true:

- Appearance of ≥1 new lesion, and/or
- Unequivocal progression of existing non-target lesions.

  Note: Marked enlargement of the non-target lesion must be comparable to an increase in disease that would be considered progression for a target lesion. Non-target disease evaluation should not normally trump target lesion status. The non-target disease evaluation must be representative of overall disease status change, not a single lesion increase.

Non-CR/non-PD: The criteria for non-CR/non-PD are fulfilled if the following is true:

- There is persistence of non-target lesions, and the criteria for PD or CR are not met.

Complete response: The criteria for CR are fulfilled if the following are true:

- There is complete disappearance of all non-target lesions (if thoracic non-nodal), and
- There is regression of thoracic nodal disease such that all malignant thoracic lymph nodes have a short axis <10 mm.

Assignment of best overall response

The best overall response represents the best response recorded from the start of the treatment until completion of the patient's involvement in the study. For assignment of CR, PR, and SD, there is a requirement of confirmation with a CT at least 4 weeks later.

Table 2. Summary of Key Points for Modified Response Evaluation Criteria in Solid Tumors 1.1

Minimum lesion size for target lesions	Pleural (radial pleural thickness): 7 mm Thoracic non-pleural, thoracic non-nodal (longest diameter): 10 mm Thoracic nodal (short axis): 15 mm
Default measurement for target lesions that become too small to measure	Pleural: 2 mm Thoracic non-pleural, thoracic non-nodal: 5 mm Thoracic lymph nodes become "disappeared" when <10 mm in the short axis
Number of target lesions to include in time point sum	If only pleural disease: 6 lesions[1] If mix of pleural and thoracic non-pleural: maximum of 5 target lesions and no more than 2 per organ[2]

1. When measuring pleural lesions, no more than 2 lesions per image slice. Image slices should be at least 1 cm apart.
2. Pleura count as 1 organ, even if bilateral disease.

Source: Armato SG, Nowak AK. Revised modified Response Evaluation Criteria in Solid Tumors for assessment of response in malignant pleural mesothelioma (version 1.1). J Thorac Oncol. 2018 Jul;13(7):1012-1021.

APPENDIX D: CYTOCHROME P450 INHIBITORS, INDUCERS, AND SUBSTRATES

A listing of cytochrome P450 inhibitors, inducers, and substrates can be found using the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Table 3. Inhibitors, Inducers, and Substrates of Cytochrome P450 1A2, 2C9, and 2D6

Cytochrome P450	Substrate	Inhibitor	Inducer
1A2	Amitriptyline, caffeine, clomipramine, clozapine, cyclobenzaprine, duloxetine, estradiol, fluvoxamine, haloperidol, imipramine N-DeMe, mexiletine, nabumetone, naproxen, olanzapine, ondansetron, phenacetin, acetaminophen, NAPQI, propranolol, riluzole, ropivacaine, tacrine, theophylline, tizanidine, triamterene, verapamil, (R)warfarin, zileuton, zolmitriptan	Fluvoxamine, ciprofloxacin, cimetidine, amiodarone, efavirenz, fluoroquinolones, fluvoxamine, furafylline, interferon, methoxsalen, mibefradil, ticlopidine	Broccoli, brussel sprouts, carbamazepine, char-grilled meat, insulin, methylcholanthrene, modafinil, nafcillin, beta-naphthoflavone, omeprazole, rifampin, tobacco
2C9	Diclofenac1, ibuprofen, lornoxicam, meloxicam, S-naproxen, piroxicam, suprofen, tolbutamide, glipizide, losartan, irbesartan, glyburide, glibenclamide, glipizide, glimepiride, tolbutamide, amitriptyline, celecoxib, fluoxetine, fluvastatin, glyburide, nateglinide, phenytoin-4-OH2, rosiglitazone, tamoxifen, torsemide, valproic acid, S-warfarin, zafirlukast	Fluconazole, amiodarone, efavirenz, fenofibrate, fluconazole, fluvastatin, fluvoxamine, isoniazid, lovastatin, metronidazole, paroxetine, phenylbutazone, probenecid, sertraline, sulfamethoxazole, sulfaphenazole, teniposide, voriconazole, zafirlukast	Carbamazepine, enzalutamide, nevirapine, phenobarbital, rifampin, secobarbital, St. John's Wort
2D6	Tamoxifen, carvedilol, S-metoprolol, propafenone, timolol, amitriptyline, clomipramine, desipramine, fluoxetine, imipramine, paroxetine, venlafaxine, haloperidol, perphenazine, risperidone, thioridazine, zuclopenthixol, alprenolol, amphetamine, aripiprazole, atomoxetine, bufuralol, chlorpheniramine, chlorpromazine, clonidine, codeine, debrisoquine, dexfenfluramine, dextromethorphan, donepezil, duloxetine, encainide, flecainide, fluvoxamine, lidocaine, metoclopramide, methoxyamphetamine, mexiletine, minaprine, nebivolol, nortriptyline, ondansetron, oxycodone, perhexiline, phenacetin, phenformin, promethazine, propafenone, propranolol, risperidone, sparteine, tramadol	Bupropion, cinacalcet, fluoxetine, paroxetine, quinidine, duloxetine, sertraline, terbinafine, amiodarone, cimetidine, celecoxib, chlorpheniramine, chlorpromazine, citalopram, clemastine, clomipramine, cocaine, diphenhydramine, doxepin, doxorubicin, escitalopram, halofantrine, haloperidol, histamine H1 receptor antagonists, hydroxyzine, levomepromazine, methadone, metoclopramide, mibefradil, midodrine, moclobemide, perphenazine, promethazine, ranitidine, reduced-haloperidol, ritonavir, ticlopidine, tripelennamine	Dexamethasone, rifampin

NAPQI = N-acetyl-p-benzoquinone imine.
Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

APPENDIX E: GRADING AND MANAGEMENT OF CYTOKINE RELEASE SYNDROME

Table 4. Cytokine Release Syndrome Revised Grading System

Grade	Toxicity
Grade 1	Symptoms are not life-threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgias, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose of 1 vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose[1] or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

Note: Grade 2 through Grade 4 organ toxicity and Grade 4 transaminitis refer to Common Terminology Criteria for Adverse Events v4.03 grading.

1. High vasopressor doses are defined in Table 5.

Source: Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95.

Table 5. High Vasopressor Doses

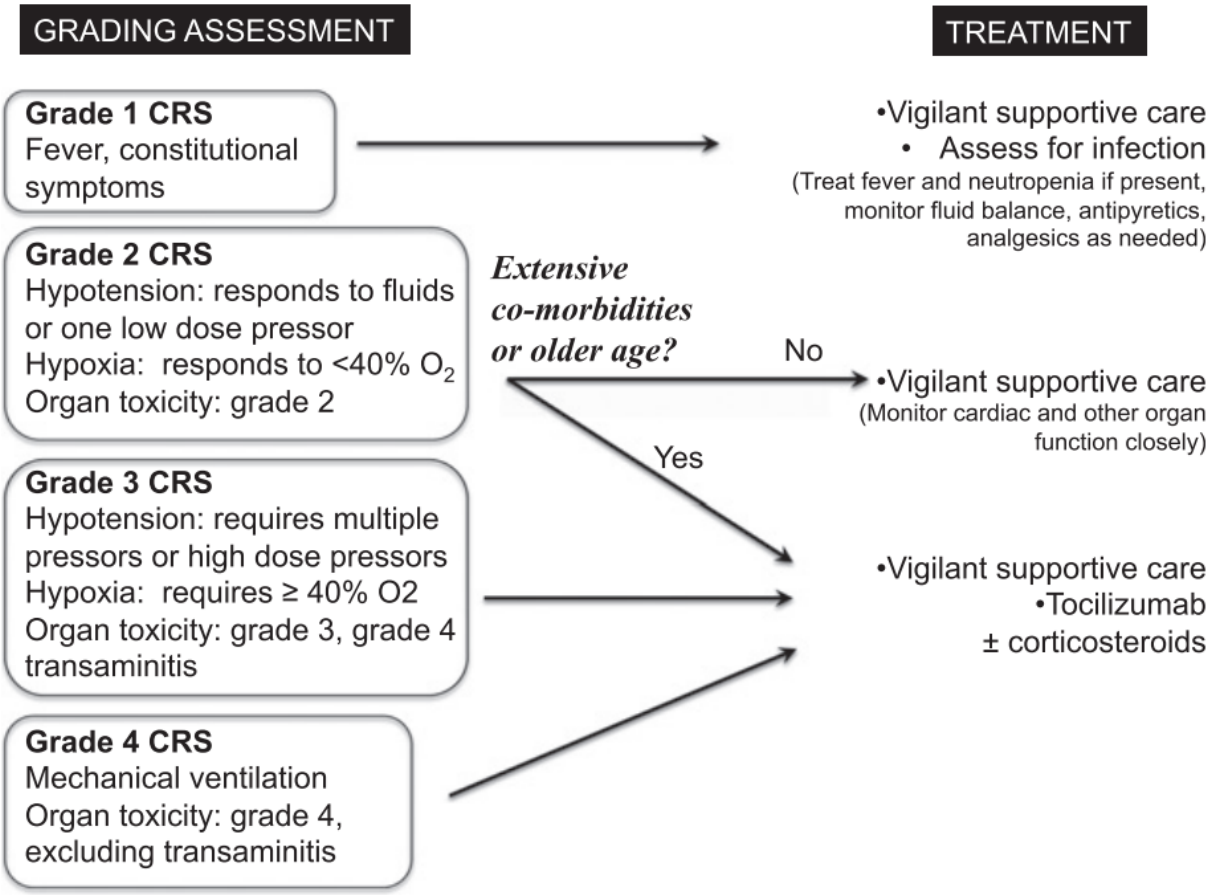
Pressor	Dose
Norepinephrine monotherapy	≥20 μg/min
Dopamine monotherapy	≥10 μg/kg/min
Phenylephrine monotherapy	≥200 μg/min
Epinephrine monotherapy	≥10 μg/min
If on vasopressin	Vasopressin and norepinephrine equivalent of ≥10 μg/min[1]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 μg/min[1]

Note: All doses are required for ≥3 hours.

1. Vasopressin and Septic Shock Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (μg/min)] + [dopamine (μg/kg/min)/2] + [epinephrine (μg/min)] + [phenylephrine (μg/min)/10].

Source: Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95.

Figure 2. Treatment Algorithm for Management of Cytokine Release Syndrome Based on the Cytokine Release Syndrome Revised Grading System



Note: Grade 2 through Grade 4 organ toxicity and Grade 4 transaminitis refer to Common Terminology Criteria for Adverse Events v4.03 grading.
CRS = cytokine release syndrome.
Source: Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95.

APPENDIX F: DOSE MODIFICATION STRATEGIES FOR CELECOXIB AND GEMCITABINE

Table 6. Dose Modification Strategies for Celecoxib and Gemcitabine for All Toxicities

	Celecoxib	Gemcitabine
Temporary discontinuation	Not applicable	For severe (CTCAE Grade 3 or 4) non-hematological toxicity, except nausea/vomiting, treatment with gemcitabine should be withheld or decreased depending on the judgment of the Investigator. Treatment should be withheld until toxicity has resolved.
Permanent discontinuation	1. Appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity 2. CTCAE Grade 3 or higher deterioration in renal or hepatic function	1. Unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity 2. Severe hepatic toxicity 3. Posterior reversible encephalopathy syndrome 4. Capillary leak syndrome 5. Hemolytic uremic syndrome If pulmonary effects, such as pulmonary edema, interstitial pneumonitis, or adult respiratory distress syndrome, develop at any time during the study, the Investigator should discuss with the Sponsor and consider discontinuing gemcitabine.
Dose modification	Not applicable	Dose modifications due to hematological toxicities for all cycles should be performed in accordance with Table 7.

CTCAE = Common Terminology Criteria for Adverse Events.

Table 7. Dose Modification of Gemcitabine Due to Hematological Toxicities for All Cycles

Absolute Granulocyte or Neutrophil Count ($\times 10^9$/L)		Platelet Count ($\times 10^9$/L)	% of Total Dose
>1	and	>100	100
0.5-1	or	50-100	75
<0.5	or	<50	Withhold[1]

1. Withheld treatment will not be reinstated within a cycle before the absolute granulocyte count reaches at least 0.5×10^9/L and the platelet count reaches 50×10^9/L.

Gemcitabine Missed Doses and Treatment Delay

The following rules will be applied if any of the following gemcitabine doses are missed in the 21-day gemcitabine cycle:

- Day 1 of any cycle can be delayed by a maximum of 7 days to accommodate a maximum of 21 days between the Day 1 dose and the previous cycle's Day 8 dose;
- Day 8 of any cycle can be delayed by a maximum of 7 days to accommodate a maximum of 14 days between the Day 1 dose and the Day 8 dose of the same cycle; and
- If Day 8 of any cycle is delayed, then the Day 1 dose for the next cycle must occur at least 14 days and up to a maximum of 21 days after the previous cycle's Day 8 dose.

If the maximum delay between a scheduled dose and the next dose is greater than what is described above, then this would be considered a missed dose.

If the time required for recovery from gemcitabine toxicity is more than 21 days, consideration should be given to permanently discontinue the patient from study treatment, unless the patient is demonstrating benefit overall; in which case, the possibility of remaining on study treatment should be discussed between the Investigator, Medical Monitor, and Sponsor after review of the associated risks and benefits.

APPENDIX G: PLEURAL FLUID SAMPLE COLLECTION PROCEDURE

The following steps are instructions to access the intrapleural catheter (IPC) or similar device and drain the pleural fluid:

1. Remove dressing;
2. Clean the skin area with ChloraPrep™, povidone-iodine, or a suitable alternative;
3. Clean the IPC or similar device with ChloraPrep™, povidone-iodine, or a suitable alternative;
4. Gown and glove;
5. Prepare sterile field;
6. Remove valve cap;
7. Clean the IPC or similar device tip with at least 3 alcohol swabs;
8. Clamp drainage line set and attach to the IPC or similar device. Insert the tip of the drainage tube into the valve. Continue to push the tip into the valve until you hear a click indicating that the valve and drainage tube are firmly connected;
9. Attach a 3-way stop cock to the drainage line;
10. Use a syringe of suitable volume to aspirate up to 20 mL of fluid for research specimens. If fluid is not obtained, see instructions below for pleural lavage;
11. Clamp drainage line;
12. If vacuum bottle is required to drain pleura, remove syringe and place a 16 gauge needle (or suitable alternative). Insert the needle into the vacuum bottle, release the clamp in the bottle, and release the clamp in the drainage tube. Fluid will immediately flow into the bottle;
13. When drainage is complete, grasp the drainage tube and pull the tip out of the IPC or similar device valve;
14. Wipe the valve with at least 3 alcohol swabs;
15. Place a new cap on the valve; and
16. Dress the IPC or similar device site as per local standard of care.