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Cover Page for Statistical Analysis Plan (SAP)

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	05 March 2024

STATISTICAL ANALYSIS PLAN
(SAP)

PROTOCOL rAd-IFN-MM-301

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
Development Phase:	3
Sponsor:	Trizell, Ltd.
Protocol Version (Date):	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
SAP Version:	V3.0
SAP Date:	05 March 2024

SAP SIGNATURE PAGE

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

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DOCUMENT REVISION HISTORY		
Document Version	**Document Date**	**Revisions**
1.0	13 September 2019	Create version 1.0
2.0	15 July 2022	Update based on Protocol V6.0
3.0	05 March 2024	Update based on Protocol V8.0

TABLE OF CONTENTS

ABBREVIATIONS & TERMS

ADI	Actual dose intensity
AE	Adverse event
ALP	Alkaline
ALT	Alanine Aminotransferase
ASBI	Average symptom burden index
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BMI	Body mass index
BOR	Best overall response
BUN	Blood Urea Nitrogen
CBR	Clinical benefit rate
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ECOG PS	Eastern Clinical Oncology Group Performance Status
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	European Quality of Life 5 dimensions 5 levels
ET	Early termination
FPFV	First patient first visit
GGT	Gamma-glutamyl transferase
HCT	Hematocrit
HR	Hazard ratio
ICF	Informed consent form
INR	International Normalized Ratio
IPC	Intrapleural catheter
IRT	Interactive Response Technology
KM	Kaplan-Meier
LCSS-Meso	Lung Cancer Symptom Scale-mesothelioma
LS	Lest squares
MedDRA	Medical Dictionary for Regulatory Activities

MPM	Malignant pleural mesothelioma
mRECIST	Modified RECIST criteria adapted to the growth pattern of MPM
NCI	National Cancer Institute
NE	Inevaluable
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDI	Planned dose intensity
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PT	Prothrombin time
aPTT	Activated partial thromboplastin time
Q1	First Quartile
Q3	Third Quartile
QoL	Quality of life
QTcF	Corrected QT interval by Fridericia formula
rAd-IFN	Recombinant adenovirus vector containing the human interferon alpha-2b gene
RBC	Red Blood Cell
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumor
REML	Restricted Maximum Likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease or Standard deviation(s)
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLFs	Table, listings, and figures
TTR	Time to response
ULN	Upper limit of normal
VAS	Visual Analogue Scale
vp	Viral particles
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol rAd-IFN-MM-301 and describes in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. Any deviations to the planned analyses specified within the SAP, will be justified in writing and described as such within the final Clinical Study Report (CSR).

2 STUDY OBJECTIVES

2.1 Primary Objective

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 malignant pleural mesothelioma (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 (CR), partial response (PR), or stable disease (SD)); 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 Objective

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 OVERVIEW

3.1 Overall Study Design

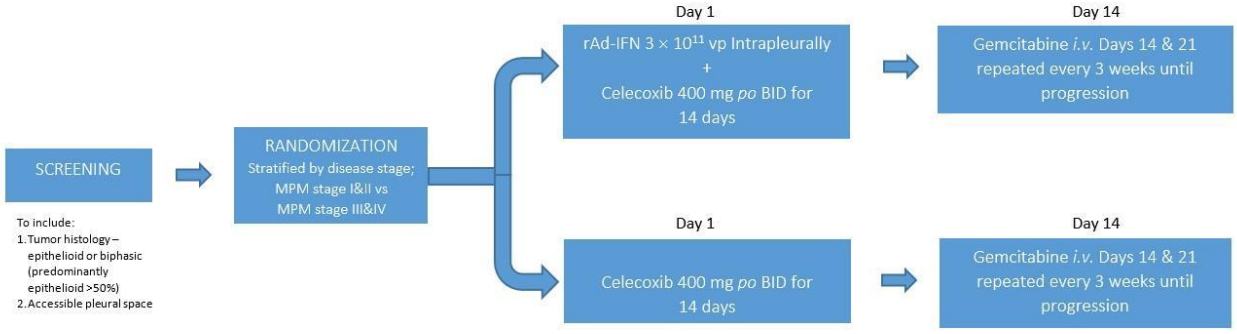
The study is an open-label, randomized, parallel group study conducted in patients with MPM and confirmed epithelioid or biphasic histology (if biphasic, histology must be predominantly [≥50%] epithelioid) who have received a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of 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 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 repeated every 3 weeks until disease progression/ET).

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.

3.2 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.

3.3 Study Centers

This is a multi-center study and will include up to 45 sites globally.

3.4 Study Population

The population for this study 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.

Specific inclusion and exclusion criteria are available in Sections 4.1 and 4.2 of the protocol.

3.5 Study Treatment

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 intrapleural catheter (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 and continued every 3 weeks until disease progression/ET.

3.6 Study Duration and End of Study

The study will consist of the following periods:

- Screening Period of up to 28 days,
- 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 repeated every 3 weeks until disease progression/ET, and
- Clinical Follow-Up Visits every 6 months (±14 days) for up to 5 years from date of treatment with rAD-IFN:

- 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 the survival/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 of the protocol). 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.

3.7 Randomization and Blinding

This is an open-label study. Eligible patients will be randomized to 1 of the 2 treatment groups (rAd-IFN treatment group or control treatment group).

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 each disease stage between treatment groups 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 assessment of tumor response will be performed by persons unblinded to treatment allocation. 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 asked to confirm if they will agree to survival follow up even if they withdraw from other study activities.

3.8 Study Assessments

For the detailed schedule of expected events and study procedures to be conducted during the study at each visit, please refer to Table 1 (Schedule of Procedures) in the protocol.

3.9 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.

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

4 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.

5 STUDY ENDPOINTS

5.1 Primary Efficacy Endpoint

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

5.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is progression-free survival (PFS), defined as the time from randomization to the time when the modified Response Evaluation Criteria in Solid Tumor (mRECIST) criteria (mRECIST or mRECIST 1.1) for disease progression are first met, or when death from any cause occurs.

Other secondary efficacy endpoints include:

- Survival rates at 12 months, and every 6 months thereafter (i.e., 18 months, 24 months, etc.); and
- Tumor response per mRECIST criteria (mRECIST or mRECIST 1.1) after randomization:
  - Best overall response (in the order of CR, PR, SD, and PD)
  - Objective response rate (ORR: CR+PR),

- Disease control rate (DCR: CR+PR+SD),
- Clinical benefit rate (CBR: CR+PR+SD ≥ 6 months)
- Duration of response (DoR)
- Time to response (TTR)

Tumor assessment will be performed by a unblinded assessor on site, in accordance with mRECIST or mRECIST 1.1 criteria based on the contrast-enhanced thoracic CT scan of known sites of disease.

Definitions for tumor response related endpoints are provided in Section 8.10.3.1.

5.2.1 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Change in total score and individual components of the EQ-5D-5L and Lung Cancer Symptom Scale-mesothelioma (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.

5.3 Safety Endpoints

The safety endpoints are:

- To evaluate the number of patients with Common Terminology Criteria for Adverse Events (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 include the assessment of adverse events including adverse events of special interest (AESI), as well as physical examinations, vital sign measurements, clinical laboratory assessments, and electrocardiographic data through electrocardiogram (ECG).

6 ANALYSIS SETS

6.1 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set includes all randomized patients.

This ITT Analysis Set will be used for the demographics and baseline characteristics analyses and patients will be analyzed according to their assigned treatment arm.

6.2 Full Analysis Set

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 Full Analysis Set will be the primary analysis set for efficacy data and patients will be analyzed according to their assigned treatment arm.

6.3 Safety Analysis Set

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

The Safety Analysis Set will be used for all safety analyses and patients will be analyzed based on whether or not they received a dose of rAd-IFN.

7 GENERAL STATISTICAL CONSIDERATIONS

Descriptive statistics on continuous variables will include the number of observations (n), mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum, while categorical variables will be summarized using the frequency count and percentage in each category. Additionally, confidence intervals (CIs) for parameters to be estimated will be presented as 2-sided 95% confidence intervals.

All analyses will be performed using SAS® for Windows® (version 9.4).

7.1 Study Day Conventions

Study Day will be calculated in reference to the date of the first dose of study drug (rAd-IFN, celecoxib, or gemcitabine) as follows:

- Assessment date/event date – first dose date of study drug + 1, if assessment date or event date ≥ first dose date;
- Assessment date/event date – first dose date of study drug, if assessment date or event date < first dose date.

Under the convention specified above, Study Day 1 represents the date of the first dose of study drug. The day prior to the first dose date of study drug is identified as ‘Day -1’ (with no intervening “Day 0”).

7.2 Baseline and Data Considerations

Baseline Definition

Unless otherwise specified, baseline for all efficacy and safety variables is defined as the last measurement obtained prior to the first administration of study drug (rAd-IFN, celecoxib, or gemcitabine).

Unless the collection time or label indicates otherwise, assessments performed on the same day as the first dose of study drug will be considered as performed prior to treatment. AEs and medications with a start date on the date of first dose of study drug will be considered to have occurred after the start of treatment.

Visit Windows

In general, for by-visit summaries, nominal visits will be presented (i.e. visit windowing will not be applied). Unscheduled measurements will not be included in by-visit table summaries but will contribute to the best or worst-case values table summaries. Listings will include both scheduled and unscheduled data.

7.3 Handling of Dropouts or Missing Data

Missing Disease Assessment per mRECIST/mRECIST 1.1

For derivation of PFS, missing disease assessment per mRECIST or mRECIST 1.1 will be handled per the rules specified in Section 8.10.2.1.

Missing/Partial Dates:

- In cases of missing or incomplete dates (e.g. AE or concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For the detailed missing/partial dates handling conventions for treatment-emergent adverse events and concomitant medications, see Appendix A. The actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.
- For patients who died but with missing and incomplete death dates:
  - If the death date is completely missing, then the death date will be imputed as the day of "Last known to be alive" + 1;
  - If only day is missing and year and month of the death date are the same as the day of "Last known to be alive", the day of "Last known to be alive" + 1 will be used; otherwise the 1st day of the month will be used.
  - If day and month are missing and year of death is the same as the day of "Last known to be alive", then the day of "Last known to be alive" + 1 will be used; otherwise the 1st of January will be used
- Time from initial diagnosis (months) is calculated as (date of first dose of study drug - date of initial diagnosis + 1)/30.4375. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1st for the calculation. If this imputation rule yields a date of initial diagnosis after the first dose date, then the partial date of the initial diagnosis will be imputed as January 1st when only a year is provided and the 1st of the month when only a month and year are provided.

Other Missing Values:

- For safety and biomarker summaries, values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the data listings.
- Missing values for other individual data points will remain as missing unless otherwise specified. Missing values will not be imputed and only observed values will be used in data analyses and presentations unless otherwise stated.

7.4 Strata and Covariate Adjustment

The stratification factor for the randomization for the study is disease stage: stage I/II versus stage III/IV (without extrathoracic metastasis). The stratification factor is captured in the IRT system and on the electronic case report forms (eCRFs).

Stratification factor or covariate adjustment will not be considered for the primary efficacy analysis due to the small sample size of the study.

7.5 Multicenter Studies

The center effect will not be considered for this study.

7.6 Multiple Comparisons/Multiplicity

The study has only one primary efficacy variable to be compared once at a one-sided 2.5% level. Therefore, no multiplicity adjustment is necessary for the primary efficacy analysis.

A hierarchical testing strategy will be used to control the overall type I error rate for the key secondary efficacy analysis, where the key secondary efficacy endpoint PFS will only be formally tested and interpreted at a one-sided 0.025 level of significance if the primary analysis of OS is statistically significant.

There is no plan to adjust multiplicity for other secondary efficacy endpoints.

7.7 Data and Safety Monitoring Board (DSMB)

An independent DSMB has been convened for this study to monitor safety, efficacy, and study integrity. The DSMB consists 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 are detailed in a finalized DSMB charter.

8 STATISTICAL ANALYSIS

The statistical analysis will be performed by Medpace Inc.

8.1 Patient Disposition

The number of patients screened, randomized, and screened patients who were not randomized will be tabulated. For patients who were screened but not randomized, the reason for screen failure will be provided.

Patient disposition information will be summarized for each randomized treatment arm and in total for all randomized patients (ITT Set). The following disposition categories will be included:

- Patients who were randomized,
- Patients who did not receive any assigned study drug,
- Patients who were treated,
- Patients who discontinued randomized study drug, and
- Patients who discontinued from the study

For patients who discontinued from study drug or discontinued early from the study after randomization, a summary will be provided by reason of discontinuation.The number and percentage of patients who discontinued early from the study drug or study due to COVID-19 impact will be summarized.

In addition, the number and percentage of patients in each analysis set will be presented. A listing will be provided that indicates each patient's inclusion/exclusion from the analysis set.

All disposition data will be listed by patient.

8.2 Protocol Deviations

Protocol deviations will be identified and reported according to the process described in the current version of the study Protocol Deviation Plan.

The number and percentage of patients with major (i.e., 'CSR reportable' in the Protocol Deviation Plan) protocol deviations will be tabulated by category and by treatment arm and in total for the ITT Set.

The number and percentage of patients with COVID-19 related CSR reportable deviations will also be summarized.

All protocol deviations will be listed by patient.

8.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the ITT Set, Full Analysis Set, and the Safety Analysis Set by treatment arm and in total. If 2 analysis sets are identical to each other, the table will be presented only once.

Categorical baseline variables (e.g., sex, age group, race, ethnicity, region (North America or Rest of World), and Eastern Clinical Oncology Group Performance Status [ECOG PS] at screening and at baseline) will be summarized by the number and percentage of patients in corresponding categories. Continuous baseline variables such as age at informed consent, body weight, height, and body mass index (BMI) will be summarized by descriptive statistics (number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum).

All demographic and baseline characteristics data will be listed by patient.

8.4 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized descriptively for the ITT Set, Full Analysis Set, and the Safety Analysis Set by treatment arm and in total. If 2 analysis sets are identical to each other, the table will be presented only once.

- Histological type of MPM (Epithelioid, Sarcomatoid, Biphasic (<50% epithelioid), Biphasic (≥50% epithelioid), Unknown)
- Tumor stage at initial diagnosis and at study entry (Stage 0, Stage I, Stage II, Stage III, Stage IV, Unknown)
- Extrathoracic metastases at study entry (Yes, No)
- Tumor burden at study entry (sum of the diameters of target lesions)
- Location of target lesion (pleural, thoracic non-pleural)
- Stratification factor per IRT (Stage I/II, Stage III/IV [without extrathoracic metastasis]),
- Number of previous recurrences,
- Time from initial diagnosis to date of randomization
- Prior cancer resection to the pulmonary site (Yes, No) and type of prior cancer resection to the pulmonary site (Curative, Palliative, Biopsy, Other)
- Prior MPM therapy/medications (Yes, No) and type (Chemotherapy, Immunotherapy, Radioimmunotherapy, Other)
- Number of prior MPM regimens
- Prior anti-folate and platinum combination regimen

- Best Response to the last prior MPM therapy
- Best Response to the first line MPM therapy
- Prior radiation therapy (Yes, No) and type (Curative, Palliative)
- Presence of measurable target lesions (Yes, No) and location (plural, non-pleural)
- Presence of adenovirus type 5 neutralizing antibodies at baseline (Yes, No)
- Serum mesothelin at baseline
- Serum fibulin-3 at baseline
- Programmed death-ligand 1 (PD-L1) expression at baseline

All MPM history and prior MPM treatment (medication, cancer resection to the pulmonary site, and radiation therapy) will be listed by patient.

8.5 Medical History

Medical/surgical history (Non-MPM) will be collected at the screening visit. The reported medical/surgical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0).

Medical/surgical history (Non-MPM) will be summarized for the ITT Set by system organ class and preferred term, and by treatment arm and in total.

All reported medical and surgical history will be listed by patient.

8.6 Prior and Post-Treatment Cancer Resection to the Pulmonary Site

Prior and post-treatment cancer resection to the pulmonary site will be coded by MedDRA (version 23.0) and will be listed by patient. Prior cancer resections to the pulmonary site are resections performed before or on the first dose date of study drug. Post-treatment cancer resections are resections that were performed after the first dose of study drug.

Both prior and post-treatment cancer resection to the pulmonary site will be summarized for each treatment arm and in total for the Safety Analysis Set by type of resection, system organ class, and preferred term.

8.7 Prior and Concomitant Medications

8.7.1 Non-MPM Medications

Prior and concomitant non-MPM medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2019 Global B3) to give the Anatomical Therapeutic Chemical (ATC) classes and preferred term for each medication.

Medications will be categorized as prior or concomitant:

- Prior medications are medications used and stopped before the first dose of study drug.
- Concomitant medications are medications taken any time from the start of the first dose of study drug until 30 days following end of study drug administration.

Medications with missing or partially missing start or end dates will be handled according to the conventions described in Appendix A. If a determination cannot be made whether a medication was a prior medication due to partial medication start or end dates, the medication will be considered concomitant.

Prior and concomitant medications will be summarized for the Safety Analysis Set by ATC class and preferred term. Although a patient may have taken two or more medications, the patient is counted only once within an ATC classification. The same patient may contribute to two or more preferred terms in the same classification.

All medications will be listed by patient.

8.7.2 Transfusions

Prior transfusions are transfusions used and stopped before the first dose of study drug. Concomitant transfusions are transfusions taken any time from the start of the first dose of study drug until 30 days following end of study drug administration. Transfusions with missing or partially missing start or end dates will be handled similarly according to the conventions described in Appendix A.

The number and percentage of patients who received concomitant blood and platelet transfusions and the number of concomitant blood and platelet transfusions will be summarized for each treatment arm and in total for the Safety Analysis Set.

All blood and platelet transfusions will be listed by patient.

8.7.3 Prior MPM Therapy/Medications

Prior MPM therapies will be tabulated by type of regimen (chemotherapy, immunotherapy, radioimmunotherapy, other) and by ATC class and preferred term for each treatment arm and in total for the Safety Analysis Set.

8.7.4 Subsequent MPM Therapy/Medications

Subsequent MPM therapies (as reported on the Post-Treatment MPM Therapy/Medications CRF page) will be summarized for the Safety Analysis Set and will present the number and percentage of patients with any subsequent MPM therapy/medications overall and by type of regimen (chemotherapy, immunotherapy, radioimmunotherapy, other) and by ATC class and preferred term.

All subsequent MPM therapy/medications will be listed by patient.

8.8 Radiotherapy

Prior radiotherapy is radiotherapy received prior to the first dose of study drug. Concomitant radiotherapy is radiotherapy received any time from the start of the first dose of study drug until 30 days following end of study drug administration. Radiotherapy with missing or partially missing start or end dates will be handled similarly according to the conventions described in Appendix A.

The number and percentage of patients who received prior and concomitant radiotherapy will be presented by treatment arm and in total for the Safety Analysis Set. The site of radiotherapy and indication of radiotherapy (curative or palliative) will also be tabulated.

All prior and concomitant radiotherapy will be listed by patient.

8.9 Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized and listed for the Safety Analysis Set.

8.9.1 rAd-IFN

rAd-IFN is a non-replicating IFN-α2b gene therapy vector. The rAd-IFN concentrate is prepared as a single dose of 3×10^{11} vp, diluted to a volume of 25 mL using sterile normal saline by site personnel as per local institutional standards. For the rAd-IFN treatment arm, rAd-IFN will be administered at room temperature into the pleural space (after drainage of fluid from the intrapleural space, if required) via an IPC or similar intrapleural device by the Principal Investigator or designee to rAd-IFN treatment group patients.

The following summaries of study drug exposure to rAd-IFN will be presented for patients who received rAd-IFN:

- Duration of infusion (minutes),
- Actual volume administered (mL),
- Percentage of volume administered (actual volume (mL)/planned volume (25 mL))
- Frequency and percentage of patients with infusion interruptions

8.9.2 Celecoxib

All patients in the treatment arm and the control arm will take oral celecoxib 400 mg BID on Study Days 1 to 14. The first dose of celecoxib will be administered 1 to 2 hours prior to rAd-IFN administration (rAd-IFN treatment group) or during the Study Day 1 Visit (control group).

The duration of treatment (days) for celecoxib will be calculated as the last dose date minus the first dose date plus 1. The duration of treatment for celecoxib will be summarized by treatment arm using descriptive statistics. In addition, contingency tables will be provided to

show the number and percentage of patients in each treatment arm with exposure in the following categories: <7 days, 7-14 days, >14 days.

Overall compliance rate to celecoxib will be calculated as the total number of capsules taken divided by the total presumed number of capsules taken during the course of the trial then multiplied by 100. The total presumed number of capsules taken is the number of medication days multiplied by the number of capsules (4) per day taking into consideration of any potential dose adjustment for celecoxib.

$$\%\text{compliance} = \frac{\text{total No. of capsules taken*100}}{\text{4*(total No. of medication days in the treatment period)}}$$

Overall compliance rate to celecoxib will also be summarized by treatment arm using descriptive statistics. Contingency tables will be provided to show the number and percentage of patients in each treatment arm with compliance rate in the following categories: <80%, 80% to <90%, ≥90%.

Additionally, the number and percentage of patients with dose adjustment for celecoxib will also be presented.

8.9.3 Gemcitabine

Gemcitabine will be administered for all patients in the treatment arm and the control arm 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 and continued every 3 weeks until disease progression/ET. The regimen will be administered in compliance with local clinical practice and manufacturer guidelines. Gemcitabine dosage can be changed in relation to gemcitabine-related toxicity per Investigator discretion throughout the study.

The following summaries of study drug exposure to gemcitabine will be presented:

- Number of cycles initiated
- Treatment duration, calculated as the last dose date minus the first dose date plus 1
- Number of doses administered
- Frequency and percentage of patients with at least one dose reduction
- Frequency and percentage of patients with at least one dose interruption
- Frequency and percentage of patients with at least one dose omitted
- Actual dose intensity (ADI) of gemcitabine per cycle (mg/m^2) is defined as the cumulative dose of gemcitabine administered divided by the number of adjusted treatment cycles
    - Cumulative dose of gemcitabine administered is the sum of the actual dose (mg/m^2) administered at a given visit up to the last dose date. When deriving the actual dose administered, the volume before and after infusion will also be considered.

- Number of adjusted treatment cycle:
  - If the last dosed cycle is Cycle 1, the number of adjusted treatment cycles is considered to be 1.
  - If the last dosed cycle is Cycle 2 or beyond, then the number of adjusted treatment cycles will be calculated [(End date of last cycle – First dose date + 1) / 21], where the end date of last cycle is calculated as [First dose date of last cycle + (number of doses received in the last cycle up to the last dose date) *10].

- The planned dose intensity (PDI) of gemcitabine per cycle is (1250 mg/m^2) *2.
- Relative dose intensity (RDI) (%) of gemcitabine is defined as the actual dose intensity divided by the planned dose intensity then multiplied by 100.

In addition to the descriptive summary, the frequency and percentage of patients will be presented the relative dose intensity categories: <70%, 70-<80%, 80% to <90%, ≥90%.

All study drug administration data will be listed by patient.

8.10 Efficacy Analyses

All efficacy analyses will be performed based on the Full Analysis Set. Additionally, supportive analyses will be performed based on the ITT Set for the primary and key secondary efficacy endpoints.

Unless otherwise noted, all hypothesis tests will be performed at the one-sided 0.025 significance level and a two-sided 95% confidence interval will be used for all confidence intervals.

8.10.1 Primary Efficacy Endpoint

8.10.1.1 Definition

The primary efficacy endpoint is OS, defined as the time to death (from any cause) from randomization. Patients who are alive or lost to follow-up as of the data cut-off date for analysis will be censored at the date the patient was last known to be alive.

The last date the patient was known to be alive will be determined based on the latest of the following: visit date, study assessment/procedure date (e.g., physical examination, vital signs, ECOG performance status, ECG, QoL, laboratory test, radiological evaluation, etc.), study drug dosing date, AE/medication start and stop dates, date of disposition, and last contact date for survival follow-up.

8.10.1.2 Hypotheses and Analysis of the Primary Efficacy Endpoint

The hypotheses for the primary efficacy endpoint OS in this study will be:

- H_0: the distribution of the OS time is the same in the two treatment arms

- H_1: the distribution of the OS time in the treatment arm is superior to the control arm

The hypotheses for OS will be tested using a log-rank test based on the Full Analysis Set. A Cox proportional hazards regression model with treatment as an explanatory variable will be used to estimate the Hazard Ratio (HR) between the two treatment arms along with the associated 95% CI.

The final analysis of OS will be performed when approximately 44 deaths have been observed.

The Kaplan-Meier (KM) survival analysis method will be used to estimate the OS curve for each treatment arm. Point estimates and 2-sided 95% CIs for the first quartile, median, and third quartile for the OS curve of each arm will be estimated. Plots of the Kaplan-Meier estimate of the survival distribution function over time for OS will be presented by treatment arm.

Median follow-up time for OS will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith, 1996), which will be calculated using the inverse of the censoring rules for OS.

8.10.1.3 Sensitivity Analyses of the Primary Efficacy Endpoint

The following sensitivity analyses will be carried out for OS to evaluate the robustness of the primary analysis results:

- **OS Sensitivity Analysis 1 (Fleming-Harrington's Weighted Log-rank test):** Given the mechanism of the study drug, the treatment effect of rAd-IFN may be delayed. To account for the potential delay of the treatment effect in OS, a sensitivity analysis using the Fleming-Harrington's weighted log-rank test based on the $G^{\rho,\gamma}$ weight function will be conducted (Fleming, 1991). For the sensitivity analysis assessing for a late treatment effect, we will choose $\rho=0$ and $\gamma=1$ for the weight function.
- **OS Sensitivity Analysis 2** (censoring for receiving subsequent anticancer therapy): analysis of OS will be performed using the same method as the primary analysis but with survival times censored at the date where any post-treatment anti-cancer therapy is first administered on the Full Analysis Set.

8.10.2 Key Secondary Efficacy Endpoint

8.10.2.1 Definition

The key secondary efficacy endpoint is PFS, defined as the time from randomization to the time when the mRECIST or mRECIST 1.1 criteria for disease progression are first met, or when death from any cause occurs, whichever occurred earlier.

If neither death nor disease progression is observed at the time of analysis, PFS time will be censored on the date of the last evaluable tumor assessment. The PFS censoring rules are defined below in Table 1.

Table 1 Date of Progression or Censoring Rules for PFS

Situation	Date of progression or censoring	Outcome
No baseline disease assessment	Date of randomization	Censored
No evaluable post-baseline disease assessments and no deaths	Date of randomization	Censored
No documented progression and no death (with a post-baseline disease assessment)	Date of last adequate disease assessment	Censored
Disease progression between planned disease assessments	Date of first disease assessment showing disease progression	Progressed
Death before first planned disease assessment	Date of death	Progressed
Death between planned disease assessments	Date of death	Progressed
Subsequent anticancer treatment started before disease progression or death (without disease progression beforehand)	Date of last adequate disease assessment prior to surgery or start of subsequent anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments	Date of last adequate disease assessment visit without documentation of disease progression before the first missed visit	Censored

Note: An adequate disease assessment is defined as a radiological assessment where CR, PR, SD was determined.

8.10.2.2 Hypotheses and Analysis of the Key Secondary Efficacy Endpoint

The hypotheses for the key secondary efficacy endpoint PFS will be:

- H_0: the distribution of the PFS time is the same in the two treatment arms
- H_1: the distribution of the PFS time in the treatment arm is superior to the control arm

A hierarchical testing strategy will be used to control the overall type I error rate, where PFS will only be formally tested and interpreted at a one-sided 0.025 level of significance if the primary analysis of OS is statistically significant. The P-value from the final analysis of PFS is substantive if the OS final analysis is significant and is indicative otherwise.

The same analysis as described for the primary efficacy endpoint OS will be performed for PFS based on the Full Analysis Set. The p-value obtained from the log-rank test will be presented together with the estimated PFS Hazard Ratio of rAd-IFN versus control and the associated two-sided 95% CI obtained from the Cox model.

The KM survival analysis method will be used to estimate the PFS curve for each treatment arm. Point estimates and 2-sided 95% CIs for the first quartile, median, and third quartile for the PFS curve of each arm will be estimated. The PFS rates at 6 months intervals and the 2-sided 95% CIs will also be estimated using KM method for each treatment arm. Plots of the Kaplan-Meier estimate of the survival distribution function over time for PFS will be presented by treatment arm.

Median follow-up time for PFS will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith, 1996), which will be calculated using the inverse of the censoring rules for PFS.

The following sensitivity analyses on PFS will be performed:

- **PFS Sensitivity Analysis 1** (PFS1): PFS1 is defined as the time from randomization to the time when the mRECIST or mRECIST 1.1 criteria for disease progression are first met, or when death from any cause occurs, whichever occurred earlier. The event/censoring rules will follow the definitions specified in Table 1 except that death or disease progression after missing two or more consecutively scheduled disease assessments will be considered as events. The analysis of PFS1 will be performed using the same method as the primary analysis based on the Full Analysis Set.

- **PFS Sensitivity Analysis 2** (PFS2): PFS2 is defined as the time from randomization to the time when the mRECIST 1.1 criteria for disease progression are first met, or when death from any cause occurs, whichever occurred earlier. The event/censoring rules will follow the definitions specified in Table 1. Note: this sensitivity analysis will be performed based on the Full Analysis Set excluding patients who had tumor response assessed per mRECIST.

8.10.3 Other Secondary Efficacy Endpoints

8.10.3.1 Definition

- *Survival rates at 12 months and every 6 months thereafter*

  The survival rates at 12 months, and every 6 months thereafter (i.e., 18 months, 24 months, etc.) for each arm will be estimated using the KM method.

- *Best overall response (BOR)*

  Best overall response (BOR) is defined as the best response designation (in the order of CR, PR, SD, PD, NE) for each patient that is recorded between the date of randomization and the date of documented disease progression per mRECIST or mRECIST 1.1 criteria or the date of subsequent anticancer therapy or cancer-related surgery (i.e., surgical resection of tumor) whichever occurs first.

A BOR of CR or PR will not require confirmation for this study. To classify BOR as SD, it must also meet the minimum interval of 6 weeks from randomization. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second assessment and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow up after the first SD assessment would be considered as inevaluable (NE).

- *Objective response rate (ORR)*

  ORR is defined as the proportion of patients with a best overall response of CR or PR.

- Disease *control rate (DCR)*

  DCR is defined as the proportion of patients with a best overall response of CR, PR, or SD.

- *Clinical benefit rate (CBR)*

  CBR is defined as the proportion of patients with a best overall response of CR, PR, or SD ≥ 6 months.

- *Duration of response (DoR)*

  DoR is defined only for responders (patients with of BOR of CR or PR). It is measured from the start date of PR or CR (whichever response is recorded first) to the date of documented disease progression or death due to any cause, whichever occurs earlier. The DoR will be censored according to the same rules as PFS (see Table 1).

- *Time to response (TTR)*

  TTR is defined only for responders (patients with of BOR of CR or PR). It is measured from the date of randomization to the date at which criteria are first met for PR or CR.

8.10.3.2 Analyses of Other Secondary Efficacy Endpoints

Survival rates at 12 months and every 6 months thereafter

The point estimates and the corresponding 2-sided 95% CIs of the survival rates at 12 months, and every 6 months thereafter (i.e., 18 months, 24 months, etc.) until the largest time point will be estimated for each arm using the KM method for the Full Analysis Set. The difference in the KM estimates of the survival rates between treatment arms at 12 months, 18 months, and 24 months until the largest time point will be compared using a *Chi-square* statistic, standardized using the Greenwood variance estimator of the Kaplan-Meier estimate.

Best Overall Response

BOR will be summarized descriptively by treatment arm for the Full Analysis Set to show the number and percentage of patients in each response category.

Objective Response Rate, Disease Control Rate, and Clinical Benefit Rate

For ORR, DCR, and CBR, the point estimates and 2-sided exact binomial 95% CIs will be calculated for each treatment arm. The treatment difference in ORR, DCR, and CBR will be tested using Fisher's exact test based on the Full Analysis Set.

Duration of Response

For patients with CR or PR, DoR will be analyzed using survival analysis methods on the Full Analysis Set. The KM estimate for the first quartile, median, and third quartile for DoR and the associated 95% CIs will be estimated for each treatment arm. The DoR rates at 6 months intervals and the 2-sided 95% CIs will also be estimated using the KM method for each treatment arm. Plots of the Kaplan-Meier estimate of the survival distribution function over time for DoR will be presented by treatment arm.

Time to Response

TTR will be summarized using descriptive statistics by treatment arm for patients with CR or PR on the Full Analysis Set.

8.10.4 Exploratory Efficacy Variables

8.10.4.1 Analysis of Quality of Life (QoL)

EQ-5D-5L

EuroQol/EQ-5D is a standardized, reliable and validated instrument to measure quality of life. It consists of the EQ-5D descriptive system and the EQ Visual Analogue scale (EQ VAS). The EQ-5D 5 level version (EQ-5D-5L) descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D index score is calculated based on the descriptive system using a set of item weights (value sets) to derive a single score ranging from 0 to 1 with 1 representing full health. The value sets for the US from the Crosswalk Index Value Calculator will be used for the calculation of the EQ-5D normalized index score based on the five responses, also known as the 5L profile for each patient assessment. The EQ VAS records the respondent's self-rated health status on a graduated (0-100) scale. With 100 = best imaginable health state and 0 = worst imaginable health state.

A summary table on compliance measures at each scheduled visit will be provided by treatment arm for EQ-5D 5L, where the percentage compliance at a visit will be calculated as the number of completed EQ-5D assessments at the visit divided by the number of expected EQ-5D assessments at the visit and then multiplied by 100. The number of expected assessments is determined by the number of patients who are ongoing at the specified visit.

The treatment differences in the mean changes in both the index score and the VAS from baseline across scheduled time points will be analyzed using a mixed effects repeated

measures model with time point, treatment, and time point-by-treatment interaction as factors and baseline score as a covariate. Restricted Maximum Likelihood (REML) method and an unstructured covariance matrix will be utilized.

The analysis will include all cycles for which at least 25% of patients in each arm have an assessment. In case of convergence problems in the mixed effects model, the following variance covariance structures will be used in the order of 1) heterogeneous compound symmetry, 2) compound symmetry. The first (co)variance structure which does not have convergence problems will be used for the analysis.

Least squares (LS) means, corresponding standard errors, and 95% two-sided CIs will be presented for the within-group change. For the between-treatment group comparison at each time point and overall, the difference in LS means, corresponding standard errors, and 95% two-sided CIs, and two-sided p-value will be derived from the mixed effects model and presented.

In addition to the analysis described above, the EQ-5D 5L responses for each item will be summarized by frequency and percentages for each treatment arm at each scheduled time point. Descriptive statistics for the index score and VAS and the changes from baseline will be presented by arm at each scheduled time point.

The mean score and the mean change from baseline in index score and VAS will be plotted by time point and treatment arm.

Lung Cancer Symptom Scale-Mesothelioma (LCCS-Meso)

The LCSS-Meso is a reliable and valid instrument to measure disease-related symptoms of MPM and their impact on health-related quality of life. The patient scale consists of eight 100-mm visual analogue scales (5 symptoms plus 3 summary items). A counterpart observer scale assesses the same 5 symptoms using a 5-point categorical scale providing context (Hollen PJ, et. al, 2004, 2006).

A summary table on compliance measures for LCSS-Meso at each scheduled visit will be provided by treatment arm, where the percentage compliance at a visit will be calculated as the number of completed LCSS-Meso assessments at the visit divided by the number of expected LCSS-Meso assessments at the visit and then multiplied by 100. The number of expected assessments is determined by the number of patients who are ongoing at the specified visit.

The following outcomes will be calculated for the patient scale:

- Total score (mean of all 8 patient items)
- Global quality of life score (the single QoL summative item)
- Average symptom burden index (ASBI) (the mean of the 5 major LC symptoms)

The treatment differences in the mean changes in patient scale total score, global QoL score, and ASBI from baseline across scheduled time points will be analyzed using the same mixed effects repeated measures model as described above for EQ-5D index score and VAS. The analysis will include all cycles for which at least 25% of patients in each arm have an assessment.

Descriptive statistics for the patient scale total score, global QoL score, and ASBI and the changes from baseline will be presented by arm at each scheduled time point. The LCSS-Meso observer scale responses for each item will be summarized by frequency and percentages for each treatment arm at each scheduled time point.

The mean score and the mean change from baseline in patient scale total score, global QoL score, and ASBI will be plotted by time point and treatment arm.

8.10.4.2 Analysis of Other Exploratory Efficacy Endpoints

Other exploratory efficacy endpoints include:

- Correlation between the presence of adenovirus type 5 neutralizing antibodies prior to treatment and overall survival (OS),
- Correlation between pre- and post-treatment levels of serum mesothelin and treatment outcomes (e.g., OS, PFS, ORR), and
- Correlation between pre- and post-treatment levels of serum fibulin-3 and treatment outcomes (e.g., OS, PFS, ORR)

The number and percentage of patients with adenovirus type 5 neutralizing antibodies prior to treatment will be tabulated by treatment arm for the Full Analysis Set. Serum mesothelin and fibulin-3 levels and changes from baseline will be summarized by treatment arm using descriptive statistics at each scheduled time point for the Full Analysis Set, including the minimum post-treatment value. The median value, the median changes, and median percent changes from baseline in mesothelin and fibulin-3 will be plotted over time by treatment arm.

The following analyses will be performed to evaluate the relationship between the exploratory efficacy endpoints and the treatment outcomes (e.g., OS, PFS, ORR) if data warrant:

Correlation of presence of adenovirus type 5 neutralizing antibodies at baseline and OS

The correlation between presence of adenovirus type 5 neutralizing antibodies at baseline (Yes or No) and OS will be evaluated using a Cox proportional hazards model with presence of baseline adenovirus type 5 neutralizing antibodies and treatment as explanatory variables. The predictive value of the presence of adenovirus type 5 neutralizing antibodies at baseline on OS will also be evaluated by investigating the potential interaction between the presence of adenovirus type 5 neutralizing antibodies at baseline and treatment using a Cox proportional hazards model including treatment arm, presence of adenovirus type 5 neutralizing antibodies at baseline, and treatment-by-presence of adenovirus type 5 neutralizing antibodies interaction.

The biomarker hazard ratio for the presence of adenovirus type 5 neutralizing antibodies at baseline (Yes vs. No) and the corresponding 95% CIs will be obtained from the Cox proportional hazards models. Additionally, the biomarker hazard ratio within each treatment arm separately, the treatment hazard ratio within each biomarker group separately, and the ratio of treatment hazard between the two biomarker groups and the corresponding 95% CIs will be presented. The p-value for the interaction term will also be presented.

Correlation of pre-treatment levels of serum mesothelin and fibulin-3 and treatment outcomes (OS, PFS, and ORR)

The correlation between the pre-treatment serum mesothelin and fibulin-3 values and survival treatment outcomes (OS and PFS) will be evaluated using the same method as described above for the correlation analysis of the presence of adenovirus type 5 neutralizing antibodies at baseline and OS. The pre-treatment levels of serum mesothelin and fibulin-3 will be included in the Cox model as either a continuous or a categorical variable (e.g., ≤ median/threshold or > median/threshold).

The correlation between the pre-treatment serum mesothelin and fibulin-3 values and ORR will be evaluated using a logistic regression model after adjusting for the biomarker and treatment. The predictive value of the pre-treatment serum mesothelin and fibulin-3 levels on ORR will also be evaluated by investigating the potential interaction between the pre-treatment serum mesothelin and fibulin-3 values and treatment using a logistic regression model including treatment arm, pre-treatment serum mesothelin or fibulin-3, and treatment-by-pre-treatment serum mesothelin or fibulin-3 interaction. The pre-treatment levels of serum mesothelin and fibulin-3 will be included in the logistic regression model as either a continuous or a categorical variable (e.g., ≤ median/threshold or > median/threshold).

The number and percentage of patients with ORR will be summarized by the categories of pre-treatment serum mesothelin and fibulin-3 for each treatment arm and overall. The biomarker odds ratio estimate for pre-treatment serum mesothelin and fibulin-3 (> median/threshold vs. ≤ median/threshold) and the corresponding 95% CIs will be obtained from the logistic regression models. Additionally, the biomarker odds ratio within each treatment arm separately, the treatment odds ratio within each biomarker group separately, and the ratio of treatment odds between the two biomarker groups and the corresponding 95% CIs will be presented. The p-value for the interaction term will also be presented.

Correlation of treatment outcomes (OS, PFS, and ORR) and post-treatment levels of serum mesothelin and fibulin-3

To evaluate the relationship between post-treatment levels of serum mesothelin and fibulin-3 and treatment outcomes, the percent change in serum mesothelin and fibulin-3 from baseline will be calculated and categorized into the following groups at each scheduled time point:

- Decreased group (decreased by more than 25% of the baseline values),

- Stable/increased group (remained within 25% of the baseline or increased by more than 25% of the baseline value)

The correlation between the percent change (as a categorical variable) in serum mesothelin and fibulin-3 from baseline and the time-to-event treatment outcomes (OS and PFS) will be evaluated using the same method as described above for the pre-treatment serum mesothelin and fibulin-3. Since the biomarker values at post baseline are evaluated at each treatment cycle and is time-dependent, a landmarking approach will be used for the Cox proportional hazards model at selected landmark time points (e.g., at Cycle 3 Day 1 and Cycle 6 Day 1 post treatment). The biomarker group (decreased vs. stable/increased) for each patient will be assessed at each selected landmark time point. Subsequent Cox proportional hazards regression analysis will be based on the landmark dataset using the landmark time point as the starting point for calculation of OS/PFS. This means that all patients who had events or were censored prior to the landmark time point will be excluded from the analysis at that landmark time point.

The correlation between the percent change in serum mesothelin and fibulin-3 from baseline at selected time point (e.g., at Cycle 3 Day 1 and Cycle 6 Day 1) and ORR will be evaluated using the same logistic regression model as described above for the pre-treatment serum mesothelin and fibulin-3. If a patient had progression per mRECIST or mRECIST 1.1 or discontinued prior to the selected time point, they will be excluded from the analysis.

A contingency table will be presented if the planned analysis model does not converge.

Forest plots by biomarker status (adenovirus type 5 neutralizing antibodies, mesothelin, and fibulin-3) will be generated displaying hazard ratios for OS and PFS and the corresponding 95% CI obtained from the Cox model (if appropriate).

All mesothelin and fibulin-3 measurements will be listed by patient.

8.11 Safety Analyses

Safety assessments include adverse events, AEs of CTCAE Grade 3 or 4, AESIs, as well as physical examinations, vital sign measurements, clinical laboratory assessments, and electrocardiographic data through electrocardiogram (ECG). Post-treatment levels of rAd-IFN-related viral DNA in biological samples collected up to 28 days after Study Day 1 will be evaluated in a sub-set of patients.

All safety analyses will be performed based on the Safety Analysis Set.

8.11.1 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.

Adverse events and other safety variables such as laboratory test results 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/or gemcitabine). The severity of adverse events except for cytokine release syndrome (CRS) will be graded according to the CTCAE Version 4.03. CRS will be graded according to the CRS grading specified in Appendix E of the protocol. All AEs will be coded using the MedDRA (Version 23.0).

A treatment-emergent adverse event (TEAE) is defined as any adverse event with an onset or worsening date/time after the first dose of study drug (rAd-IFN, celecoxib, and/or gemcitabine) until 30 days after the last dose of study drug.

An overview of adverse events will be provided which summarizes patient incidence of the following information:

- Any TEAEs,
- TEAEs by worst CTCAE grade,
- Drug-related TEAEs,
    - rAd-IFN-related TEAEs
    - Celecoxib-related TEAEs
    - Gemcitabine-related TEAEs
- Drug-related TEAEs by worst CTCAE Grade,
    - rAd-IFN-related TEAEs by worst CTCAE Grade
    - Celecoxib-related TEAEs by worst CTCAE Grade
    - Gemcitabine-related TEAEs by worst CTCAE Grade
- Treatment-emergent SAEs,
- Drug-related treatment-emergent SAEs,
- TEAEs leading to discontinuation of study drug
- TEAEs leading to deaths
- TEAEs of special interest

The number and percentage of patients with TEAEs will be tabulated by SOC and preferred term by treatment arm. Drug-related TEAEs, grade 3/4/5 TEAEs, drug-related grade 3/4/5 TEAEs, treatment emergent SAEs, drug-related treatment-emergent SAEs, and TEAEs leading to discontinuation of study drug will be summarized in the same manner. For these summaries, patients with multiple adverse events will be counted only once per SOC and preferred term.

Summaries will be provided by the worst NCI-CTCAE grade, system organ class and preferred term for the number and percentage of patients with TEAEs and drug-related TEAEs. For these summaries, patients with multiple adverse events will be counted only once by the worst NCI-CTCAE grade within an SOC and preferred term.

Adverse Events of Special Interest (AESI)

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 site.

Summaries will be provided by the worst NCI-CTCAE grade (or worst CRS grade for CRS AEs as applicable), system organ class and preferred term for the number and percentage of patients with treatment emergent AESIs and drug-related treatment emergent AESIs.

Listings will be provided for SAEs, grade 3/4/5 AEs, AEs leading to discontinuation of study drug, and AEs leading to deaths. A by-patient AE (including treatment-emergent) data listing including, but not limited to, verbatim term, preferred term, system organ class, NCI-CTCAE grade, and relationship to study drugs will be provided.

8.11.2 Deaths

A summary table will be provided by treatment arms for the Safety Analysis Set and will present:

- All deaths with the corresponding cause of death
- On-study deaths (deaths that occurred within 30 days of treatment discontinuation) with the corresponding cause of death

All deaths will be presented in a patient listing, which will include the primary cause of death and the date of death.

8.11.3 Clinical Laboratory Assessments

Blood samples for determination of clinical chemistry and hematology and urine samples for determination of urinalysis parameters will be taken at the times given in the Schedule of Study Assessments (Table 1 in the protocol). The following clinical laboratory tests will be performed by the local laboratory:

- Clinical chemistry: Sodium, Potassium, Calcium, Chloride, Bicarbonate (HCO3-), Inorganic Phosphorus, Magnesium, Calcium, Glucose, BUN, Uric Acid, Creatinine, Creatine Kinase, Albumin, Total Protein, Alkaline Phosphatase, AST, ALT, GGT,

Total Bilirubin, Total Cholesterol, Amylase, Lipase, Triglycerides, and estimated glomerular filtration rate (eGFR, Screening visit only).

- Hematology: Hemoglobin, HCT, RBC, WBC, Platelets, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Reticulocytes
- Coagulation assessments: PT, aPTT, INR
- Urinalysis: Specific Gravity, PH, Protein, Glucose, Ketones, Blood, Leukocyte esterase, Nitrites, Bilirubin, Urobilinogen, and microscopy (performed as needed)
- Pregnancy test

Descriptive statistics will be provided for selected clinical laboratory test results (hematology, blood chemistry, and coagulation parameters) and changes from baseline for the maximum post-treatment value, minimum post-treatment value, and the last post-treatment value. Both scheduled and unscheduled post-treatment values will be considered for the summaries of the maximum, minimum, and last post-treatment values.

Abnormal laboratory results will be graded according to NCI-CTCAE Version 4.03, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Both scheduled and unscheduled post-treatment values during the treatment period will be considered.

The number and percentage of patients with the following potentially clinically significant abnormal liver function test will be summarized:

- ALT ≥3×ULN, ≥5×ULN, ≥10×ULN, and ≥20×ULN
- AST ≥3×ULN, ≥5×ULN, ≥10×ULN, and ≥20×ULN
- Total bilirubin ≥2×ULN
- Potential Hy's Law cases: ALT or AST >3×ULN, total bilirubin ≥2×ULN, and ALP < 2×ULN (at the same visit)

The number and percentage of patients with treatment-emergent laboratory abnormalities (any grade and grade ≥ 3) will be presented for hematology and serum chemistry laboratory parameters if applicable. Treatment-emergent laboratory abnormalities are defined as post baseline laboratory abnormalities with worsening CTCAE grade from baseline. Post-baseline laboratory abnormality with unknown baseline grade will be considered as treatment-emergent.

All clinical laboratory data will be listed, and values deemed clinically significant will be flagged.

8.11.4 Vital Signs

Vital sign measurements will be taken at scheduled visits according to the Schedule of Study Assessments (Table 1 of the protocol) 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.

Descriptive statistics will be provided for the vital signs measurements (systolic blood pressure, diastolic blood pressure, heart rate, body temperature, respiratory rate, and body weight) and changes from baseline for the maximum, minimum and last post-treatment values. Both scheduled and unscheduled post-treatment values will be considered for summaries of the maximum, minimum, and last post-treatment values.

The number and proportion of patients with potentially clinically significant changes in vital signs will be presented based on the following thresholds:

- Systolic blood pressure ≥ 160 mmHg and increase ≥ 20 mmHg from baseline
- Systolic blood pressure ≤ 90 mmHg and decrease ≥ 20 mmHg from baseline
- Diastolic blood pressure ≥ 100 mmHg and increase ≥ 15 mmHg from baseline
- Diastolic blood pressure ≤ 50 mmHg and decrease ≥ 15 mmHg from baseline
- Heart rate ≥ 120 bpm with increase ≥ 15 bpm from baseline
- Heart rate ≤ 50 bpm with decrease ≥ 15 bpm from baseline

All vital sign data will be listed by patient.

8.11.5 Cardiac Telemetry and Pulse Oximetry

Immediately before, during, and immediately after rAd-IFN administration, patients should be monitored using cardiac telemetry and pulse oximetry. Heart rate, blood pressure, respiratory rate, and pulse oximetry will be monitored hourly for 6 hours post-rAd-IFN administration.

Heart rate, respiratory rate, and pulse oximetry results at each scheduled time point and changes from pre-dose will be summarized descriptively for patients receiving rAd-IFN. The number and percentage of patients with clinically significant abnormalities observed during Pulse Oximetry Monitoring and during Cardiac Telemetry Monitoring will be tabulated.

All cardiac telemetry and pulse oximetry assessment will be listed by patient.

8.11.6 12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at time points as outlined in the Schedule of Study Assessments (Table 1 of the protocol).

Electrocardiogram parameters (heart rate, PR, RR, QRS, and QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of

evaluation, including the maximum post-treatment value. Both scheduled and unscheduled post-treatment values will be considered for summaries of the maximum post-treatment values.

The incidence of notable ECG changes in maximum absolute QTcF intervals (> 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QTcF maximum changes from baseline (> 30 and > 60 ms) over all post-treatment evaluations will be summarized.

ECG rhythms will be tabulated at each scheduled time point by treatment arm.

A listing of ECG data will be provided.

8.11.7 Physical Examination

The physical examination appropriate to the physical condition of the patient will be performed at time points as outlined in the Schedule of Study Assessments (Table 1 of the protocol).

All physical examination data will be listed by patient.

8.11.8 ECOG Performance Status

ECOG data will be listed by patient.

8.11.9 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 sputum, urine, IPC in situ content samples (where applicable), 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.

The viral shedding measurement will be summarized descriptively at each schedule time point by the sample type for patients enrolled in the Viral Shedding Cohort.

Viral shedding data will be listed by patient.

8.12 Timing of Analyses

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.

8.13 Data Review Meeting

A data review meeting will be convened by the study team before the final analysis. The data review meeting will take place after the data have been cleaned but prior to the database being locked for analysis. Participants at the data review meeting will not have knowledge of the

treatment allocation of any patient, and data presented at that meeting will not reveal the treatment allocation of any patient.

The terms of reference of the Data Review Meeting before the final analysis shall include but not be limited to:

- the determination of whether protocol violations are 'major' or 'minor', or not a protocol violation at all
- the allocation of patients to analysis sets
- a review of missing data and of outliers
- a review of the distribution of the efficacy variables, considering any implications for the proposed method of statistical analysis
- a review of whether additional covariates need to be included in the analyses
- the amendment of the SAP if needed.

8.14 Changes from Analyses Specified in the Protocol

Protocol version 6.0 states PFS is 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.

However, since patients enrolled earlier in the study under protocol versions 1.0 to 3.0 were evaluated using mRECIST as opposed to mRECIST 1.1, PFS is defined as the time from randomization to the time when the modified Response Evaluation Criteria in Solid Tumors (mRECIST or mRECIST 1.1) for disease progression are first met, or when death from any cause occurs.

9 REFERENCES:

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10 APPENDICES:

Appendix A: Partial Date Conventions

Table 10-1: Algorithm for Treatment-emergent Adverse Events

AE Start Date	AE Stop Date	Action
Known	Known/Partial/Missing	If start date < study drug start date, then not TEAE If start date ≥ study drug start date and ≤ (end of treatment +30 days), then TEAE If start date > (end of treatment +30 days), then not TEAE
Partial, but the known date components show that it cannot be on or after study drug start date	Known/Partial/Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (ie, last day of month if day is unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (ie, last day of month if day is unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing	Assumed TEAE

TEAE = treatment-emergent AE

Table 10-2: Algorithm for Concomitant Medications

CM Start Date	CM Stop Date	Action
Known	Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, and start date ≤ end of treatment +30 days, assign as CONCOMITANT If stop date ≥ study drug start date and start date > 30 days after the end of treatment, assign as POSTTREATMENT
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, and start date ≤ end of treatment +30 days, assign as CONCOMITANT If stop date ≥ study drug start date, and start date > 30 days after the end of treatment, assign as POSTTREATMENT
	Missing	If stop date is missing, then PRIOR will never be assumed or assigned If start date ≤ end of treatment, assign as CONCOMITANT If start date > 30 days after the end of treatment, assign as POSTTREATMENT
Partial	Known	Impute start date as earliest possible date (ie, first day of month if day unknown or 01-Jan if day and month unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date and start date ≤ end of treatment + 30 days, assign as CONCOMITANT If stop date ≥ study drug start date and start date > 30 days after the end of treatment, assign as POSTTREATMENT
	Partial	Impute start date as earliest possible date (ie, first day of month if day unknown or 01-Jan if day and month are unknown) and impute stop date as latest possible date (ie, last day of month if day unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date and start date ≤ end of treatment + 30 days, assign as CONCOMITANT If stop date ≥ study drug start date and start date > 30 days after the end of treatment, assign as POSTTREATMENT
	Missing	Impute start date as earliest possible date (ie, first day of month if day unknown or 01 Jan if day and month unknown), then: If stop date is missing, then PRIOR will never be assumed or assigned

CM Start Date	CM Stop Date	Action
		If start date ≤ end of treatment + 30 days, assign as CONCOMITANT If start date > 30 days after the end of treatment, assign as POSTTREATMENT
Missing or Unknown	Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT If start date is missing, then POST-TREATMENT will never be assumed or assigned
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT If start date is missing, then POSTTREATMENT will never be assumed or assigned
	Missing	Assign as CONCOMITANT

Appendix B: SAS Procedures

This section provides sample SAS code to illustrate statistical tests specified in the statistical methods section. All computer output from SAS statistical procedures serving as a basis for extracted results will be retained for quality control procedures.

1) log-rank test for OS between treatment to obtain the p-value:

```
Proc lifetest method=KM CONFTYPE=LOGLOG;
        Time OS*censor (1);
        Strata trt;
Run;
```

```
Proc lifetest method=KM
        CONFTYPE=LOGLOG;
        Time OS*censor (1);
        Strata trt;
        Test trt / weight= FLEMING(0,1);
Run;
```

2) Cox proportional hazard model for OS to obtain the hazard ratio and the corresponding confidence interval:

```
Proc phreg;
        Class trt (ref='control')
        Model  OS*censor (1) =trt/risklimits ties=efron;
Run;
```

3) Fisher exact test for ORR

```
Proc freq;
        Tables trt*resp/fisher;
Run;
```

4) Exact 95% Confidence interval on ORR

```
Proc freq;
        By trt;
        Tables resp;
        Exact binomial;
Run;
```

5) Logistic regression analysis for ORR to obtain odds ratio:

```
Proc logistic;
        Class trt (ref="control") stage (ref="III/IV")/ param=glm;
        Model resp (event='1') = trt / influence lackfit;
        Contrast 'trt vs. control' trt 1 -1/ alpha=0.05 estimate=exp;
Run;
```

6) Mixed effects model for repeated measurements for change in QoL score between treatment:

Proc mixed;

Class trt stage timepoint usubjid;

*Model QoL_chng = trt timepoint timepoint*trt base_QoL/solution ddfm=kr;*

Repeated timepoint/subject=usubjid type=un;

Lsmeans trt/pdiff cl;

Run;

7) The OS rates are estimated using Kaplan-Meier method. The difference between treatment arms is compared using a Chi-square statistic, standardized using the Greenwood variance estimator of the Kaplan-Meier estimate.

proc lifetest

TIMELIST=t

Appendix C: Shells for Tables, Listings, and Figures for Analysis

The mockup shells of the Tables, Listings, and Figures (TLFs) will be described in a stand-alone programming specification document, which will be finalized before the database lock.