

## STATISTICAL ANALYSIS PLAN

**Polaris Group**

**POLARIS2015-003**

**Protocol Title:** Randomized, Double-Blind, Phase 2/3 Study in Subjects with Malignant Pleural Mesothelioma with Low Argininosuccinate Synthetase 1 Expression to Assess ADI-PEG 20 with Pemetrexed and Cisplatin (ATOMIC-Meso Phase 2/3 Study)

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## 1 STATISTICAL ANALYSIS PLAN APPROVAL

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### 3 LIST OF ABBREVIATIONS

**Table 1 List of Abbreviations**

Abbreviation	Definition
ADI	Arginine deiminase
ADIPemCis	Combination therapy of ADI-PEG 20, pemetrexed and cisplatin
AE	Adverse event
ALT	Alanine transaminase (also known as SGPT)
ANC	Absolute neutrophil count
ASS1	Argininosuccinate synthetase (also known as ASS)
AST	Aspartate transaminase (also known as SGOT)
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CPO	Conditional Power for OS
CPS	Conditional Power for the OS evaluation in the biomarker-positive subpopulation
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
DCR	Disease Control Rate
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End-of-treatment
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IM	Intramuscular
ITT	Intent- to-treat
IWRS	Interactive Web Response System

Abbreviation	Definition
LCMS	Liquid chromatography mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MPM	Malignant pleural mesothelioma
MRI	Magnetic Resonance Imaging
NE	Not evaluable
OS	Overall survival
PD	Progressive disease
PEG	Polyethylene glycol
PFS	Progression free survival
PlaceboPemCis	Combination therapy of placebo, pemetrexed and cisplatin
PP	Per-Protocol
PR	Partial response
QTcF	Corrected QT interval using Fridericia's correction
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SD	Stable disease
SE	Standard error
SI	Système International
TEAE	Treatment-emergent adverse event
WBC	White blood cell count
WHO	World Health Organization

## 4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Polaris Group, Protocol POLARIS2015-003 (Randomized, Double-Blind, Phase 2/3 Study in Subjects with Malignant Pleural Mesothelioma with Low Argininosuccinate Synthetase 1 Expression to Assess ADI-PEG 20 with Pemetrexed and Cisplatin (ATOMIC-Meso Phase 2/3 Study)). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Conference on Harmonization (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized prior to data analysis and before treatment unblinding and database lock at the interim analysis to provide full details, including templates for tables, listings, and figures, to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

## 5 STUDY OBJECTIVES

### 5.1 Primary Study Objective

The primary objective of this study is:

- Determine efficacy as determined by the objective response rate (RR), measured by modified RECIST criteria for local pleural disease and RECIST 1.1 criteria for metastatic lesions (phase 2 portion) and overall survival (OS) (phase 3 portion)

### 5.2 Secondary Study Objectives

The key secondary objective of the phase 2 portion is:

- Determine the duration of response (DOR)

The key secondary objectives of the phase 3 portion are:

- Assess progression free survival (PFS)
- Determine the objective response rate (RR)
- Determine the duration of response (DOR)

Other secondary objectives of this study are:

- Determine the disease control rate (DCR)
- Assess safety and tolerability of ADI-PEG 20 in combination with pemetrexed and cisplatin



- Determine the pharmacodynamics of ADI-PEG 20 in combination with pemetrexed and cisplatin
- Determine the immunogenicity of ADI-PEG 20 in combination with pemetrexed and cisplatin
- Determine the pharmacokinetics of ADI-PEG 20 in combination with pemetrexed and cisplatin

The goal of the phase 2 portion of the trial is to provide data to support accelerated approval by the United States Food & Drug Administration, and the goal of the phase 3 portion of the trial is to provide a confirmatory study that would be ongoing at the time of the marketing application.

## 6 INVESTIGATIONAL PLAN

### 6.1 Overall Study Design

This is a randomized, double-blind, multi-center, phase 2/3 trial of ADI-PEG 20 in combination with pemetrexed and cisplatin in subjects with advanced MPM of sarcomatoid or biphasic histologies.

Both ASS1-deficient and non-deficient (i.e., all-comers) will be considered for participation at the start of the study (phase 2), and under the adaptive design, this may later be restricted to ASS1-deficient MPM only based on the outcome of interim analysis.

Weekly ADI-PEG 20 at 36 mg/m<sup>2</sup> (or placebo) will be combined with pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> both given every 3 weeks as first-line chemotherapy to non-epithelioid (biphasic and sarcomatoid) MPM. Eligible subjects will be randomized in a 1:1 ratio to ADI-PEG 20 with pemetrexed and cisplatin (ADIPemCis) or Placebo with pemetrexed and cisplatin (PlaceboPemCis). The randomization will be stratified by tumor histology (biphasic or sarcomatoid). Subjects may receive a maximum of 6, 3-week cycles of ADIPemCis or PlaceboPemCis for a total of 18 weeks of treatment. Those subjects completing ADIPemCis or PlaceboPemCis treatment may continue on ADI-PEG 20 or placebo monotherapy if they have stable disease (SD) or better. Subjects who do not tolerate cisplatin may be switched to carboplatin.

Approximately 176 subjects (88 per arm) will be enrolled in the phase 2 portion of the trial and 386 subjects (193 per arm) in the whole phase 2/3 trial. At the end of the phase 2 portion of the trial, an interim analysis will occur for possible sample size re-estimation for the phase 3 portion of the trial. In addition, the treatment effect of ADI-PEG 20 in combination with pemetrexed and cisplatin on OS will be evaluated in the overall population as well as the pre-defined ASS1-deficient subpopulation of biomarker-positive subjects at the interim analysis to select the most appropriate subject population for the phase 3 portion. This includes the option to discontinue the enrollment of biomarker-negative subjects (subjects without ASS1 deficiency) after the interim analysis.

Radiological (CT/MRI) scans for assessing tumor response will be performed at baseline, every 6 weeks during ADIPemCis or PlaceboPemCis dosing, and every 8 weeks during ADI-PEG 20 or placebo only dosing. Tumor response will be assessed by a blinded independent central review (BICR) using modified RECIST for MPM for intra-thoracic pleural disease and RECIST 1.1 for extra-pleural metastatic disease as applicable. In case of tumor response (complete or partial response) repeat imaging will be performed 4 weeks later to confirm response. The same imaging modality is to be used throughout the triplet treatment duration.

Efficacy endpoints include RR, OS, PFS, DOR, and DCR; RR, PFS, DOR, and DCR will be derived based on the tumor response assessments by BICR. BICR results will be used for eligibility determination and for decisions on continued treatment in the phase 2 portion. Safety assessments include adverse events (AEs), laboratory tests, vital signs, ECGs and physical examinations. Efficacy and safety endpoints are described in Section 6.4 and will be measured according to the Schedule of Assessments described in Section 6.2.

## **6.2 Schedule of Assessments**

For the complete schedule of assessments, refer to Section 1.4 of the clinical study protocol. Schedule of assessments for the blinded and open-label extension at study end is presented in Section 4.1.2 of the clinical study protocol.

## **6.3 Treatments**

### **6.3.1 *Treatments Administered***

ADI-PEG 20 at 36 mg/m<sup>2</sup> (or placebo) will be administered weekly by intramuscular (IM) injection. Pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> will be administered intravenously every 3 weeks. For each cycle, day 1 administration of ADI-PEG 20 (or placebo) will be administered 60-90 minutes prior to pemetrexed and cisplatin, except for the first cycle where the doublet chemotherapy will be administered on day 3.

The starting dose represents 100% of the recommended dose of cisplatin and pemetrexed and ADI-PEG 20 as determined in the phase 1 trial. Criteria for withholding treatment, dose adjustments, or switching from cisplatin to carboplatin based on toxicity are described in Section 7.3.3 of the clinical study protocol.

Tumor response will be evaluated at the end of week 6. In the event of disease progression, the triplet chemotherapy will be stopped and the subject offered an alternative treatment plan. In the absence of disease progression requiring other therapeutic interventions, subjects may receive additional cycles of ADIPemCis or PlaceboPemCis treatment following the same procedures and schedule as week 7 and onward for up to 18 weeks.

Subjects may continue to receive treatments unless, one of the following occurs at any time during the course of therapy: (1) unacceptable AEs, or (2) death, or (3) progressive

disease, or (4) significant noncompliance on the part of the subject, or (5) refusal of the subject to continue treatment or observations, or (6) decision by the Investigator that termination is in the subject's best medical interest, or (7) unrelated medical illness or complication, or (8) lost to follow-up. Any subject with tumor and stable disease or partial response should continue treatment until progression, unless the investigator thinks a better option is available. Thus, subjects completing ADIPemCis or PlaceboPemCis may continue to receive ADI-PEG 20 or placebo treatment, following the schema of week 13 and onward or week 19 and onward if 12 or 18 weeks of triple therapy is completed. Any subject with a complete response may receive 4 more weekly treatments of ADI-PEG 20 or placebo. The maximum number of cycles of pemetrexed + cisplatin is 6 (18 weeks at every 3 weeks cycle).

Subjects ongoing at study end (once the required number of events have been observed for the final analysis) may continue to receive treatment on ADIPemCis or PlaceboPemCis (or ADI-PEG 20/placebo alone), depending on where the subjects are in the treatment schedule, until the study is unblinded. Once the study treatment assignments are known, the subjects receiving ADI-PEG 20 may continue to receive ADIPemCis (or ADI-PEG 20 alone) until 1 of the following occurs: (1) unacceptable AEs, or (2) death, (3) PD or (4) decision by the Sponsor. Subjects receiving placebo should be consulted regarding alternative treatment options.

### **6.3.2      *Method of Assigning Subjects to Treatment Groups***

Subjects will be randomly assigned in a 1:1 ratio to receive ADI-PEG 20 drug product or matching placebo in a double-blind fashion via a centralized Interactive Web Response System (IWRS) system. ADI-PEG 20 drug product and placebo will be identical in appearance in order to preserve the blinding. The randomization will be stratified by tumor histology (biphasic or sarcomatoid).

## **6.4      Efficacy and Safety Variables**

### **6.4.1      *Efficacy Variables***

#### **6.4.1.1      *Primary Efficacy Variables***

The primary efficacy endpoint of the phase 2 portion of the study is:

- Objective response rate (RR): calculated as the proportion of subjects whose best tumor response from all post-baseline tumor assessments is complete response (CR) or partial response (PR)

Tumor response at each time point where CT/MRI scans are performed will be assigned by the BICR as complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD). In case of CR or PR, repeat imaging will be performed 4 weeks later to confirm response. If the response is not confirmed by the repeat assessment, the response of CR or PR will be treated as SD for that time point.

For subjects with intra-thoracic pleural disease, modified RECIST for MPM (Byrne 2004) will be used to determine response at each post-baseline time point as follows:

**Modified RECIST Criteria for MPM**

Response	Definition
CR	disappearance of all target lesions with no evidence of tumor elsewhere
PR	at least a 30% reduction in the total tumor measurement
PD	an increase of at least 20% in the total tumor measurement over the nadir measurement, or the appearance of one or more new lesions
SD	those who fulfilled the criteria for neither PR nor PD

For subject with extra-pleural metastatic disease, RECIST 1.1 (Eisenhauer 2009) will be used to determine response at each post-baseline time point. Assessment of target lesions, non-target lesions, new lesions, and overall response will be assigned as follows:

**RECIST 1.1 evaluation of target lesions:**

Response	Definition
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters on study.

### RECIST 1.1 evaluation of non-target lesions:

Response	Definition
CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
SD	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Appearance of one or more new lesions and/or <i>unequivocal progression</i> of existing non-target lesions.

### RECIST 1.1 overall response:

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PR	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The primary efficacy endpoint of the phase 3 portion of the study is:

- Overall survival (OS): calculated as the time from randomization until death. In the event that no death is documented prior to study termination or analysis cutoff, OS will be censored at the last known date the subject is known to be alive, either through completion of on-study visits or through survival follow-up contact.

#### 6.4.1.2 Secondary Efficacy Variables

The key secondary efficacy endpoint of the phase 2 portion of the study is:

- Duration of response (DOR): calculated for subjects who have a best tumor response of CR or PR as the time from date of initial response of CR or PR until date of tumor progression or death. Subjects without tumor progression or death at the end of treatment will be censored using the date of the last tumor assessment demonstrating no tumor progression.

The key secondary efficacy endpoints of the phase 3 portion of the study include the following:

- Progression-free survival (PFS): calculated as the time from randomization until date of tumor progression or death. In the event that no tumor progression or death is documented prior to end of treatment, analysis cutoff, or the start of confounding anticancer therapy, PFS will be censored at the date of the last tumor assessment demonstrating no tumor progression.
- Objective response rate (RR): as defined in Section 6.4.1.1.
- Duration of response (DOR): as defined above.

Other secondary efficacy endpoints of the phase 3 portion of the study include:

- Disease control rate (DCR): calculated as the proportion of subjects whose best tumor response from all post-baseline tumor assessments is CR, PR, or SD.

## **6.4.2 Description of Safety Variables**

### **6.4.2.1 Adverse Events**

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Note: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of Polaris studies to include any events, intercurrent diseases and accidents observed while the subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre and post-treatment periods.

Adverse events will be recorded from administration of first dose of study drug until 30 days after last study drug administration. Adverse events related to ADI-PEG 20 that were still ongoing at end of treatment (EOT) visit should be followed up until resolution or stabilization or until all attempts to determine resolution of the event are exhausted.

### **6.4.2.2 Laboratory Parameters**

Clinical laboratory tests listed in Table 2 will be obtained as per the schedule of events. Blood samples will be collected before ADI-PEG 20 or placebo administration. A certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

**Table 2 Clinical Laboratory Tests**

<b>Hematology (CBC)</b>	<b>Serum Chemistry</b>
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Red blood cell (RBC) count	Blood urea nitrogen (BUN)
White blood cell (WBC) count	Calcium
Absolute Neutrophil Count (ANC)	Chloride
Lymphocytes (Absolute values)	Creatinine
Monocytes (Absolute values)	Glucose (non-fasting)
Basophils (Absolute values)	HCG (at screening only)
Eosinophils (Absolute values)	Potassium
Platelet count (estimate not acceptable)	Serum glutamic-oxaloacetic transaminase (SGOT/AST)
	Serum glutamic-pyruvic transaminase (SGPT/ALT)
	Sodium
	Total bilirubin
	Total protein
	Uric acid

#### 6.4.2.3 Vital Signs

Vital signs (blood pressure, respiratory rate, heart rate, and temperature) will be obtained at screening, weekly during ADI-PEG 20/placebo treatment, and at the EOT visit. On days of ADI-PEG 20/placebo administration, vital signs will be obtained before and 1 hour ( $\pm$  15 minutes) after ADI-PEG 20 or placebo treatment.

#### 6.4.2.4 Electrocardiograms

Electrocardiograms (ECG) will be performed at screening, day 1 of cycle 2, day 15 of cycle 4, and during cycle 6 and beyond only as clinically indicated. On days of ADI-PEG 20/placebo administration, ECGs will be performed 1 hour ( $\pm$  15 minutes) after ADI-PEG 20 or placebo treatment.

The results will include ventricular rate, P-R interval, R-R interval, QRS duration, QT interval, QTcF interval, and overall interpretation (normal, abnormal and not clinically significant, abnormal and clinically significant).

The corrected QT interval will be corrected for respiratory rate using Fridericia's correction:  $QTcF = QT/R-R^{0.33}$ .

#### 6.4.2.5 Physical Examination

A comprehensive physical examination, including height and weight, will be performed at the screening visit. Weight and body surface area (BSA) will be captured on day 1 of each cycle. Symptom directed examinations may be performed as clinically indicated.



### **6.4.3      *Description of Pharmacodynamic, Immunogenicity, and Pharmacokinetic Variables***

Approximately 10 mL of peripheral blood will be collected as plasma prior to ADI-PEG 20 or placebo dosing and used for pharmacodynamics, pharmacokinetics and immunogenicity studies. A central laboratory will be utilized to process and provide results of blood sampling.

Pharmacodynamics will be assessed by measurement of peripheral blood levels of arginine and citrulline by liquid chromatography mass spectrometry (LCMS). Subjects will also be assessed to determine if they experience arginine depletion and/or citrulline increase. Arginine depletion will be defined as blood levels  $\leq 10 \mu\text{M}$  and citrulline increase will be defined as increase from baseline  $\geq 50\%$ .

Immunogenicity will be assessed by measurement of peripheral blood antibodies to ADI-PEG 20. Blood will also be available for testing for anti-PEG antibodies.

Pharmacokinetics will be assessed by measurement of peripheral blood ADI-PEG 20 levels.

Arginine, citrulline, anti-ADI-PEG 20 antibody, and ADI-PEG 20 levels will be obtained on day 1 and day 8 of cycle 1, day 1 of each subsequent cycle during combination therapy, and at weeks 19, 22, and 25 of ADI-PEG 20 or placebo only treatment.

### **6.5      Data Quality Assurance**

Report summaries will be generated using validated Base SAS<sup>®</sup> software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.



## 7 STATISTICAL METHODS

### 7.1 General Methodology

Data will be analyzed by Agility Clinical biostatistics personnel. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

#### 7.1.1 Reporting Conventions

Tables and figures will be summarized by treatment group. Tables summarizing demographics and other baseline characteristics will also include a column for all subjects combined. In general, all data collected and any derived data will be presented in subject data listings, for all enrolled subjects. Listings will be ordered by site, subject number, treatment group, and assessment or event date. The treatment group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the population sample size (N), number of subjects with available data (n), mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by the N, n, number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

P-values will be reported for all statistical tests, rounded to four decimal places. P-values less than 0.0001 will be displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999".

### 7.1.2 *Summarization by Visit*

Data summarized by study visit (e.g., laboratory and vital signs) will be based on the nominal, scheduled visit label as reported on the eCRF including the EOT assessment where applicable.

### 7.1.3 *Standard Calculations*

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose, if the assessment/event date is prior to the date of first dose; and
- The assessment/event date minus the date of first dose, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
  - Later date – (earlier date + 1), if the earlier date is on or after the date of first dose of study drug; or
  - Later date – earlier date, if the earlier date is prior to the date of first dose of study drug.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by  $(365.25 / 12)$ ;
- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25;
- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value;
- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

## 7.2 *Analysis Populations*

The analysis populations are defined as follows:

- **Safety Population:** Includes all randomized subjects who received at least one dose of the study medication. Assignment of subjects to treatment group is based on the treatment actually received.
- **Intent-to-Treat (ITT) Population:** Includes all randomized subjects who received at least one dose of the study medication. Assignment of subjects to treatment group is based on the randomized treatment assignment.
- **Per-Protocol (PP) Population:** Includes all ITT subjects who have at least one post-baseline assessment and have no major protocol violations that may potentially affect the primary and secondary efficacy measures (e.g., no MPM, no measurable disease). Subjects to be excluded from the PP Population will be determined prior to database lock and prior to breaking the blind of the treatment group assignments. Assignment of subjects to treatment group is based on the randomized treatment assignment.

In addition, efficacy endpoints at the interim analysis and final analysis will be presented on a pre-defined ASS1-deficient subpopulation of all biomarker-positive subjects in the ITT Population.

Data summaries to be presented on both the Safety Population and the ITT Population will only be produced on both analysis sets if there is a difference in the population groups (e.g., at least one subject receives a different treatment than they were originally assigned).

### **7.3 Study Subjects**

#### **7.3.1 *Disposition of Subjects***

Subject disposition will be summarized for all randomized subjects by treatment group and over all subjects combined. Summaries will include the number and percentage of subjects in each analysis population, the primary reason for discontinuing ADI-PEG 20 or Placebo, and the primary reason for study termination. Subject disposition will also be summarized separately for each study center.

#### **7.3.2 *Protocol Deviations***

Major protocol deviations will be summarized by treatment group and over all subjects combined for the Safety Population. Major protocol deviations will be identified, reviewed, and entered into the database as described in a separate Protocol Deviation Management Guideline document.

All major protocol deviations will be determined and appropriately categorized prior to database lock and prior to breaking the blind of the treatment group assignments. The number and percentage of subjects with any major protocol deviations as well as the number and percentage of subjects with deviations within each category will be presented.

## **7.4 Efficacy**

### **7.4.1 *Datasets Analyzed***

All efficacy summaries will be based the ITT Population and the ASS1-deficient subpopulation; select efficacy summaries will also be produced on the PP Population. A data listing of subjects excluded from the ITT or PP Population, to include the reason for exclusion, will be presented.

### **7.4.2 *Demographic and Other Baseline Characteristics***

Demographic variables including age, sex, ethnicity and race, will be summarized by treatment group and over all subjects combined for the Safety, ITT, and PP Populations and the ASS1-deficient subpopulation. Age will be calculated relative to date of informed consent, as follows:

- If the month and day portion of the informed consent date is prior to the month and day portion of the birth date, age will be calculated as the year of informed consent minus the year of birth, minus one;
- If the month and day portion of the informed consent date is on or after the month and day portion of the birthdate, age will be calculated as the year of informed consent minus the year of birth.

Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of subjects in each parameter category.

Baseline characteristics include: medical history, disease history (type of histology, stage of MPM, ASS1 status, any radiation or surgery treatment for actual cancer), height, weight, body surface area (BSA), and ECOG performance status. Height, weight, and BMI at baseline will be summarized using descriptive statistics. ECOG performance status and disease history will be summarized using frequency counts and percentages. Subjects reporting abnormal medical history will be presented only in subject data listings by subject and body system. All other baseline characteristics will be summarized by treatment group and over all subjects combined for the Safety, ITT, and PP Populations and the ASS1-deficient subpopulation.

### **7.4.3 *Primary Efficacy Endpoint Analysis Methods***

#### **7.4.3.1 *Objective Response Rate***

The first primary efficacy analysis will be the analysis of RR at the interim analysis (end of the phase 2 portion). The number and percentages of subjects responding (CR or PR) as well as the number and percentages of subjects in each best tumor response category (CR, PR, SD, PD, missing or not evaluable) will be summarized by treatment group. The objective response rate will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by tumor histology (biphasic versus sarcomatoid). The point estimate of the relative risk ratio and the corresponding two-

sided confidence interval will be provided. The significance level and coverage probability to be used in the RR analysis will be based on  $\alpha=0.05$  (two-sided). The primary analysis will be based on the ITT Population. Summaries will also be provided for the ASS1-deficient subpopulation and the PP population.

#### **7.4.3.2 Overall Survival**

The second primary efficacy endpoint of OS will be analyzed at the final analysis. Results will be presented by treatment group. The Kaplan-Meier method will be used to provide estimates of the OS curves, including the median, 25<sup>th</sup> and 75<sup>th</sup> percentiles and their corresponding 95% CIs. The number and percentage of subjects who experienced the event of interest and those who are censored will be presented along with minimum and maximum survival times. The Kaplan-Meier curves will also be plotted. A Cox proportional hazard model with an adjustment for tumor histology (biphasic versus sarcomatoid) will be used to compute the estimated hazard ratio and two-sided 95% confidence interval. The treatment effect on OS will be evaluated using the stratified log-rank test (stratified by tumor histology). The significance level to be used in the OS test at the final analysis will be derived using the closure principle and combination function approach (see Section 7.4.5.5 and Appendix A). The primary population at the final analysis will be determined based on decisions made at the interim analysis (see Section 7.4.5.3). Summaries will be provided for the ITT and PP populations and the ASS1-deficient subpopulation.

#### **7.4.4 Secondary Efficacy Endpoint Analysis Methods**

The key secondary efficacy endpoint at the interim analysis is DOR.

The key secondary efficacy endpoints at the final analysis are: PFS, RR, and DOR.

PFS will be analyzed at the final analysis using the same statistical methodologies as applied to OS as described in Section 7.4.3.2.

DOR will be analyzed at the interim and final analyses using the same statistical methodologies as applied to OS as described in Section 7.4.3.2.

RR will be analyzed at the final analysis using the same methodologies as described for the primary analysis of RR at the interim analysis as described in Section 7.4.3.1.

DCR will be analyzed at the interim and final analyses along with RR using the same methodologies, but is not part of the closed testing procedure and only unadjusted p-values will be presented.

The significance levels to be used in the key secondary endpoint tests will be derived using the closure principle and combination function approach described in Section 7.4.5.5 and Appendix A.

Summaries of secondary efficacy endpoints will be provided for the ITT and PP populations and the ASS1-deficient subpopulation.

#### **7.4.5      *Statistical/Analytical Issues***

##### **7.4.5.1      *Adjustments for Covariates***

The analyses of each of the primary and key secondary efficacy endpoints will be adjusted for the randomization stratification factor (biphasic histology versus sarcomatoid histology).

##### **7.4.5.2      *Handling of Dropouts or Missing Data***

Subjects with no post-baseline tumor response will be included in the denominator for calculation of RR and DCR and will be treated as non-responders.

For time to event endpoints (OS, PFS, DOR), subjects with no follow-up assessment will be censored using a censored value of 1 day.

No other imputations of missing data will be made.

##### **7.4.5.3      *Interim Analyses and Data Monitoring***

This study will employ an adaptive biomarker-driven design with an interim analysis to be conducted at the end of the Phase 2 portion, after adequate response assessment of the 176<sup>th</sup> subject. The interim analysis will evaluate the treatment effect on the first primary endpoint (RR) in the overall subject population. Overall survival data will also be evaluated at the time of the interim analysis in the overall population as well as the ASS1-deficient subpopulation to support the adaptive design decisions described below. The interim analysis will be performed in an unblinded manner at the end of the phase 2 portion and it is estimated that approximately 50% of the planned total number of OS events (338) will have occurred at the time of this interim analysis.

The RR data will be analyzed at the interim analysis to support accelerated approval. Further, the available OS data will be analyzed to support the following decisions:

- Futility stopping: Terminate the study due to futility at the interim analysis.
- Subject population selection: Discontinue the enrollment of biomarker-negative subjects after the interim analysis.
- Sample size re-estimation: Increase the target number of OS events after the interim analysis.

A futility stopping rule will be applied at the interim analysis to support a decision to terminate the study due to futility. The treatment's futility will be evaluated at the interim analysis based on the comparison of the median OS times in the ADIPemCis or PlaceboPemCis groups. The study may be terminated if the median OS in the ADIPemCis group is less than that in the PlaceboPemCis group. This futility stopping rule will be non-binding and can be overridden by the DSMB and/or Polaris.

A subject population selection rule will be applied at the interim analysis to support a decision to discontinue the enrollment of biomarker-negative subjects in the Phase 3 portion of the study. The rule will be based on conditional power (Lan 1982). Let conditional power for OS (CPO) define the conditional power for the OS evaluation in the overall population computed at the interim analysis, i.e., the probability of establishing a significant treatment effect on OS in the overall population at the final analysis conditional upon the OS data available at the interim analysis using the planned sample size. The probability will be evaluated under the assumption that the true treatment difference after the interim analysis is equal to the treatment difference computed at the time of the interim analysis.

The subject population selection rule will be defined based on CPO. The subject enrollment in the phase 3 portion of the study may be modified at the interim analysis as follows:

- Option 1: All subjects will be enrolled in the phase 3 portion if CPO is 50% or greater and the futility stopping rule is not met.
- Option 2: Only biomarker-positive subjects (ASS1-deficient subjects) will be enrolled in the phase 3 portion if CPO is less than 50% and the futility stopping rule is not met.

A sample size re-estimation rule will be applied at the interim analysis to support a decision to increase the target number of OS events in the subject population selected based on the subject selection option chosen. The target number of OS events may be modified at the interim analysis based on the conditional power for the OS evaluation in the overall population (CPO) and conditional power for the OS evaluation in the biomarker-positive subpopulation (denoted by CPS). CPS is defined similarly to CPO.

The following sample size re-estimation rule will be applied at the interim analysis:

- Option 1: Retain the planned target number of OS events in the overall population, i.e., 338 events, if CPO is 80% or greater and the futility stopping rule is not met (all subjects will be enrolled in the phase 3 portion in this case).
- Option 2: Increase the target number of OS events in the overall population if CPO is between 50% and 80%, and the futility stopping rule is not met (all subjects will be enrolled in the phase 3 portion in this case). The target number of OS events will be increased to achieve CPO of 80% or increased by 50%, whichever is smaller.
- Option 3: Retain the target number of OS events in the biomarker-positive subpopulation, i.e., 308 events, if CPO is less than 50%, CPS is 80% or greater or less than 50%, and the futility stopping rule is not met (only biomarker-positive subjects will be enrolled in the phase 3 portion in this case).



- Option 4: Increase the target number of OS events in the biomarker-positive subpopulation if CPO is less than 50%, CPS is between 50% and 80%, and the futility stopping rule is not met (only biomarker-positive subjects will be enrolled in the phase 3 portion in this case). The target number of OS events will be increased to achieve CPS of 80% or increased by 50%, whichever is smaller.

In addition to the explicit adjustment of the target number of OS events based on an unblinded interim analysis described above, the number of enrolled subjects may be adjusted in a blinded manner to achieve the desired number of OS events. Specifically, if Options 2, 3, or 4 are chosen the original number of enrolled subjects may need to be adjusted in order to achieve the desired number of OS events in the chosen subject population for Phase 3. Target enrollment adjustments will be accomplished using standard event forecasting methods (Anisimov 2011).

A DSMB will be instituted for this study to ensure the safety of the subjects. Recommendations for continuation of the study will be guided by safety evaluations at safety data reviews. The committee will include two independent oncologists with experience in thoracic oncology and an independent statistician. Safety meetings will be held as per the DSMB charter, approximately every 6 months and more often if deemed necessary. Decisions on study termination, amendment, or cessation of subject recruitment, based on safety or outcome findings, will be made after recommendations from the DSMB have been assessed by Polaris. The DSMB will not be expected to conduct the key efficacy analyses at the interim or final analysis.

#### 7.4.5.4 *Multicenter Studies*

This is a global, multicenter study. Efficacy data collected from all study centers will be pooled for data analysis. The effect of study center on the efficacy analysis results may be explored post-hoc, as needed.

#### 7.4.5.5 *Multiple Comparisons/Multiplicity*

The first primary endpoint (RR) will be evaluated at the interim analysis at  $\alpha = 0.05$  (two-sided) for the purpose of determining if the data supports accelerated approval. The second primary endpoint (OS) and key secondary endpoints will be tested at  $\alpha = 0.025$  (one-sided) at the final analysis.

To address multiplicity induced by the analysis of several endpoints (second primary endpoint and key secondary endpoints) at multiple decision points (interim and final analyses) in multiple subject populations (overall population and ASS1-deficient subpopulation), a multiplicity adjustment will be applied to the endpoints evaluated at the end of the phase 3 portion of the study:

- Endpoint P: Overall survival (OS).
- Endpoint S1: Progression-free survival (PFS).



- Endpoint S2: Objective response rate.
- Endpoint S3: Duration of response.

The treatment effect on the four endpoints will be evaluated in the overall population and the ASS1-deficient subpopulation unless a decision is made to restrict subject enrollment to the subset of ASS1-deficient subjects after the interim analysis. The resulting 8 tests are labeled as follows:

- Test PO (Endpoint P in the overall population).
- Test PS (Endpoint P in the ASS1-deficient subpopulation).
- Test S1O (Endpoint S1 in the overall population).
- Test S1S (Endpoint S1 in the ASS1-deficient subpopulation).
- Test S2O (Endpoint S2 in the overall population).
- Test S2S (Endpoint S2 in the ASS1-deficient subpopulation).
- Test S3O (Endpoint S3 in the overall population).
- Test S3S (Endpoint S3 in the ASS1-deficient subpopulation).

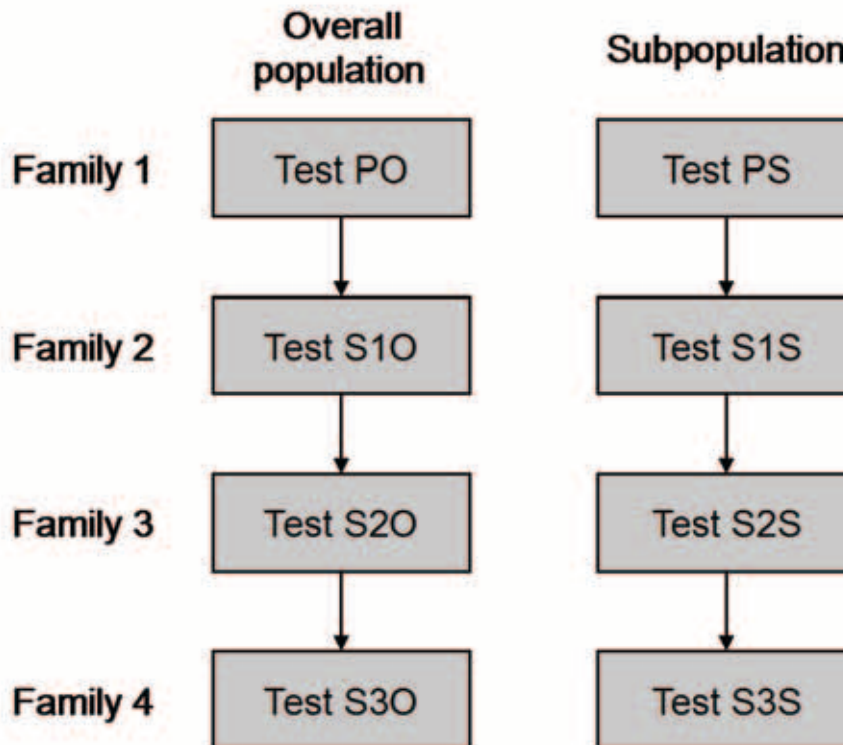
The 8 tests will be grouped into 4 families:

- Family 1: Tests PO and PS.
- Family 2: Tests S1O and S1S.
- Family 3: Tests S2O and S2S.
- Family 4: Tests S3O and S3S.

Note that, if subject enrollment is restricted to the ASS1-deficient population after the interim analysis, the overall population tests, i.e., Tests PO, S1O, S2O and S3O, will not be considered and only the subpopulation tests, i.e., Tests PS, S1S, S2S and S3S, will be carried out at the final analysis.

The general testing strategy under the assumption that the overall population and subpopulation analyses are performed at the final analysis is defined in Figure 1. Each branch in this decision tree corresponds to a single subject population (overall population or ASS1-deficient subpopulation) and, within each branch, the tests will be carried out sequentially beginning with the tests on Endpoint P (Overall survival), i.e., Tests PO and PS. An arrow indicates the dependence between the two corresponding tests, e.g., Test S1O will be carried out only if Test PO is significant and Test S2O will be carried out only if Test S1O is significant.

**Figure 1**      **Testing Strategy for the 8 Primary and Secondary Tests**



A multiplicity adjustment (gatekeeping procedure) will be developed using the mixture methodology proposed in Dmitrienko and Tamhane (2011, 2013) based on the closure principle. Key features of the gatekeeping procedure include:

- The gatekeeping procedure accounts for the logical restrictions among the 8 tests displayed in Figure 1.
- The gatekeeping procedure utilizes powerful Hochberg-type tests (regular and truncated Hochberg tests) for testing the hypotheses within each family. These tests account for positive correlations between the test statistics within each family, which leads to a uniform power gain compared to Bonferroni-based gatekeeping procedures. It is important to note that the test statistics within each family follow a bivariate normal distribution with a positive correlation induced by the fact that the subpopulation is a subset of the overall population. Under these conditions, the positive dependence condition (MTP2 condition), which guarantees local Type I error rate control within each family, is met (Sarkar and Chang, 1997; Sarkar, 1998).

- The gatekeeping procedure uses truncated Hochberg tests in the first 3 families because they serve as gatekeepers for other families. The regular Hochberg test is applied in Family 4 since it is the last family in the sequence. Thanks to truncated Hochberg tests, the gatekeeping procedure can proceed to the next family even if only one comparison is significant (the treatment effect is significant in only one population) in the current family. The truncated Hochberg tests in Families 1, 2 and 3 will be defined using a pre-specified truncation parameter  $\gamma=0.8$ .

The resulting gatekeeping procedure controls the overall Type I error rate across the four trial endpoints in the strong sense in a fixed-design setting. This gatekeeping procedure will be applied in conjunction with the combination function approach at the interim and final analyses to ensure strong Type I error rate control in the adaptive design considered in this trial.

A detailed description of the testing algorithm used in the gatekeeping procedure, including the closed testing representation of this procedure and computation of multiplicity-adjusted p-values for each primary and key secondary endpoints, is provided in Appendix A.

#### *7.4.5.6 Use of an “Efficacy Subset” of Subjects*

The primary efficacy analysis will be performed on the ITT population; the PP population will be utilized as a sensitivity analysis. The PP population will exclude subjects who did not have any post-baseline assessments and those subjects with major protocol violations that may potentially affect the primary and secondary efficacy measures. In addition, efficacy endpoints will be analyzed on the ASS1-deficient subpopulation at the interim and final analyses.

#### *7.4.5.7 Active-Control Studies Intended to Show Equivalence*

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

#### *7.4.5.8 Examination of Subgroups*

There are no planned analyses to assess efficacy results by subgroups.

### **7.4.6 Pharmacodynamics**

Blood levels of arginine and citrulline will be summarized by treatment group. Descriptive statistics (including n, mean, SD, median, Q1, Q3, minimum, and maximum values) will be presented for results and change from baseline at each visit where blood samples were scheduled to be collected. The baseline value will be defined as the last value reported prior to first study drug administration. The number and percentage of subjects with arginine depletion and citrulline increase will also be presented at each visit. Blood levels of arginine and citrulline will also be displayed graphically over time by treatment group.

Arginine and citrulline results may also be correlated with RR and OS by examining RR and OS results for subjects who demonstrate arginine depletion or citrulline increase at select time points compared to those subjects who do not.

#### **7.4.7      *Immunogenicity***

Blood levels of antibodies to ADI-PEG 20 and anti-PEG antibodies will be summarized for ADI-PEG 20 treated subjects. Descriptive statistics will be presented for results and change from baseline at each visit where blood samples were scheduled to be collected. The baseline value will be defined as the last value reported prior to first study drug administration. Blood levels of antibodies to ADI-PEG 20 and anti-PEG antibodies will also be displayed graphically over time.

#### **7.4.8      *Pharmacokinetics***

Blood concentration levels of ADI-PEG 20 will be summarized for ADI-PEG 20 treated subjects. Descriptive statistics will be presented for observed concentrations at each visit where blood samples were scheduled to be collected. Blood concentration levels of ADI-PEG 20 will also be displayed graphically over time.

Analysis of derived pharmacokinetic parameters or correlation to efficacy endpoints may be performed and summarized in a separate report and is outside the scope of this SAP.

### **7.5      *Safety Analysis***

Safety analysis will be carried out for the Safety Population, to include all subjects who receive at least one dose of study drug. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to first study drug administration.

#### **7.5.1      *Extent of Exposure and Treatment Compliance***

Extent of exposure to study treatment will be summarized for the Safety Population by treatment group. The number of doses taken and the total dose administered will be summarized for each study drug: ADI-PEG 20/Placebo, Pemetrexed, Cisplatin, and Carboplatin. The number and percentages of subjects who had at least one dose withheld and the number and percentages of subjects who at least one dose reduced along with the corresponding reasons for doses being withheld or reduced for each study drug, where applicable, will be summarized.

Compliance to ADI-PEG 20/Placebo, Pemetrexed, and Cisplatin/Carboplatin will be determined as the total number of doses received divided by the expected number of doses received, multiplied by 100. Expected number of doses will be determined by the number of weeks on study for ADI-PEG 20/Placebo dosing and the number of cycles initiated for Pemetrexed and Cisplatin/Carboplatin dosing prior to permanent discontinuation of study treatment.

Dosing compliance will be summarized using descriptive statistics, by treatment group, based on the Safety Population.

### **7.5.2      *Adverse Events***

Treatment-emergent adverse events (TEAEs) are defined as those adverse events (AEs) with onset after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by treatment group. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0 or most current version at the time of analysis).

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent serious adverse events (SAEs) and subject incidence of TEAEs meeting various criteria;
- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of the most frequently-occurring TEAEs (e.g., TEAEs occurring in  $\geq 10\%$  of the Safety Population) by MedDRA preferred term;
- Subject incidence of TEAEs by CTCAE grade, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to ADI-PEG 20/Placebo, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to Pemetrexed, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to Cisplatin, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to Carboplatin, MedDRA system organ class, and preferred term;
- Subject incidence of  $\geq$  Grade 3 TEAEs related to ADI-PEG 20/Placebo by MedDRA system organ class and preferred term; and

- Subject incidence of  $\geq$  Grade 3 TEAEs related to Pemetrexed by MedDRA system organ class and preferred term; and
- Subject incidence of  $\geq$  Grade 3 TEAEs related to Cisplatin by MedDRA system organ class and preferred term; and
- Subject incidence of  $\geq$  Grade 3 TEAEs related to Carboplatin by MedDRA system organ class and preferred term; and
- Subject incidence of TEAEs leading to discontinuation of ADI-PEG 20/Placebo by MedDRA system organ class and preferred term; and
- Subject incidence of TEAEs leading to discontinuation of Pemetrexed by MedDRA system organ class and preferred term; and
- Subject incidence of TEAEs leading to discontinuation of Cisplatin by MedDRA system organ class and preferred term; and
- Subject incidence of TEAEs leading to discontinuation of Carboplatin by MedDRA system organ class and preferred term; and
- Subject incidence of SAEs by MedDRA system organ class and preferred term.

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by CTCAE grade, subjects will be counted once at the highest CTCAE grade reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship to study drug.

Adverse event data will be presented in data listings by subject, treatment group, and event. Serious AEs and AEs leading to discontinuation of ADI-PEG 20/Placebo, Pemetrexed, Cisplatin, and Carboplatin will be presented in separate data listings.

#### **7.5.3      *Deaths, Other Serious Adverse Events, and Other Significant Adverse Events***

All deaths during the study, including the post treatment follow-up period, will be listed by subject, to include the primary cause of death. Serious AEs and AEs that led to withdrawal, interruption, or dose reduction of ADI-PEG 20/Placebo, Pemetrexed, Cisplatin, and Carboplatin, will be provided in separate subject data listings.

#### **7.5.4      *Clinical Laboratory Evaluation***

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included

in by-subject data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by subject, laboratory test, and unit.

Clinical laboratory measurements, including serum chemistry and hematology, will be summarized by treatment group. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Where applicable, hematology and chemistry results for select parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services *Common Terminology Criteria for Adverse Events (CTCAE)*, version 4.03 (Jun 2010). Five-by-five contingency tables will be presented for lab tests where toxicity grading can be applied to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Death related to AE (i.e., Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Summary results will include the count and percentage of subjects within each shift category.

Where applicable, laboratory results will be classified as “low,” “normal,” or “high” with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for laboratory parameter that cannot be assigned a CTCAE toxicity grade to summarize the shift from the baseline category to the worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of the study. Summary results will include the count and percentage of subjects within each shift category and treatment group.

## **7.5.5      *Vital Signs, Physical Findings, and Other Observations Related to Safety***

### **7.5.5.1      *Vital Signs***

Vital sign parameter measurements will be presented in subject data listings by subject and study visit.

### **7.5.5.2      *12-Lead Electrocardiogram***

Twelve-Lead ECG interval parameters will be summarized by treatment group. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected.

Twelve-lead ECG will be classified by the investigator as “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant.” Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of subjects within each shift category and treatment group.



Prolonged QT intervals will be summarized as QTcF measurements (msec) that are > 450, > 470, and > 500 at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change > 30 or > 60 relative to the baseline value. Summary results will include the percentage of subjects within each category and treatment group.

#### *7.5.5.3 Physical Examination*

Results of any symptom directed physical examination will be presented in subject data listings by subject and study visit.

#### *7.5.5.4 Prior and Concomitant Medications*

Medications will be coded using the World Health Organization (WHO Drug 2016Q1, enhanced) dictionary. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Concomitant medications will be summarized by treatment group for all medications reported on the Concomitant Medications eCRF. The number and percentage of subjects receiving any medication will be summarized by treatment group, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class.

### **7.6 Determination of Sample Size**

Extensive clinical trial simulations were performed to support power and sample size calculations for the adaptive biomarker-driven design in this study.

The sample size calculation for the first primary endpoint (RR) assumed that the objective response rate in the PlaceboPemCis arm was 15%. A total sample size of 176 subjects (88 per arm) in the phase 2 portion of the study will provide more than 80% power to detect an improvement in the RR from 15% to 35% at the interim analysis.

The sample size calculation for the second primary endpoint (OS) assumed that the median OS was 6 months in the PlaceboPemCis arm (the same median OS was assumed in the subpopulation of ASS1-deficient subjects and complementary subpopulation). Considering the ADIPemCis arm, the median OS was assumed to equal 8.7 months in the ASS1-deficient subpopulation, corresponding to a hazard ratio (HR) of 0.69. Assuming a median OS of 8.4 months (corresponding to a HR of 0.714) in the complementary subpopulation, 338 OS events will provide power of 90% for the OS analysis in the overall patient population. Further, the required number of OS events to achieve power of 90% for the OS analysis in the ASS1-deficient subpopulation was 308. Assuming uniform accrual over a 24-month period and a total study duration of 36 months, the



planned total sample size in the study was 386 subjects. The target number of events may be increased at the interim analysis, which will affect the total number of subjects.

The study will include an unblinded interim analysis at the end of the phase 2 portion, which will be performed by an Independent Analysis Group. The DSMB will review the interim analysis report and provide final recommendations related to futility stopping, subject population selection and sample size re-estimation after the interim analysis. The interim analysis decision rules are defined in Section 7.4.5.3.

## 7.7 Changes in the Conduct of the Study or Planned Analyses

This SAP includes the following modifications to the planned analyses as described in the protocol (Version 4; 05 December 2016):

- Both the first primary endpoint (RR) and the second primary endpoint (OS) will be tested at the  $\alpha = 0.05$  level. The Type I error rate will not be split between the two endpoints. RR will be tested to support accelerated approval and OS will be tested as the primary endpoint for the phase 3 portion of the study.
- Revised estimates of OS median survival are used in the sample size and power calculations. Power is also adjusted since the Type I error rate will no longer be split between RR and OS endpoints.
- The DCR endpoint is clarified to not be included in the set of key secondary endpoints.
- The definition of the PP population is updated. The condition that a subject completes the study is removed. Also, clarification is provided that not all major protocol violations will exclude a subject from the PP population. Major protocol violations will be reviewed prior to database lock to determine ones that may potentially affect the primary and secondary efficacy measures.

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## APPENDIX A: ADAPTIVE DESIGN METHODOLOGY

### Combination Function Approach

The decision rules employed in the proposed adaptive design will be applied along with the multiplicity adjustment (gatekeeping procedure) described in Section 7.4.5.5 based on the combination function approach (Cui 1999, Brannath 2002). This general strategy is commonly used to construct adaptive designs in confirmatory trials. The combination function approach will be applied using the weighted inverse-normal combination function in conjunction with the gatekeeping procedure to ensure that the overall Type I error rate will be protected at the nominal level across the second primary endpoint (OS) and key secondary endpoints evaluated in the phase 3 portion of the study regardless of the type of design modifications at the interim analysis.

In what follows, the combination function approach will be used to compute the multiplicity-adjusted  $p$ -values for the following null hypotheses of no effect (or, equivalently, associated treatment effect tests):

- Null hypothesis  $H_1$ : Test PO (Endpoint P in the overall population).
- Null hypothesis  $H_2$ : Test PS (Endpoint P in the ASS1-deficient subpopulation).
- Null hypothesis  $H_3$ : Test S1O (Endpoint S1 in the overall population).
- Null hypothesis  $H_4$ : Test S1S (Endpoint S1 in the ASS1-deficient subpopulation).
- Null hypothesis  $H_5$ : Test S2O (Endpoint S2 in the overall population).
- Null hypothesis  $H_6$ : Test S2S (Endpoint S2 in the ASS1-deficient subpopulation).
- Null hypothesis  $H_7$ : Test S3O (Endpoint S3 in the overall population).
- Null hypothesis  $H_8$ : Test S3S (Endpoint S3 in the ASS1-deficient subpopulation).

A closed family associated with these null hypotheses will be defined. The closed family contains  $2^8 - 1 = 255$  intersections of the 8 original null hypotheses. Each intersection hypothesis is identified by considering an index set  $I$  that contain the indices of the null hypotheses included in this intersection hypothesis. For example, if an intersection hypothesis is based on the intersection of  $H_3$ ,  $H_7$  and  $H_8$ , the associated index set is given by  $I = \{3, 7, 8\}$ .

According to the combination function approach, the amount of evidence to reject the 8 original null hypotheses at the final analysis will be evaluated separately in Stages 1 and 2 that are defined as follows:

- Stage 1 (subjects enrolled in the trial prior to the interim analysis) defines the phase 2 portion of the trial.

- Stage 2 (subjects enrolled in the trial after the interim analysis) defines the phase 3 portion of the trial.

Let  $p_i$  and  $q_i$  denote the one-sided  $p$ -values for testing the null hypothesis  $H_i$ ,  $i = 1, 2, \dots, 8$ , based on the data in Stages 1 and 2, respectively. A normally distributed version of the logrank test statistic defined in Jennison and Turnbull (2000) needs to be used to compute these  $p$ -values. Specifically,  $p_i$  is the  $p$ -value computed from the test associated with the null hypothesis  $H_i$ ,  $i = 1, 2, \dots, 8$ , based on all Stage 1 patients, i.e., the patients enrolled in the trial prior to the interim analysis. OS and PFS outcomes for a Stage 1 patient will be considered censored if the patient is still alive or has not experienced disease progression, respectively, at the end of a 18-month period after the interim analysis. Further,  $q_i$  is the  $p$ -value computed from the test associated with the null hypothesis  $H_i$ ,  $i = 1, 2, \dots, 8$ , based on all Stage 2 patients, i.e., the patients enrolled in the trial after the interim analysis. OS and PFS outcomes for a Stage 2 patient will be considered censored if the patient is still alive or has not experienced disease progression, respectively, at the end of the trial. As shown in Magirr et al. (2016), this “patient-wise separation” approach to designing adaptive survival trials is consistent with the combination function framework as long as of the follow-up period for the Stage 1 patients is pre-defined.

Let  $H(I)$  denote an arbitrary intersection hypothesis from the closed family, which is associated with the index set  $I$ . Let  $p(I)$  and  $q(I)$  denote the local  $p$ -values based on the gatekeeping procedure that are associated with this intersection hypothesis. These local  $p$ -values are computed from the Stage 1 and Stage 2 data sets defined above, respectively. The derivation of the local  $p$ -values is described in the section below describing the closed testing representation of the gatekeeping procedure.

As shown in Wassmer (2011), the local  $p$ -values will need to be modified if the interim analysis data support the decision to restrict the subject enrollment after the interim analysis to the ASS1-deficient subpopulation. Specifically, if Option 2 (only ASS1-deficient subjects will be enrolled in the phase 3 portion of the trial) is selected, the Stage 2  $p$ -values corresponding to the overall population tests will be removed from the intersection hypotheses set. For example, considering the intersection hypothesis based on the intersection of  $H_3$ ,  $H_7$  and  $H_8$ , the Stage 2  $p$ -values for  $H_3$  and  $H_7$  will be removed when  $q(I)$  is computed because these  $p$ -values are based on overall population tests.

The inferences for the selected intersection hypothesis will be performed at the final analysis using the composite local  $p$ -values that will be defined as follows. Let  $w_1$  and  $w_2$  denote the pre-specified stagewise weights, i.e.,

$$w_1 = 0.5, w_2 = 0.5.$$

The combination function to be used at the final analysis is given by:

$$c(x_1, x_2) = 1 - \Phi \left[ \sqrt{w_1} \Phi^{-1}(1 - x_1) + \sqrt{w_2} \Phi^{-1}(1 - x_2) \right],$$

where  $\Phi(x)$  denotes the cumulative distribution function of the standard normal distribution.

This combination function will be applied to the local  $p$ -values  $p(I)$  and  $q(I)$  computed from the Stage 1 and Stage 2 data sets and the composite local  $p$ -value for the intersection hypothesis  $H(I)$  to be used at the final analysis will be defined as

$$r(I) = c(p(I), q(I)) = 1 - \Phi \left[ \sqrt{w_1} \Phi^{-1}(1 - p(I)) + \sqrt{w_2} \Phi^{-1}(1 - q(I)) \right].$$

Using the composite local  $p$ -values for all intersection hypotheses in the closed family, the multiplicity-adjusted  $p$ -value for any of the 8 original null hypotheses is defined as the maximum over all composite local  $p$ -values  $r(I)$  such that the index set  $I$  contains the index of the selected null hypothesis. For example, to compute the multiplicity-adjusted  $p$ -value for the null hypothesis  $H_1$ , the maximum needs to be computed over all intersection hypotheses in the closed family that include  $H_1$ .

A significant treatment effect will be claimed at the final analysis (i.e., the treatment will be declared superior to the control) with respect to a particular test if the resulting one-sided multiplicity-adjusted  $p$ -value for the corresponding null hypothesis is less than or equal to  $\alpha$ , where  $\alpha = 0.025$  (one-sided).

The proposed set of decision rules in the adaptive design guarantees overall Type I error rate control with respect to the second primary endpoint (OS) and key secondary endpoints. The Type I error rate control is retained even if the sample size is adjusted at the interim analysis or a decision to restrict the subject enrollment to the ASS1-deficient subpopulation is made.

### Closed Testing Representation of the Gatekeeping Procedure

The closed testing representation of the Hochberg-based gatekeeping procedure will be defined using the general approach developed in Dmitrienko et al. (2016). This representation is used above to compute multiplicity-adjusted  $p$ -values for the 8 individual tests (null hypotheses) at the final analysis.

The 8 null hypotheses of no treatment effect (Null hypothesis  $H_1$  through  $H_8$ ) will be defined as above. The null hypotheses will be grouped into 4 families:

- Family 1: Null hypotheses  $H_1$  and  $H_2$ .
- Family 2: Null hypotheses  $H_3$  and  $H_4$ .
- Family 3: Null hypotheses  $H_5$  and  $H_6$ .
- Family 4: Null hypotheses  $H_7$  and  $H_8$ .

The following compact notation will be used in this section to derive the closed testing representation of the Hochberg-based gatekeeping procedure. The 4 families will be defined as follows:

$$F_1 = \{H_i, i \in N_1\}, F_2 = \{H_i, i \in N_2\}, F_3 = \{H_i, i \in N_3\}, F_4 = \{H_i, i \in N_4\},$$

where the family index sets are defined as

$$N_1=\{1,2\}, N_2=\{3,4\}, N_3=\{5,6\}, N_4=\{7,8\}.$$

Finally, the overall index set of 8 hypotheses is denoted by  $N$ , i.e.,

$$N=\{1,2,\dots,8\},$$

Let  $p_i, i=1,2,\dots,8$ , denote the one-sided  $p$ -values for testing the 8 null hypotheses.

The testing algorithm in the gatekeeping procedure utilizes the closure principle and specifies the decision rules for all intersection hypotheses in the closed family associated with the 8 null hypotheses. As stated above, the closed family contains  $2^8 - 1 = 255$  intersections of the original null hypotheses. Let  $H(I)$  denote an arbitrary intersection hypothesis from the closed family, which is associated with the index set  $I$ . A local  $p$ -value will be computed for the intersection hypothesis  $H(I)$  in three steps as shown below.

### Step 1

To ensure that the final gatekeeping procedure is consistent with the logical relationships among the null hypotheses, the following restrictions need to be imposed on the hypotheses within each intersection. These restrictions ensure, for example, that the null hypothesis  $H_3$  cannot be rejected if the null hypothesis  $H_1$  is not rejected ( $H_3$  will be automatically accepted if  $H_1$  is not rejected).

Consider an arbitrary intersection hypothesis corresponding to the index set  $I \subseteq N$ . This intersection hypothesis is denoted by  $H(I)$ . Define the index sets  $I_k = I \cap N_k, k=1, 2, 3, 4$ , for the intersection hypothesis. Note that some of the index sets may be empty.

The logical restrictions are applied to the index sets  $I_2, I_3$  and  $I_4$  as follows:

- Family 1 serves as a gatekeeper with serial restrictions for Family 2 and therefore the index set  $I_2$  will need to be modified. Specifically, certain indices may need to be removed from this index set to ensure that the gatekeeping procedure is consistent with the logical relationships among the null hypotheses. Suppose, for example, that  $I_1=\{1\}, I_2=\{3,4\}$ . The hypothesis  $H_3$  needs to be deleted from the index set  $I_2$  since  $H_3$  depends on  $H_1$ , which is included in the index set  $I_1$ .
- Since Families 2 and 3 also serve as gatekeepers with serial restrictions for the next family in the sequence, the same restrictions will be applied to Families 3 and 4.

### Step 2

This step deals with defining  $p$ -values for each family within a given intersection. These family-specific  $p$ -values are defined sequentially as demonstrated below.

Beginning with Family 1, let  $m_1$  denote the number of hypotheses included in the index set  $I_1$  and let  $n_1$  denote the total number of hypotheses in Family 1, i.e.,  $n_1=2$ . If  $m_1>0$ , the truncated Hochberg  $p$ -value is defined using the ordered  $p$ -values associated with the null hypotheses included in the index set  $I_1$ , denoted by

$$p_{1(1)} \leq \dots \leq p_{1(m_1)}.$$

The truncated Hochberg  $p$ -value in Family 1 is given by

$$p_1(I_1) = \min_{i=1, \dots, m_1} \frac{p_{1(i)}}{\gamma/(m_1-i+1) + (1-\gamma)/n_1},$$

where the truncation parameter  $\gamma$  is equal to 0.8. For example, if both  $H_1$  and  $H_2$  are included in the selected intersection hypothesis and thus the index set  $I_1 = \{1, 2\}$ . In this case  $m_1=2$  and thus the truncated Hochberg  $p$ -value in Family 1 is given by

$$p_1(I_1) = \min \left( \frac{p_{1(1)}}{\gamma/2 + (1-\gamma)/2}, \frac{p_{1(2)}}{\gamma/1 + (1-\gamma)/2} \right) = \min \left( 2p_{1(1)}, \frac{2p_{1(2)}}{1+\gamma} \right).$$

Further, if only one hypothesis from Family 1 is included in the intersection, say,  $H_2$ , the index set  $I_1 = \{2\}$  and  $m_1=1$ . This means that the truncated Hochberg  $p$ -value in Family 1 is simply equal to

$$p_1(I_1) = \frac{p_2}{\gamma/1 + (1-\gamma)/2} = \frac{2p_2}{1+\gamma}.$$

Finally, if no hypothesis from Family 1 is included in the selected intersection, the truncated Hochberg  $p$ -value in Family 1 is set to 1, i.e.,

$$p_1(I_1) = 1.$$

Continuing to Family 2, let  $m_2$  denote the number of hypotheses included in the index set  $I_2$  after the logical restrictions described in Step 1 have been applied. Further, let  $n_2$  denote the total number of hypotheses in Family 2 after accounting for the logical restrictions.

If  $m_2>0$ , let

$$p_{2(1)} \leq \dots \leq p_{2(m_2)}$$

denote the ordered  $p$ -values for the hypotheses remaining in the index set  $I_2$ . The truncated Hochberg  $p$ -value in Family 2 is given by



$$p_2(I_2) = \min_{i=1, \dots, m_2} \frac{p_{2(i)}}{\gamma/(m_2 - i + 1) + (1 - \gamma)/n_2}.$$

If  $m_2=0$ , the Hochberg  $p$ -value in Family 2 is set to 1, i.e.,

$$p_2(I_2) = 1.$$

To illustrate the process of computing this  $p$ -value, suppose that the selected intersection hypothesis includes the null hypothesis  $H_1$  from Family 1 and null hypotheses  $H_3$  and  $H_4$  from Family 2. This means that

$$I_1 = \{1\} \text{ and } I_2 = \{3, 4\}.$$

Recall that the hypothesis  $H_3$  needs to be deleted from the index set  $I_2$  since it depends on  $H_1$ . As a result, only one null hypothesis is retained in Family 2, namely, the null hypothesis  $H_4$ , after accounting for the logical restrictions. This means that  $m_2=1$ . A similar argument is used to compute  $n_2$ . This number is found by excluding the null hypotheses from the index set  $I_2$  that become untestable if the only null hypothesis in the index set  $I_1$  is accepted. It is easy to see that, if null hypothesis  $H_1$  is indeed accepted, the null hypothesis  $H_3$  needs to be removed from the index set  $I_2$ , which implies that  $n_2=1$ . As a result, the truncated Hochberg  $p$ -value in Family 2 is given by

$$p_2(I_2) = \frac{p_4}{\gamma/1 + (1 - \gamma)/1} = p_4.$$

The same principle is applied to compute the truncated Hochberg  $p$ -values with  $\gamma=0.8$  in Family 3 and regular Hochberg  $p$ -values with  $\gamma=1$  in Family 4.

### Step 3

The final step in the testing algorithm specifies the rules for computing the local  $p$ -value for the selected intersection hypothesis  $H(I)$ . The local  $p$ -value is derived by combining the family-specific  $p$ -values across the 4 families.

Consider the selected intersection and the four family-specific  $p$ -values, i.e.,  $p_i(I_i)$ ,  $i=1, 2, 3, 4$ . Each family is assigned a weight denoted by  $b_i$  and, based on these weights, the overall  $p$ -value for the intersection hypothesis, is given by

$$p(I) = \min \left( \frac{p_1(I_1)}{b_1}, \frac{p_2(I_2)}{b_2}, \frac{p_3(I_3)}{b_3}, \frac{p_4(I_4)}{b_4} \right).$$

The family weight for Family 1 is set to 1 ( $b_1=1$ ) and the family weight for Family  $k$ ,  $k=2, 3, 4$ , is computed from the error rate function of the truncated Hochberg test using the following sequential approach:

$$b_k = b_{k-1}(1 - f(s_{k-1}, r_{k-1})),$$

where  $f(s_{k-1}, r_{k-1})$  is the error rate function of the truncated Hochberg test in Family  $k-1$ . This function depends on the number of null hypotheses included in the selected intersection within the current family before an adjustment for the logical restrictions ( $s_{k-1}$ ) as well as the total number of null hypotheses in the current family before an adjustment for the logical restrictions ( $r_{k-1}$ ). Note that the latter is always equal to 2. As shown in Brechenmacher et al. (2011),

$$f(s_k, r_k) = \gamma + \frac{(1-\gamma)s_k}{r_k}$$

if  $s_k$  is a positive number and  $f(s_k, r_k) = 0$  if  $s_k = 0$ .

In simple terms, the numerical value of a family weight determines the fraction of the overall Type I error rate that is transferred to the next family. As an illustration, suppose as in Step 2 that the selected intersection hypothesis includes the null hypothesis  $H_1$  from Family 1. It is easy to check that  $s_1 = 1$  and  $r_1 = 2$ . Recall that the family weight for Family 1 is set to 1 and thus the weight of Family 2 is given by

$$b_2 = b_1(1 - f(s_1, r_1)) = 1 - \gamma - \frac{(1-\gamma)s_1}{r_1} = \frac{1-\gamma}{2}.$$

The resulting local  $p$ -values for the intersection hypotheses, i.e.,  $p(I)$  for each  $H(I)$ , are utilized for computing the multiplicity-adjusted treatment effect  $p$ -values for the 8 primary and secondary tests at the final analysis.

### Conditional Power

Conditional power (CP) calculations for the second primary endpoint (OS) in the overall population and the ASS1-deficient subpopulation will be performed at the interim analysis based on the following closed-form expression for CP.

Beginning with CP calculations in the overall population, let  $n_1$  and  $n_2$  denote the total number of OS events in the overall population in the Stage 1 and Stage 2 data sets, respectively. Here  $n_2$  defines the total number of OS events based on the *planned* final analysis, i.e., based on the total of 338 events. As in Section 3, let  $w_1$  and  $w_2$  denote the pre-specified weights of the two stages in the trial, i.e.,  $w_1 = w_2 = 0.5$ .

Conditional power for the OS test in the overall population is given by (see, for example, Chang, 2008)

$$CPO = \Phi \left[ \sqrt{\frac{w_1}{w_2}} Z_1 + \theta \sqrt{\frac{n_2}{4}} - \frac{c}{\sqrt{w_2}} \right].$$

Here  $Z_1$  is the logrank test statistic for the OS test computed at the interim analysis (note that a normally distributed version of the logrank test statistic defined in Jennison and

Turnbull, 2000, needs to be used). Further,  $\theta$  is the observed effect size, i.e., the log-hazard ratio at the interim analysis, and  $c$  is the critical value of the standard normal distribution corresponding to  $\alpha = 0.025$  (one-sided), i.e.,  $c = 1.96$ .

Based on the sample size re-estimation rule defined above, the target number of OS events may be increased to achieve conditional power of 80% before the multiplicity adjustment. The updated Stage 2 event count is computed by setting CPO to 80%. This event count is given by

$$n_2 = \frac{4}{\theta^2} \left[ \Phi^{-1}(0.8) + \frac{c}{\sqrt{w_2}} - \sqrt{\frac{w_1}{w_2}} Z_1 \right]^2 = \frac{4}{\theta^2} [3.168 - Z_1]^2.$$

As explained above, a cap will be applied to the increase in the target event count in Stage 2.

Conditional power in the ASS1-deficient subpopulation (CPS) is computed using the same approach. Specifically,  $n_1$  and  $n_2$  will denote the total number of OS events in the subpopulation in the Stage 1 and Stage 2 data sets, respectively. Again,  $n_2$  defines the total number of OS events based on the *planned* final analysis within this subpopulation, i.e., based on the total of 308 events. This event count will be computed based on a projection that utilizes the observed prevalence of ASS1-deficient subjects and observed hazard rate in the interim analysis database.

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## STATISTICAL ANALYSIS PLAN

**Polaris Group**

**POLARIS2015-003**

**Protocol Title:** Randomized, Double-Blind, Phase 2/3 Study in Subjects with Malignant Pleural Mesothelioma to Assess ADI-PEG 20 with Pemetrexed and Cisplatin (ATOMIC-Meso Phase 2/3 Study)

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### 3 LIST OF ABBREVIATIONS

**Table 1 List of Abbreviations**

Abbreviation	Definition
ADI	Arginine deiminase
ADIPemPlatinum	Combination therapy of ADI-PEG 20, pemetrexed and cisplatin (or carboplatin)
AE	Adverse event
ALT	Alanine transaminase (also known as SGPT)
ANC	Absolute neutrophil count
ASS1	Argininosuccinate synthetase (also known as ASS)
AST	Aspartate transaminase (also known as SGOT)
BICR	Blinded independent central review
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CP	Conditional power
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCR	Disease Control Rate
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End-of-treatment
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IM	Intramuscular
ITT	Intent- to-treat
IWRS	Interactive Web Response System
LCMS	Liquid chromatography mass spectrometry

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MPM	Malignant pleural mesothelioma
MRI	Magnetic Resonance Imaging
NE	Not evaluable
OS	Overall survival
PD	Progressive disease
PEG	Polyethylene glycol
PFS	Progression free survival
PlaceboPemPlatinum	Combination therapy of placebo, pemetrexed and cisplatin (or carboplatin)
PP	Per-Protocol
PR	Partial response
QTcF	Corrected QT interval using Fridericia's correction
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation or stable disease depending on context
SE	Standard error
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SI	Système International
TEAE	Treatment-emergent adverse event
WBC	White blood cell count
WHO	World Health Organization

## 4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Polaris Group, Protocol POLARIS2015-003 (Randomized, Double-Blind, Phase 2/3 Study in Subjects with Malignant Pleural Mesothelioma to Assess ADI-PEG 20 with Pemetrexed and Cisplatin (ATOMIC-Meso Phase 2/3 Study)). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Conference on Harmonization (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized prior to data analysis and before treatment unblinding and database lock at the interim analysis to provide full details, including templates for tables, listings, and figures, to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

Notable changes from version 1.0 to version 2.0 of this SAP correspond to similar changes from version 4 to version 5 of the protocol and include:

- Removal of secondary endpoints of objective response rate and duration of response in phase 3. Both endpoints will remain as endpoints for phase 2.
- Removal of disease control rate as a secondary endpoint in phase 3.
- The timing of the interim analysis to assess futility and potential sample size increase was modified from occurring at the end phase 2 to be performed at a separate time from the end of phase 2 analysis when 50% of planned overall survival events have occurred in order to obtain more reliable sample size estimates for phase 3.
- Removal of the subject population selection rule at the interim analysis. Interim analysis methods and options were updated and simplified accordingly.
- The cap for percent increase in sample size at the interim analysis was modified from 50% to 30%.
- Methods for addressing multiplicity were modified based on the removal of secondary endpoints and the removal of the subject population selection rule at the interim analysis.

Changes from version 2.0 to version 4.0 of this SAP are based on DSMB recommendations and other minor clarifications as follows:

- The original planned sample size will be changed from 386 subjects to all enrolled up to August 15, 2021 (249 subjects); and the deaths for the original planned final analysis of OS will be changed from 338 to the actual number of deaths occurred on August 14, 2022. Also, an administrative penalty of  $\alpha=0.00001$  will be paid for second interim analysis, and the allocated  $\alpha=0.04999$  will be used for the final analysis.

## 5 STUDY OBJECTIVES

### 5.1 Primary Study Objective

The primary objective of this study is:

- Determine efficacy as determined by the objective response rate (RR), measured by modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for local pleural disease and RECIST 1.1 criteria for metastatic lesions (phase 2 portion) and overall survival (OS) (phase 3 portion)

### 5.2 Secondary Study Objectives

The secondary objective of the phase 2 portion is:

- Determine the duration of response (DOR)

The secondary objective of the phase 3 portion is:

- Assess progression free survival (PFS)

Other objectives of this study are:

- Assess safety and tolerability of ADI-PEG 20 in combination with pemetrexed and cisplatin
- Determine the pharmacodynamics of ADI-PEG 20 in combination with pemetrexed and cisplatin
- Determine the immunogenicity of ADI-PEG 20 in combination with pemetrexed and cisplatin
- Determine the pharmacokinetics of ADI-PEG 20 in combination with pemetrexed and cisplatin

The goal of the phase 2 portion of the trial is to provide data to support accelerated approval by the United States Food & Drug Administration (FDA), and the goal of the phase 3 portion of the trial is to provide a confirmatory study that would be ongoing at the time of the marketing application.

## 6 INVESTIGATIONAL PLAN

### 6.1 Overall Study Design

This is a randomized, double-blind, multi-center, phase 2/3 trial of ADI-PEG 20 in combination with pemetrexed and cisplatin in subjects with unresectable malignant pleural mesothelioma (MPM) of sarcomatoid or biphasic histologies.

Weekly ADI-PEG 20 at 36 mg/m<sup>2</sup> (or placebo) will be combined with pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> both given every 3 weeks as first-line chemotherapy to non-epithelioid (biphasic and sarcomatoid) MPM. Eligible subjects will be randomized in a 1:1 ratio to ADI-PEG 20 with pemetrexed and cisplatin (ADIPemPlatinum) or Placebo with pemetrexed and cisplatin (PlaceboPemPlatinum). The randomization will be stratified by tumor histology (biphasic or sarcomatoid). Subjects may receive a maximum of 6, 3-week cycles of ADIPemPlatinum or PlaceboPemPlatinum for a total of 18 weeks of treatment. Those subjects completing ADIPemPlatinum or PlaceboPemPlatinum treatment may continue on ADI-PEG 20 or placebo monotherapy if they have stable disease (SD) or better. Subjects who do not tolerate cisplatin may be switched to carboplatin.

Approximately 176 subjects (88 per arm) will be enrolled in the phase 2 portion of the trial and 386 subjects (193 per arm) in the whole phase 2/3 trial. At the end of the phase 2 portion of the trial an interim analysis will be conducted to evaluate RR in the first 176 subjects (phase-2 subjects). A second interim analysis will be conducted once 50% of the estimated OS events for phase 3 have occurred to determine whether to terminate the study for futility or for possible sample size re-estimation for the phase 3 portion of the trial.

Based on DSMB recommendations, the original planned sample size will be changed from 386 subjects to all enrolled up to August 15, 2021 (249 subjects). Radiological (CT/MRI) scans for assessing tumor response will be performed at baseline, every 6 weeks during ADIPemPlatinum or PlaceboPemPlatinum dosing, and every 8 weeks during ADI-PEG 20 or placebo only dosing. Tumor response will be assessed using modified RECIST for MPM for intra-thoracic pleural disease and RECIST 1.1 for extra-pleural metastatic disease as applicable. In case of tumor response (complete or partial response) repeat imaging will be performed 4 weeks later to confirm response. The same imaging modality is to be used throughout the triplet treatment duration.

Efficacy endpoints include RR, DOR, OS, and PFS; RR and DOR will be derived based on the tumor response assessments by a blinded independent central review (BICR) for phase 2 and PFS will be derived based on the tumor response assessments by the investigator for phase 3. Safety assessments include adverse events (AEs), laboratory tests, vital signs, electrocardiograms (ECGs) and physical examinations. Efficacy and safety endpoints are described in Section 6.4 and will be measured according to the Schedule of Assessments described in Section 6.2.

## 6.2 Schedule of Assessments

For the complete schedule of assessments, refer to Section 1.4 of the clinical study protocol. Schedule of assessments for the blinded and open-label extension at study end is presented in Section 4.1.2 of the clinical study protocol.

## 6.3 Treatments

### 6.3.1 *Treatments Administered*

ADI-PEG 20 at 36 mg/m<sup>2</sup> (or placebo) will be administered weekly by intramuscular (IM) injection. Pemetrexed 500 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> will be administered intravenously every 3 weeks. For each cycle, day 1 administration of ADI-PEG 20 (or placebo) will be administered 60-90 minutes prior to pemetrexed and cisplatin, except for the first cycle where the doublet chemotherapy will be administered on day 3.

The starting dose represents 100% of the recommended dose of cisplatin and pemetrexed and ADI-PEG 20 as determined in the phase 1 trial. Criteria for withholding treatment, dose adjustments, or switching from cisplatin to carboplatin based on toxicity are described in Section 7.3.4 of the clinical study protocol.

Tumor response will be evaluated at the end of week 6. In the event of disease progression, the triplet chemotherapy will be stopped, and the subject offered an alternative treatment plan. In the absence of disease progression requiring other therapeutic interventions, subjects may receive additional cycles of ADIPemPlatinum or PlaceboPemPlatinum treatment following the same procedures and schedule as week 7 and onward for up to 18 weeks.

Subjects may continue to receive treatments unless, one of the following occurs at any time during the course of therapy: (1) unacceptable AEs, or (2) death, or (3) progressive disease, or (4) significant noncompliance on the part of the subject, or (5) refusal of the subject to continue treatment or observations, or (6) decision by the Investigator that termination is in the subject's best medical interest, or (7) unrelated medical illness or complication, or (8) lost to follow-up. Any subject with tumor and stable disease or partial response should continue treatment until progression, unless the investigator thinks a better option is available. Thus, subjects completing ADIPemPlatinum or PlaceboPemPlatinum may continue to receive ADI-PEG 20 or placebo treatment, following the schema of week 13 and onward or week 19 and onward if 12 or 18 weeks of triple therapy is completed. Any subject with a complete response may receive 4 more weekly treatments of ADI-PEG 20 or placebo. The maximum number of cycles of pemetrexed + cisplatin is 6 (18 weeks at every 3 weeks cycle).

Subjects ongoing at study end (once the required number of events have been observed for the final analysis) may continue to receive treatment on ADIPemPlatinum or PlaceboPemPlatinum (or ADI-PEG 20/placebo alone), depending on where the subjects are in the treatment schedule, until the study is unblinded. Once the study treatment assignments are known, the subjects receiving ADI-PEG 20 may continue to receive ADIPemPlatinum (or ADI-PEG 20 alone) until 1 of the following occurs: (1)

unacceptable AEs, or (2) death, (3) progressive disease (PD) or (4) decision by the Sponsor. Subjects receiving placebo should be consulted regarding alternative treatment options.

### **6.3.2      *Method of Assigning Subjects to Treatment Groups***

Subjects will be randomly assigned in a 1:1 ratio to receive ADI-PEG 20 drug product or matching placebo in a double-blind fashion via a centralized Interactive Web Response System (IWRS) system. ADI-PEG 20 drug product and placebo will be identical in appearance in order to preserve the blinding. The randomization will be stratified by tumor histology (biphasic or sarcomatoid).

## **6.4      Efficacy and Safety Variables**

### **6.4.1      *Efficacy Variables***

#### **6.4.1.1      *Primary Efficacy Variables***

The primary efficacy endpoint of the phase 2 portion of the study is:

- Objective response rate (RR): calculated as the proportion of subjects whose best tumor response from all post-baseline tumor assessments is complete response (CR) or partial response (PR)

Tumor response at each time point where CT/MRI scans are performed will be assigned by the BICR as complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD). In case of CR or PR, repeat imaging will be performed 4 weeks later to confirm response. If the response is not confirmed by the repeat assessment, the response of CR or PR will be treated as SD for that time point.

For subjects with intra-thoracic pleural disease, modified RECIST for MPM ([Byrne 2004](#)) will be used to determine response at each post-baseline time point as follows:

#### **Modified RECIST Criteria for MPM**

<b>Response</b>	<b>Definition</b>
CR	disappearance of all target lesions with no evidence of tumor elsewhere
PR	at least a 30% reduction in the total tumor measurement
PD	an increase of at least 20% in the total tumor measurement over the nadir measurement, or the appearance of one or more new lesions
SD	those who fulfilled the criteria for neither PR nor PD

For subject with extra-pleural metastatic disease, RECIST 1.1 ([Eisenhauer 2009](#)) will be used to determine response at each post-baseline time point. Assessment of target lesions, non-target lesions, new lesions, and overall response will be assigned as follows:



### RECIST 1.1 evaluation of target lesions:

Response	Definition
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters on study.

### RECIST 1.1 evaluation of non-target lesions:

Response	Definition
CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
SD	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Appearance of one or more new lesions and/or <i>unequivocal progression</i> of existing non-target lesions.

### RECIST 1.1 overall response:

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PR	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The primary efficacy endpoint of the phase 3 portion of the study is:

- Overall survival (OS): calculated as the time from randomization until death. In the event that no death is documented prior to study termination or analysis

cutoff, OS will be censored at the last known date the subject is known to be alive, either through completion of on-study visits or through survival follow-up contact.

#### *6.4.1.2 Secondary Efficacy Variables*

The secondary efficacy endpoint of the phase 2 portion of the study is:

- Duration of response (DOR): calculated for subjects who have a best tumor response of CR or PR as the time from date of initial response of CR or PR until date of tumor progression or death. Subjects without tumor progression or death at the end of treatment will be censored using the date of the last tumor assessment demonstrating no tumor progression.

The secondary efficacy endpoint of the phase 3 portion of the study is:

- Progression-free survival (PFS): calculated as the time from randomization until date of tumor progression or death. In the event that no tumor progression or death is documented prior to end of treatment, analysis cutoff, or the start of confounding anticancer therapy, PFS will be censored at the date of the last tumor assessment demonstrating no tumor progression.

#### *6.4.2 Description of Safety Variables*

##### *6.4.2.1 Adverse Events*

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Note: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of Polaris studies to include any events, intercurrent diseases and accidents observed while the subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods.

Adverse events will be recorded from administration of first dose of study drug until 30 days after last study drug administration. Adverse events related to ADI-PEG 20 that were still ongoing at end of treatment (EOT) visit should be followed up until resolution or stabilization or until all attempts to determine resolution of the event are exhausted.

##### *6.4.2.2 Laboratory Parameters*

Clinical laboratory tests listed in Table 2 will be obtained as per the schedule of events. Blood samples will be collected before ADI-PEG 20 or placebo administration. A

certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

**Table 2 Clinical Laboratory Tests**

<b>Hematology (CBC)</b>	<b>Serum Chemistry</b>
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Red blood cell (RBC) count	Blood urea nitrogen (BUN)
White blood cell (WBC) count	Calcium
Absolute Neutrophil Count (ANC)	Chloride
Lymphocytes (Absolute values)	Creatinine
Monocytes (Absolute values)	Glucose (non-fasting)
Basophils (Absolute values)	HCG (at screening only)
Eosinophils (Absolute values)	Potassium
Platelet count (estimate not acceptable)	Serum glutamic-oxaloacetic transaminase (SGOT/AST)
	Serum glutamic-pyruvic transaminase (SGPT/ALT)
	Sodium
	Total bilirubin
	Total protein
	Uric acid

#### 6.4.2.3 Vital Signs

Vital signs (blood pressure, respiratory rate, heart rate, and temperature) will be obtained at screening, weekly during ADI-PEG 20/placebo treatment, and at the EOT visit. On days of ADI-PEG 20/placebo administration, vital signs will be obtained before and 1 hour ( $\pm$  15 minutes) after ADI-PEG 20 or placebo treatment.

#### 6.4.2.4 Electrocardiograms

ECG will be performed at screening, day 1 of cycle 2, day 15 of cycle 4, and during cycle 6 and beyond only as clinically indicated. On days of ADI-PEG 20/placebo administration, ECGs will be performed 1 hour ( $\pm$  15 minutes) after ADI-PEG 20 or placebo treatment.

The results will include ventricular rate, P-R interval, R-R interval, QRS duration, QT interval, QTcF interval, and overall interpretation (normal, abnormal and not clinically significant, abnormal and clinically significant).

The corrected QT interval will be corrected for respiratory rate using Fridericia's correction:  $QTcF = QT/R-R^{0.33}$ .

#### 6.4.2.5 *Physical Examination*

A comprehensive physical examination, including height and weight, will be performed at the screening visit. Weight and body surface area (BSA) will be captured on day 1 of each cycle. Symptom directed examinations may be performed as clinically indicated.

#### 6.4.3 *Description of Pharmacodynamic, Immunogenicity, and Pharmacokinetic Variables*

Approximately 10 mL of peripheral blood will be collected as plasma prior to ADI-PEG 20 or placebo dosing and used for pharmacodynamics, pharmacokinetics and immunogenicity studies. A central laboratory will be utilized to process and provide results of blood sampling.

Pharmacodynamics will be assessed by measurement of peripheral blood levels of arginine and citrulline by liquid chromatography mass spectrometry (LCMS). Subjects will also be assessed to determine if they experience arginine depletion and/or citrulline increase. Arginine depletion will be defined as blood levels  $\leq 10 \mu\text{M}$  and citrulline increase will be defined as increase from baseline  $\geq 50\%$ .

Immunogenicity will be assessed by measurement of peripheral blood antibodies to ADI-PEG 20. Blood will also be available for testing for anti-PEG antibodies.

Pharmacokinetics will be assessed by measurement of peripheral blood ADI-PEG 20 levels.

Arginine, citrulline, anti-ADI-PEG 20 antibody, and ADI-PEG 20 levels will be obtained on day 1 and day 8 of cycle 1, day 1 of each subsequent cycle during combination therapy, and at weeks 19, 22, and 25 of ADI-PEG 20 or placebo only treatment.

### 6.5 **Data Quality Assurance**

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

## 7 STATISTICAL METHODS

### 7.1 General Methodology

Data will be analyzed by Precision for Medicine biostatistics personnel. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

#### 7.1.1 Reporting Conventions

Tables and figures will be summarized by treatment group. Tables summarizing demographics and other baseline characteristics will also include a column for all subjects combined. In general, all data collected and any derived data will be presented in subject data listings, for all enrolled subjects. Listings will be ordered by site, subject number, treatment group, and assessment or event date. The treatment group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the population sample size (N), number of subjects with available data (n), mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by the N, n, number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

P-values will be reported for all statistical tests, rounded to four decimal places. P-values less than 0.0001 will be displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999".

### 7.1.2 *Summarization by Visit*

Data summarized by study visit (e.g., laboratory and vital signs) will be based on the nominal, scheduled visit label as reported on the eCRF including the EOT assessment where applicable.

### 7.1.3 *Standard Calculations*

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose, if the assessment/event date is prior to the date of first dose; and
- The assessment/event date minus the date of first dose, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
  - Later date – (earlier date + 1), if the earlier date is on or after the date of first dose of study drug; or
  - Later date – earlier date, if the earlier date is prior to the date of first dose of study drug.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by  $(365.25 / 12)$ ;
- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25;
- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value;
- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

## 7.2 *Analysis Populations*

The analysis populations are defined as follows:

- **Safety Population:** Includes all randomized subjects who received at least one dose of the study medication. Assignment of subjects to treatment group is based on the treatment actually received.
- **Intent-to-Treat (ITT) Population:** Includes all randomized subjects. Assignment of subjects to treatment group is based on the randomized treatment assignment.
- **Per-Protocol (PP) Population:** Includes all ITT subjects who have no major protocol violations that may potentially affect the primary and secondary efficacy measures (e.g., no MPM, no measurable disease). Subjects to be excluded from the PP Population will be determined prior to database lock and prior to breaking the blind of the treatment group assignments. Assignment of subjects to treatment group is based on the randomized treatment assignment.

Data summaries to be presented on both the Safety Population and the ITT Population will only be produced on both analysis sets if there is a difference in the population groups (e.g., at least one subject receives a different treatment than they were originally assigned).

### **7.3 Study Subjects**

#### **7.3.1 *Disposition of Subjects***

Subject disposition will be summarized for all randomized subjects by treatment group and over all subjects combined. Summaries will include the number and percentage of subjects in each analysis population, the primary reason for discontinuing ADI-PEG 20 or Placebo, and the primary reason for study termination. Subject disposition will also be summarized separately for each study center.

#### **7.3.2 *Protocol Deviations***

Major protocol deviations will be summarized by treatment group and over all subjects combined for the ITT Population. Major protocol deviations will be identified, reviewed, and entered into the database as described in a separate Protocol Deviation Management Guideline document.

All major protocol deviations will be determined and appropriately categorized prior to database lock and prior to breaking the blind of the treatment group assignments. The number and percentage of subjects with any major protocol deviations as well as the number and percentage of subjects with deviations within each category will be presented.



## **7.4 Efficacy**

### **7.4.1 *Datasets Analyzed***

All efficacy summaries will be based the ITT Population; select efficacy summaries will also be produced on the PP Population. A data listing of subjects excluded from the ITT or PP Population, to include the reason for exclusion, will be presented.

### **7.4.2 *Demographic and Other Baseline Characteristics***

Demographic variables including age, sex, ethnicity and race, will be summarized by treatment group and over all subjects combined for the Safety, ITT, and PP Populations. Age will be calculated relative to date of informed consent, as follows:

- If the month and day portion of the informed consent date is prior to the month and day portion of the birth date, age will be calculated as the year of informed consent minus the year of birth, minus one;
- If the month and day portion of the informed consent date is on or after the month and day portion of the birthdate, age will be calculated as the year of informed consent minus the year of birth.

Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of subjects in each parameter category.

Baseline characteristics include: medical history, disease history (type of histology, stage of MPM, any radiation or surgery treatment for actual cancer), height, weight, BSA, and Eastern Cooperative Oncology Group (ECOG) performance status. Height, weight, and body mass index (BMI) at baseline will be summarized using descriptive statistics. ECOG performance status and disease history will be summarized using frequency counts and percentages. Subjects reporting abnormal medical history will be presented only in subject data listings by subject and body system. All other baseline characteristics will be summarized by treatment group and over all subjects combined for the Safety, ITT, and PP Populations.

### **7.4.3 *Primary Efficacy Endpoint Analysis Methods***

#### **7.4.3.1 *Objective Response Rate***

The analysis of RR will be performed at the first interim analysis at the end of the phase 2 portion. The number and percentages of subjects responding (CR or PR) as well as the number and percentages of subjects in each best tumor response category (CR, PR, SD, PD, missing or not evaluable) will be summarized by treatment group. The objective response rate will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by tumor histology (biphasic versus sarcomatoid). The point estimate of the relative risk ratio and the corresponding two-sided confidence interval will be provided. The significance level and coverage probability to be used in the RR analysis will be based on  $\alpha=0.05$  (two-sided). The RR will only be tested once at



the end of the phase 2 regardless of its significance. The analysis will be based on the ITT Population. Summaries will also be provided for the PP population.

#### *7.4.3.2 Overall Survival*

The primary analysis of OS will be performed at the final analysis. Results will be presented by treatment group. The Kaplan-Meier method will be used to provide estimates of the OS curves, including the median, 25<sup>th</sup> and 75<sup>th</sup> percentiles and their corresponding 95% CIs. The number and percentage of subjects with an OS event and those who are censored will be presented along with minimum and maximum survival times. The Kaplan-Meier curves will also be plotted. A Cox proportional hazard model with an adjustment for tumor histology (biphasic versus sarcomatoid) will be used to compute the estimated hazard ratio and two-sided 95% confidence interval. The treatment effect on OS will be evaluated using the stratified log-rank test (stratified by tumor histology). The significance level to be used in the OS analysis at the final analysis will be based on  $\alpha=0.04999$  (two-sided). The analysis will be based on the ITT Population. Summaries will also be provided for the PP population.

There will be an interim analysis of OS once 50% of the planned OS events for phase 3 have occurred and will be used to determine whether to terminate the study for futility or for possible sample size re-estimation for the phase 3 portion of the trial as described in Section 7.4.5.3. An administrative penalty of  $\alpha=0.00001$  will be paid for this interim analysis, and the allocated  $\alpha=0.04999$  will be used for the final analysis. Based on DSMB recommendations, the deaths for the original planned final analysis of OS will be changed from 338 to the actual number of deaths occurring by August 14, 2022.

To take into consideration subjects who received therapies for MPM after the end of study treatment, a sensitivity analysis using rank preserving structural failure time models (Robins and Tsiatis, 1991) will be performed to evaluate the impacts introduced by such actions.

#### *7.4.4 Secondary Efficacy Endpoint Analysis Methods*

The secondary efficacy endpoint for phase 2 to be performed at the first interim analysis is DOR. DOR will be analyzed using the K-M curves to estimate its median and 95% confidence intervals.

The secondary efficacy endpoint for phase 3 to be performed at the final analysis is PFS, which will be analyzed only if the analysis of OS is statistically significant at the final analysis, with alpha level of 0.05 two-sided using the same statistical methodologies as applied to OS as described in Section 7.4.3.2.

Summaries of secondary efficacy endpoints will be provided for the ITT and PP populations.

#### **7.4.5      *Statistical/Analytical Issues***

##### **7.4.5.1      *Adjustments for Covariates***

The analyses of each of the primary and secondary efficacy endpoints will be adjusted for the randomization stratification factor (biphasic histology versus sarcomatoid histology).

##### **7.4.5.2      *Handling of Dropouts or Missing Data***

Subjects with no post-baseline tumor response will be included in the denominator for calculation of RR and will be treated as non-responders.

For time to event endpoints (OS, PFS, DOR), subjects with no follow-up assessment will be censored using a censored value of 1 day.

No other imputations of missing data will be made.

##### **7.4.5.3      *Interim Analyses and Data Monitoring***

This study will include two separate interim analyses:

- The first interim analysis will be conducted at the end of the phase 2 portion, after adequate response assessment of the first 176 subjects enrolled. This interim analysis will evaluate the treatment effect on RR in the ITT population.
- The second interim analysis will be performed once 50% of the planned OS events for phase 3 have occurred (ie, 169 of the 338 planned OS events). This interim analysis will evaluate OS in the ITT population in an unblinded manner.

The RR data will be analyzed at the end of the phase 2 portion to support accelerated approval. The OS data at the second interim analysis will be analyzed to support the following decisions:

- Futility stopping: Terminate the study due to futility at the interim analysis.
- Sample size re-estimation: Increase the target number of OS events after the second interim analysis.

A futility stopping rule will be applied at the second interim analysis to support a decision to terminate the study due to futility. The treatment's futility will be evaluated based on the comparison of the median OS times in the ADIPemPlatinum or PlaceboPemPlatinum groups. The study may be terminated if the median OS in the ADIPemPlatinum group is less than that in the PlaceboPemPlatinum group. This futility stopping rule will be non-binding and can be overridden by the Data Safety Monitoring Board (DSMB) and/or Polaris.

A sample size re-estimation rule will be applied at the second interim analysis to support a decision to increase the target number of OS events. The target number of OS events

may be modified based on the conditional power (CP) for the OS evaluation in the ITT population.

The following sample size re-estimation rule will be applied:

- Option 1: Retain the planned target number of OS events, i.e., 338 events, if CP is greater than 80% or less than 50% and the futility stopping rule is not met.
- Option 2: Increase the target number of OS events if CP is between 50% and 80%, and the futility stopping rule is not met. The target number of OS events will be increased to achieve CP of 80% or increased by 30%, whichever is smaller based on Chen et al. (2004). Target enrollment adjustments will be accomplished using standard event forecasting methods ([Anisimov 2011](#)).

An administrative penalty of  $\alpha=0.00001$  will be paid for second interim analysis, and the allocated  $\alpha=0.04999$  will be used for the final analysis. Based on Chen et al. (2004), the final test statistic after the sample size re-estimation will be the conventional test statistical which is identical to that used in a group sequential design.

A DSMB will be instituted for this study to ensure the safety of the subjects. Recommendations for continuation of the study will be guided by safety evaluations at safety data reviews. The committee will include two independent oncologists with experience in thoracic oncology and an independent statistician. Safety meetings will be held as per the DSMB charter, approximately every 6 months and more often if deemed necessary. Decisions on study termination, amendment, or cessation of subject recruitment, based on safety or outcome findings, will be made after recommendations from the DSMB have been assessed by Polaris. The DSMB will not be expected to conduct the efficacy analyses at the interim or final analyses.

#### 7.4.5.4 *Multicenter Studies*

This is a global, multicenter study. Efficacy data collected from all study centers will be pooled for data analysis. The effect of study center on the efficacy analysis results may be explored post-hoc, as needed.

#### 7.4.5.5 *Multiple Comparisons/Multiplicity*

The efficacy endpoint (RR) will be evaluated at the end of the phase 2 portion at  $\alpha = 0.05$  (two-sided) for the purpose of determining if the data supports accelerated approval. Since comparison of RR will only be tested at the end of the phase 2 portion for the purpose of providing support for accelerated approval, the type I error for phase 3 will be maintained at  $\alpha = 0.05$ .

The primary endpoint (OS) will be tested at  $\alpha = 0.04999$  (two-sided) at the final analysis at the end of the phase 3 portion. The analysis of OS at the second interim analysis will be performed for the purposes of testing for futility and possible re-estimation of sample size as described in Section 7.4.5.3. Analysis at the interim and final analysis will be

performed based on Chen et al. (2004) in order to maintain the type 1 error at  $\alpha = 0.05$  for OS at the final analysis. An administrative penalty of  $\alpha=0.00001$  will be paid for second interim analysis, and the allocated  $\alpha=0.04999$  will be used for the final analysis. The secondary endpoint of PFS will be tested only if the primary analysis of OS is statistically significant, thus maintaining the type 1 error at  $\alpha = 0.05$ .

#### **7.4.5.6**      *Use of an “Efficacy Subset” of Subjects*

The primary efficacy analysis will be performed on the ITT population; the PP population will be utilized as a sensitivity analysis. The PP population will exclude subjects who have major protocol violations that may potentially affect the primary and secondary efficacy measures.

#### **7.4.5.7**      *Examination of Subgroups*

There are no planned analyses to assess efficacy results by subgroups.

#### **7.4.6**      *Pharmacodynamics*

Blood levels of arginine and citrulline will be summarized for ADI-PEG 20 treated subjects. Descriptive statistics (including n, mean, SD, median, Q1, Q3, minimum, and maximum values) will be presented for results and change from baseline at each visit where blood samples were scheduled to be collected. The baseline value will be defined as the last value reported prior to first study drug administration. The number and percentage of subjects with arginine depletion and citrulline increase will also be presented at each visit. Blood levels of arginine and citrulline will also be displayed graphically over time.

Arginine and citrulline results may also be correlated with RR and OS by examining RR and OS results for subjects who demonstrate arginine depletion or citrulline increase at select time points compared to those subjects who do not.

#### **7.4.7**      *Immunogenicity*

Blood levels of antibodies to ADI-PEG 20 and anti-PEG antibodies will be summarized for ADI-PEG 20 treated subjects. Descriptive statistics will be presented for results and change from baseline at each visit where blood samples were scheduled to be collected. The baseline value will be defined as the last value reported prior to first study drug administration. Blood levels of antibodies to ADI-PEG 20 and anti-PEG antibodies will also be displayed graphically over time.

#### **7.4.8**      *Pharmacokinetics*

Blood concentration levels of ADI-PEG 20 will be summarized for ADI-PEG 20 treated subjects. Descriptive statistics will be presented for observed concentrations at each visit where blood samples were scheduled to be collected. Blood concentration levels of ADI-PEG 20 will also be displayed graphically over time.

Analysis of derived pharmacokinetic parameters or correlation to efficacy endpoints may be performed and summarized in a separate report and is outside the scope of this SAP.

## **7.5 Safety Analysis**

Safety analysis will be carried out for the Safety Population, to include all subjects who receive at least one dose of study drug. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to first study drug administration.

### **7.5.1 *Extent of Exposure and Treatment Compliance***

Extent of exposure to study treatment will be summarized for the Safety Population by treatment group. The number of doses taken and the total dose administered will be summarized for each study drug: ADI-PEG 20/Placebo, Pemetrexed, Cisplatin, and Carboplatin. The number and percentages of subjects who had at least one dose withheld and the number and percentages of subjects who at least one dose reduced along with the corresponding reasons for doses being withheld or reduced for each study drug, where applicable, will be summarized.

Compliance will not be evaluated as study drug is administered by staff in the clinic..

### **7.5.2 *Adverse Events***

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by treatment group. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0 or most current version at the time of analysis).

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent serious adverse events (SAEs) and subject incidence of TEAEs meeting various criteria;
- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of the most frequently-occurring TEAEs (e.g., TEAEs occurring in  $\geq 10\%$  of the Safety Population) by MedDRA preferred term;

- Subject incidence of TEAEs by common terminology criteria for adverse events (CTCAE) grade, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to ADI-PEG 20/Placebo, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to Pemetrexed, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to the Platinum agent (Cisplatin or Carboplatin), MedDRA system organ class, and preferred term;
- Subject incidence of  $\geq$  Grade 3 TEAEs related to ADI-PEG 20/Placebo by MedDRA system organ class and preferred term;
- Subject incidence of  $\geq$  Grade 3 TEAEs related to Pemetrexed by MedDRA system organ class and preferred term;
- Subject incidence of  $\geq$  Grade 3 TEAEs related to the Platinum agent (Cisplatin or Carboplatin) by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs leading to discontinuation of ADI-PEG 20/Placebo by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs leading to discontinuation of Pemetrexed by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs leading to discontinuation of the Platinum agent (Cisplatin or Carboplatin) by MedDRA system organ class and preferred term; and
- Subject incidence of SAEs by MedDRA system organ class and preferred term.

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by CTCAE grade, subjects will be counted once at the highest CTCAE grade reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship to study drug.

Adverse event data will be presented in data listings by subject, treatment group, and event. Serious AEs and AEs leading to discontinuation of ADI-PEG 20/Placebo, Pemetrexed, Cisplatin, and Carboplatin will be presented in separate data listings.

### **7.5.3      *Deaths, Other Serious Adverse Events, and Other Significant Adverse Events***

All deaths during the study, including the post treatment follow-up period, will be listed by subject, to include the primary cause of death. Serious AEs and AEs that led to



withdrawal, interruption, or dose reduction of ADI-PEG 20/Placebo, Pemetrexed, Cisplatin, and Carboplatin, will be provided in separate subject data listings.

#### **7.5.4 Clinical Laboratory Evaluation**

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in by-subject data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by subject, laboratory test, and unit.

Clinical laboratory measurements, including serum chemistry and hematology, will be summarized by treatment group. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Where applicable, hematology and chemistry results for select parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services *Common Terminology Criteria for Adverse Events (CTCAE)*, version 4.03 (Jun 2010). Five-by-five contingency tables will be presented for lab tests where toxicity grading can be applied to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Death related to AE (i.e., Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Summary results will include the count and percentage of subjects within each shift category.

Where applicable, laboratory results will be classified as “low,” “normal,” or “high” with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for laboratory parameter that cannot be assigned a CTCAE toxicity grade to summarize the shift from the baseline category to the worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of the study. Summary results will include the count and percentage of subjects within each shift category and treatment group.

#### **7.5.5 Vital Signs, Physical Findings, and Other Observations Related to Safety**

##### **7.5.5.1 Vital Signs**

Vital sign parameter measurements will be presented in subject data listings by subject and study visit.

#### 7.5.5.2 *12-Lead Electrocardiogram*

Twelve-Lead ECG interval parameters will be summarized by treatment group. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected.

Twelve-lead ECG will be classified by the investigator as “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant.” Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of subjects within each shift category and treatment group.

Prolonged QT intervals will be summarized as QTcF measurements (msec) that are > 450, > 470, and > 500 at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change > 30 or > 60 relative to the baseline value. Summary results will include the percentage of subjects within each category and treatment group.

#### 7.5.5.3 *Physical Examination*

Results of any symptom directed physical examination will be presented in subject data listings by subject and study visit.

#### 7.5.5.4 *Prior and Concomitant Medications*

Medications will be coded using the World Health Organization (WHO Drug 2016Q1, enhanced) dictionary. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Concomitant medications will be summarized by treatment group for all medications reported on the Concomitant Medications eCRF. The number and percentage of subjects receiving any medication will be summarized by treatment group, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class.

### 7.6 **Determination of Sample Size**

The sample size calculation for the phase 2 primary endpoint (RR) assumed that the objective response rate in the PlaceboPemPlatinum arm was 15%. A total sample size of 176 subjects (88 per arm) in the phase 2 portion of the study will provide approximately 87% power to detect an improvement in the RR from 15% to 35% at the interim analysis at the end of the phase 2 portion.



The sample size calculation for the phase 3 primary endpoint (OS) assumed that the median OS was 6 months in the PlaceboPemPlatinum arm. Assuming a median OS of 8.4 months in the ADIPemPlatinum arm (corresponding to a HR of 0.714), 338 OS events will provide power of approximately 87% for the OS analysis. Assuming uniform accrual over a 24-month period and a total study duration of 36 months, the planned total sample size in the study was 386 subjects. The target number of events may be increased at the second interim analysis, which will affect the total number of subjects.

The study will include an unblinded interim analysis once 50% of the planned OS events for phase 3 have occurred, which will be performed by an Independent Analysis Group. The DSMB will review the interim analysis report and provide final recommendations related to futility stopping and sample size re-estimation after the second interim analysis. The interim analysis decision rules are defined in Section 7.4.5.3.

Based on DSMB recommendations, the original planned sample size will be changed from 386 subjects to all enrolled up to August 15, 2021 (249 subjects); and the deaths for the original planned final analysis of OS will be changed from 338 to the actual number of deaths occurring by August 14, 2022. The estimated power with 249 subjects would be in a range of 73% to 80% if the true HR is in a range of 0.71 to 0.68.

## 7.7 Changes in the Conduct of the Study or Planned Analyses

This SAP follows the planned analyses as described in the protocol (Version 6; September 2021). Changes from the previous versions of the SAP and protocol are specified in Section 4.

As mentioned above, the original planned sample size will be changed from 386 subjects to all enrolled up to August 15, 2021 (249 subjects); and the deaths for the original planned final analysis of OS will be changed from 338 to the actual number of deaths occurring by August 14, 2022.

## 8 REFERENCE LIST

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[http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

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\*Narratives of deaths, other serious adverse events, and certain other significant adverse events will not be generated by analysis programming and are outside the scope of this analysis plan.

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### Polaris Statistical Analysis Plan Summary of Changes Form

Randomized, Double-Blind, Phase 2/3 Study in Subjects with Malignant Pleural Mesothelioma to Assess ADI-PEG 20 with Pemetrexed and Cisplatin (ATOMIC-Meso Phase 2/3 Study)

#### SAP Revision History 03 March 2023

VERSION	ISSUE DATE	SUMMARY OF MAJOR CHANGES AND RATIONALE
004	04 January 2022	1. The original planned sample size will be changed from 386 subjects to all enrolled up to August 15, 2021 (249 subjects).
		2. The deaths for the original planned final analysis of OS will be changed from 338 to the actual number of deaths occurred on August 14, 2022.
		3. An administrative penalty of $\alpha=0.00001$ will be paid for second interim analysis, and the allocated $\alpha=0.04999$ will be used for the final analysis.
		4. ADIPemPlatinum and PlaceboPemPlatinum changed throughout the text to be consistent with the standard of care use chemotherapy administered in the study.
		5. Administrative changes and other minor editorial corrections, clarifications and formatting changes were made.
003	07 September 2021	
002	06 November 2019	1. Removal of secondary endpoints of objective response rate and duration of response in phase 3. Both endpoints will remain as endpoints for phase 2.
		2. Removal of disease control rate as a secondary endpoint in phase 3.
		3. The timing of the interim analysis to assess futility and potential sample size increase was modified from occurring at the end phase 2 to be performed at a separate time from the end of phase 2 analysis when 50% of planned overall survival events have occurred in order to obtain more reliable sample size estimates for phase 3.
		4. Removal of the subject population selection rule at the interim analysis. Interim analysis methods and options were updated and simplified accordingly.
		5. The cap for percent increase in sample size at the interim analysis was modified from 50% to 30%.
001	02 March 2017	Original document