ADI-PEG 20

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)

(NCT02709512)

This supplement contains the following items:

1. Protocol version 6 (21Sept2021).
2. Statistical analysis plan version 4 (04Jan2022).

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Polaris Group

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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1.1 **Study Administrative Structure**

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)

Sponsor:	Polaris Group
Sponsor's Responsible Medical Officer:	John S. Bomalaski, MD
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Study Monitoring:	Polaris Group and its representatives
Clinical Laboratory:	Central Laboratory
Pharmacodynamic and Pharmacokinetic Analytical Laboratory:	Central Laboratory
Immunogenicity Analytical Laboratory:	Central Laboratory
Diagnostic Imaging Review:	Blinded Independent Central Review

1.2 Signature Page

Polaris Group Approval:

John Bomalaski 21 September 2021

John S. Bomalaski, MD Date
Executive Vice-President, Medical Affairs

1.3 **Synopsis**

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)
Sponsor:	Polaris Group
Study Phase:	Phase 2/3
Indication:	Unresectable malignant pleural mesothelioma (MPM)
Rationale:	In a previous randomized phase 2 study of ADI-PEG 20 monotherapy in MPM tumors with low argininosuccinate synthetase (ASS1) expression (ASS1-deficient) (ADAM Study), ADI-PEG 20 treatment resulted in significantly prolonged progression free survival (PFS) compared to best supportive care. In an ongoing phase 1 study of ADI-PEG 20 with pemetrexed and cisplatin (ADIPemCis) in MPM or non-squamous non-small cell lung carcinoma (NSCLC) subjects with ASS1-deficient tumors (TRAP study), this combination has resulted in a significant number of objective responses. Interestingly, most of the subjects have a non-epithelioid histology, and known poorest prognosis of the MPM histologies. Apparent prolonged PFS and OS have also been observed in these MPM treated subjects. This phase 2/3 study will treat only MPM using the same three drug regimen. In addition, it will enroll only biphasic and sarcomatoid histologies.
Objectives:	The primary objective of this study is: • Determine efficacy as determined by the objective response rate (RR), measured by modified RECIST for local pleural disease and RECIST 1.1 criteria for metastatic lesions (phase 2 portion), and OS (phase 3 portion) The key secondary objective of the phase 2 portion is: • Determine the duration of response (DOR) The key secondary objective of the phase 3 portion is: • Assess progression free survival (PFS) Other secondary objectives of this study include: • Assessment of 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.
Number of Sites:	Global – to be determined
Study Design:	This is a phase 2/3, randomized, double-blind trial. Weekly ADI-PEG 20 at 36 mg/m^2 (or placebo) will be combined with pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 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 ADIPemCis or PlaceboPemCis. The randomization will be stratified by 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 SD or better. Subjects who do not or who would not tolerate cisplatin may be switched to carboplatin.
Planned Sample Size:	Approximately 176 subjects (88 per arm) will be enrolled in the phase 2 portion of the trial (phase 2 primary outcome measure = RR) and 386 subjects (193 per arm) in the whole phase 2/3 trial (phase 3 primary outcome measure = OS). **Sample size justification:** The sample size calculation for the first efficacy 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 approximately 87% power to detect an improvement in the RR from 15% to 35% at the interim analysis. The sample size calculation for the OS assumed that the median OS was 6 months in the PlaceboPemCis arm. Assuming a median OS of 8.4 months in the ADIPemCis arm (corresponding to a 40% improvement in survival and a hazard ratio [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.
Subject Selection Criteria:	**Selection Inclusion Criteria Summary:** • Histologically proven unresectable MPM of biphasic or sarcomatoid histology • Naïve to chemotherapy or immunotherapy • ECOG PS 0-1 • Expected survival of at least 3 months • Age 18 years or over (there is no upper age limit)

	• Measurable disease by modified RECIST criteria for MPM for local pleural disease and RECIST 1.1 criteria for metastatic lesions • Written (signed and dated) informed consent and must be capable of co-operating with treatment and follow up • Adequate hematologic, hepatic, and renal function **Selection Exclusion Criteria Summary:** • Radiotherapy (except for palliative reasons) in the previous two weeks before study treatment • History of unstable cardiac disease • Ongoing toxic manifestations of previous treatments • Symptomatic brain or spinal cord metastases (patients must be stable for > 1 month post radiotherapy or surgery) • Major thoracic or abdominal surgery from which the patient has not yet recovered.
Study Drug:	ADI-PEG 20
Dose and Route of Administration:	**ADI-PEG 20 (or Placebo)** **Dose**: 36 mg/m^2 (or Placebo) given weekly **Route of Administration**: Intramuscular (IM) **Pemetrexed** **Dose:** 500 mg/m^2 every 3 weeks **Route of Administration:** Intravenous **Cisplatin** **Dose:** 75 mg/m^2 every 3 weeks **Route of Administration:** Intravenous **Carboplatin** **Dose:** area under the plasma concentration–time curve (AUC) 5 mg/ml/m^2 every 3 weeks **Route of Administration:** Intravenous
Safety Monitoring: **Response Criteria:**	Performed by the sponsor and its representatives **Safety:** Adverse events (AEs), laboratory tests, ECGs and physical examinations **Efficacy:** RR, DOR, PFS, and OS; RR and DOR will be based on the tumor response assessments by 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. BICR results will be used for decisions on continued treatment in the phase 2 portion.
Statistical Analysis:	**Analysis Populations:** All efficacy analyses will be completed in the intent-to-treat (ITT) population and additional analyses will be performed in the per-protocol (PP) population. The safety population

	(all treated subjects) will be used for all safety summaries and analyses. **Efficacy Analyses:** The analysis of RR will be performed at the first interim analysis at the end of the phase 2 portion. The treatment groups will be compared using the Cochran-Mantel-Haenszel (CMH) test, stratified by tumor histology (biphasic versus sarcomatoid). The significance level and coverage probability to be used in the RR analysis will be based on α=0.05 (two-sided). The RR will only be tested once at the end of the phase 2 regardless of its significance. The primary analysis of OS will be performed at the final analysis. 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 α=0.05 (two-sided). 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 the Statistical Analyses Plan (SAP). **Safety Analyses:** Safety will be assessed by comparing adverse events, vital signs, laboratory results, and physical examination results. **Pharmacodynamics:** Pharmacodynamics (peripheral blood arginine and citrulline levels) will be summarized for all subjects by time point for the observed value and by duration of arginine depletion and citrulline increase. **Immunogenicity:** Immunogenicity (antibodies to ADI-PEG 20) will be summarized for all subjects from the ADIPemCis arm by time point for the observed value as well as for the change from baseline value. **Pharmacokinetics**: Pharmacokinetics (peripheral blood ADI-PEG 20 levels) will be summarized for all subjects from the ADIPemCis arm.

1.4 Schedule of Assessments and Procedures

1.4.1 Screening and Schedule of Assessments and Procedures

Table 1.4.1 Study Assessments and Procedures: Pre-study (Screening) and Cycles 1 to 4[o]

	Screening Assessments		Cycle 1			Cycle 2			Cycle 3			Cycle 4		
			Day of Cycle (Week of Treatment)											
Study Procedure	**Within 4 weeks (Day -28 to 0)**	**Within 1 week (Day -7 to 0)**	**1 (1)**	**8 (2)**	**15 (3)**	**1 (4)**	**8 (5)**	**15 (6)**	**1 (7)**	**8 (8)**	**15 (9)**	**1 (10)**	**8 (11)**	**15 (12)**
Review of Inclusion and Exclusion Criteria	X													
Informed Consent	X[a]													
Demographics	X													
Medical History	X	X (update)												
Physical Examination[b]		X	X[m]			X			X			X		
Vital Signs[c]		X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X												
Weight/ Body Surface Area (BSA)		X	X[m]			X			X			X		
Performance Status (ECOG)		X	X[m]											
AE Assessment[d]			X			X			X			X		
Concomitant Medications		X	X			X			X			X		
Radiological Tumor Disease Assessment (CT, MRI)[e]	X							X						X
Serum Pregnancy Test[f]		X												
ECG		X				X[n]								X[n]
Clinical Laboratory Tests[g]														
Hematology		X	X[m]	X		X	X		X	X		X	X	

	Screening Assessments		Cycle 1			Cycle 2			Cycle 3			Cycle 4		
Study Procedure	**Within 4 weeks (Day -28 to 0)**	**Within 1 week (Day -7 to 0)**	**1 (1)**	**8 (2)**	**15 (3)**	**1 (4)**	**8 (5)**	**15 (6)**	**1 (7)**	**8 (8)**	**15 (9)**	**1 (10)**	**8 (11)**	**15 (12)**
Chemistry		X	X[m]			X			X			X		X
Creatinine Clearance[h]		X												
Special Blood Sampling[i]														
Arginine + Citrulline			X	X		X			X			X		
Anti-ADI-PEG 20 Abs			X	X		X			X			X		
ADI-PEG 20 Levels			X	X		X			X			X		
ADI-PEG 20 or Placebo Administration[j]			X	X	X	X	X	X	X	X	X	X	X	X
Pemetrexed Administration[k]			X[l]			X			X			X		
Cisplatin Administration[k, p]			X[l]			X			X			X		

Note: Visits may occur ± 3 days of the planned date except for PemCis administration on cycle 1 Day 3. All study evaluations and related procedures may occur 3 days prior to dosing except for CT or MRI which may occur ± 7 days of the planned date. See Appendices for more on modified RECIST response criteria for MPM local pleural disease (Appendix A), RECIST 1.1 response criteria for metastatic lesions (Appendix B) and performance status (Appendix C).

a. The informed consent window is extended to -42 days without requiring a reconsent.
b. Physical examination is to be performed on Day 1 of each cycle and is symptom directed as clinically indicated.
c. Vital signs to be obtained before and 1 hour ± 15 minutes after ADI-PEG 20 or placebo treatment.
d. Subjects will be assessed for AEs on Day 1 of each cycle and weekly thereafter or as clinically indicated.
   Adverse events, including serious adverse events and toxicities –These will be recorded after the first administration of study treatment 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. Any medical sign or symptom a subject may experience post signing of ICF and before first administration of study treatment should be recorded as part of medical history. If any toxicity or medical sign or symptom a subject may experience post signing of ICF meets the definition of Serious Adverse Event (SAE) per Section 9.5.7 they must be reported as an SAE per Section 9.5.8.
e. Baseline CT with contrast or MRI of the involved organs is to be conducted within 28 days prior to subject receiving the first ADI-PEG 20 or placebo dose (this may be conducted prior to signing informed consent if part of standard of care). Scans are to be performed every 6 weeks (preferably in the week after 2 cycles of ADIPemCis or PlaceboPemCis dosing) and after every 8th weekly dose of ADI-PEG 20 or placebo during ADI-PEG 20 or placebo only treatment. Tumor measurements must be noted. CT with contrast must be used unless the subject is allergic to intravenous contrast despite use of diphenhydramine and corticosteroids,

in this case CT without contrast (if borders are distinct) is the second choice and MRI a third choice if borders are not well-defined on CT. The same imaging modality is to be used throughout the study. Details are provided in the Imaging Manual. For subjects with tumor responses (complete response and partial response), scans will continue according to the regular schedule. Imaging should follow calendar days; do not adjust for changes in dosing schedule. Subjects withdrawn from treatment for reasons other than PD may continue to receive regular scans until PD.

f. Female subjects only, serum HCG.
g. Blood samples to be collected before ADI-PEG 20 or placebo administration. Hematology and Chemistry sampling from Cycle X/Day 1 should follow the chemotherapy administration day in case of a chemotherapy dosing delay. Local blood samples may be collected as part of standard of care on chemotherapy days and the results used for dosing decisions without waiting on central results provided central samples are also collected at the same time and sent in for testing. Clinically significant local laboratory findings that directly inform a dosing decision will be recorded as an adverse event. See Section 9.2 for specific studies.
h. Creatinine clearance ≥ 45 mL/min (estimated, using Cockcroft and Gault formula).
i. Blood samples to be collected before ADI-PEG 20 or placebo administration for arginine and citrulline (pharmacodynamics), antibody to ADI-PEG 20 (immunogenicity), and ADI-PEG 20 levels (pharmacokinetics). Special blood sampling should follow calendar days; do not adjust for changes in dosing schedule. See Section 10 for specific studies.
j. ADI-PEG 20 or placebo is to be administered before pemetrexed and cisplatin on days when all three drugs are given, except during cycle 1 where the chemotherapy is administered on Day 3. Pemetrexed and cisplatin administration is to begin at least 60 minutes after ADI-PEG 20 or placebo administration on the same day.
k. Supportive and pre-medications to include the following or as per local policy (see Section 7.4.2.2 for further details):
    - Folic acid 400 mcg daily, oral
    - Hydroxycobalamin 1000 mcg i.m. injection
    - Dexamethasone 4 mg bd (3 doses) preceding hospital visit by 24 hours. Dexamethasone may also be administered i.v. and at a dose per local policy.
    - Anti-emetic e.g. 5HT3 antagonist, domperidone and dexamethasone 8 mg
    - Furosemide 40 mg oral once
l. PemCis to be administered on Day 3 of cycle 1
m. These assessments at week 1 may be omitted if performed within 72 hours of the first dose.
n. ECG to be performed 1 hour ± 15 minutes after ADI-PEG 20 or placebo treatment. This assessment should include the QT/QTc interval using Fridericia's correction: QTc = QT/RR0.33
o. During the chemotherapy treatment period (Cycles 1-6), a cycle is 3 weeks. During the Single Agent period, beginning on Week 19, a cycle is defined as every 4 weeks.
p. Cisplatin is the recommended chemotherapy for use in the initial and subsequent cycles. However, subjects who do not tolerate cisplatin or who would not be expected to tolerate cisplatin may have carboplatin substituted for cisplatin at any cycle including the initial cycle at the discretion of the investigator.

1.4.2 Study Assessments and Procedures

Table 1.4.2 Study Assessments and Procedures: Weeks 13 to 18, ADI-PEG 20 or Placebo Single Agent Treatment, End of Treatment, and Follow up

Study Procedure	Cycle 5[j]			Cycle 6[j]			Cycles 7 and Beyond								
	1 (13)	8 (14)	15 (15)	1 (16)	8 (17)	15 (18)	Single Agent ADI-PEG 20/Placebo[k] 19	20	21	22	23	24	25	26[j]	EOT[a]
Physical Examination[b]	X			X			As clinically indicated								X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/ Body Surface Area (BSA)	X			X			X								
AE Assessment[d]	X			X			X			X			X		X
Concomitant Medications	X			X			X			X			X	X	X
Radiological Tumor Disease Assessment (CT, MRI)[e]						X								X	
ECG				As clinically indicated											
Clinical Laboratory Tests[f]															
Hematology	X	X		X	X			X			X			X	X
Chemistry	X			X		X		X		X		X		X	X
Special Blood Sampling[g]															
Arginine + Citrulline	X			X			X			X			X		
Anti-ADI-PEG 20 Abs	X			X			X			X			X		
ADI-PEG 20 Levels	X			X			X			X			X		
ADI-PEG 20 or Placebo Administration[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pemetrexed Administration[i]	X			X											
Cisplatin Administration[i,l]	X			X											

Note: Visits may occur ± 3 days of the planned date. All study evaluations and related procedures may occur 3 days prior to dosing except for CT or MRI which may occur ± 7 days of the planned date, but preferably after every two (2) cycles of ADIPemCis or PlaceboPemCis and after every 8th weekly dose of ADI-PEG 20 or placebo during ADI-PEG 20 or placebo only treatment.
See Appendices for more on modified RECIST response criteria for local pleural disease (Appendix A), RECIST 1.1 response criteria for metastatic lesions (Appendix B) and performance status (Appendix C).

a. EOT visit to occur 7-30 days (preferably 30 days) after last dose of treatment.
b. Physical examination is to be performed on Day 1 of each cycle and is symptom directed as clinically indicated.
c. Vital signs to be obtained before and 1 hour ± 15 minutes after ADI-PEG 20 or placebo treatment.
d. Subjects will be assessed for AEs on Day 1 of each cycle and weekly thereafter or as clinically indicated. Adverse events, including serious adverse events and toxicities – Baseline toxicities/symptoms will be recorded starting with the signing of the informed consent form (ICF). These will be recorded until 30 days after last study drug administration. Adverse events related to ADI-PEG 20 or placebo that were still ongoing at EOT visit should be followed up until resolution or stabilization. Any medical sign or symptom a subject may experience post signing of ICF and before first administration of study treatment should be recorded as part of medical history. If any toxicity or medical sign or symptom a subject may experience post signing of ICF meets the definition of SAE per Section 9.5.7 they must be reported as an SAE per Section 9.5.8.

e. Scans are to be performed every 6 weeks (preferably in the week after 2 cycles of ADIPemCis or PlaceboPemCis dosing) and after every 8th weekly dose of ADI-PEG 20 or placebo during ADI-PEG 20 or placebo only treatment. Tumor measurements must be noted. The same imaging modality is to be used throughout the study. For subjects with tumor responses (complete response and partial response), scans will continue according to the regular schedule. Imaging should follow calendar days; do not adjust for changes in dosing schedule. Subjects withdrawn from treatment for reasons other than PD may continue to receive regular scans until PD.
f. Blood samples to be collected before ADI-PEG 20 or placebo administration. Hematology and Chemistry sampling from Cycle X/Day 1 should follow the chemotherapy administration day in case of a chemotherapy dosing delay. Local blood samples may be collected as part of standard of care on chemotherapy days and results used for dosing decisions without waiting on central results provided central samples are also collected at the same time and sent in for testing. Clinically significant local laboratory findings that directly inform a dosing decision will be recorded as an adverse event. See Section 9.2 for specific studies.
g. Blood samples to be collected before ADI-PEG 20 or placebo administration for arginine and citrulline (pharmacodynamics), antibody to ADI-PEG 20 (immunogenicity), and ADI-PEG 20 levels (pharmacokinetics). Special blood sampling should follow calendar days; do not adjust for changes in dosing schedule. See Section 10 for specific studies. Special blood sampling is not required during ADI-PEG 20 or placebo only treatment after 25 weeks.
h. ADI-PEG 20 or placebo is to be administered before pemetrexed and cisplatin on days when all three drugs are given. Pemetrexed and cisplatin administration is to begin at least 60 minutes after ADI-PEG 20 or placebo administration on the same day.
i. Supportive and pre-medications to include the following or as per local policy (see Section 7.4.2.2 for further details):
   - Folic acid 400 mcg daily, oral
   - Hydroxycobalamin 1000 mcg i.m. injection
   - Dexamethasone 4 mg bd (3 doses) preceding hospital visit by 24 hours. Dexamethasone may also be administered i.v. and at a dose per local policy.
   - Anti-emetic e.g. 5HT3 antagonist, domperidone and dexamethasone 8 mg
   - Furosemide 40 mg oral once
j. Subjects who remain on treatment after 26 weeks and up to 2 years of study treatment will continue to follow the schedule in Table 1.4.2. For example, week 27 will follow visit assessments for week 19; week 28 will follow week 20 and so on. Therefore, CT scans will be obtained every 8 weeks for those still on treatment.
k. During the chemotherapy treatment period (Cycles 1-6), a cycle is 3 weeks. During the Single Agent period, beginning on Week 19, a cycle is defined as every 4 weeks.
l. Cisplatin is the recommended chemotherapy for use in the initial and subsequent cycles. However, subjects who do not tolerate cisplatin or who would not be expected to tolerate cisplatin may have carboplatin substituted for cisplatin at any cycle including the initial cycle at the discretion of the investigator.

1.4.3 Follow-up Period

Table 1.4.3 Study Assessments and Procedures: Follow-up* begins 30 days ± 7 days After End of Treatment Visit

Study Procedure	Every 3 Months (± 1 week) until end of study
Survival status	X

*Via telephone, email or clinic visit

1.5 List of Abbreviations

Abbreviation	Definition
ADI	Arginine deiminase
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphocytic leukemia
ALT	Alanine transaminase (also known as SGPT)
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
ASL	Argininosuccinate lyase
ASS1	Argininosuccinate synthetase (also known as ASS)
AST	Aspartate transaminase (also known as SGOT)
BSA	Body surface area
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CPO	Conditional Power for OS
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
DCR	Disease Control Rate
DesigneRx	DesigneRx Pharmaceuticals, Inc.
DHFR	Dihydrofolate reductase
DLT	Dose Limiting Toxicity

Abbreviation	Definition (Continued)
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EOT	End-of-treatment
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intent- to-treat
MPM	Malignant pleural mesothelioma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NSCLC	Non-small cell lung carcinoma
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PE	Physical examination
PFS	Progression free survival
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time

Abbreviation	Definition (Continued)
QTcF	Fridericia's correction formula
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
R2PD	Recommended phase 2 dose
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TBD	To be determined
TTP	Time to progression
TYMS	Thymidylate synthase (also known as TS)
SOP	Standard operating procedures
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
USA	United States of America
WBC	White blood cell count

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The following background information is being provided in addition to the information provided in the Investigator's Brochure.

2.1.1 Mesothelioma

Mesotheliomas are neoplasms arising from mesothelial cells lining the pleura, peritoneum, tunica vaginalis testis and pericardium (Kao 2010, Mirarabshahii 2012). Approximately 80-85% are malignant pleural mesothelioma (MPM), 15-20% are peritoneal, and vaginal and pericardial occur rarely (Moolgavkar 2009, Kao 2010, McDonald 2010, Turner 2012). MPM is an aggressive thoracic malignancy associated with exposure to asbestos, and its worldwide incidence is anticipated to increase during the first half of this century (Fennell 2008).

2.1.1.1 Mesothelioma: Histologic Subtypes Predict Prognosis

Malignant mesothelioma has three histologic subtypes, epithelioid, sarcomatoid and biphasic. Most patients present with advanced disease; the median age at diagnosis is 72 years and the median OS is approximately 1 year (Ettinger 2016). The majority of cases are epithelioid, which has the best prognosis. Sarcomatoid has the worst while biphasic (mixed epithelioid with sarcomatoid) has intermediate prognosis, with predominantly sarcomatoid biphasic having a worse prognosis than predominantly epithelioid biphasic (Bueno 2016). This has been confirmed by recently published epidemiology studies in the US (Surveillance, Epidemiology, and End Results [SEER] database from 2004-2010, Meyerhoff 2015), Australia (cases of malignant mesothelioma between 2002 and 2009 from the New South Wales Dust Diseases Board, Linton 2014), UK-Scotland (data from 2002-2012 from the National Health Service Grampian pathology database in the northeast of Scotland, Marshall 2015), UK-Wales+England (data from 2008-2012 from the National Lung Cancer Audit, Beckett 2015, Canada (data from 1991-2012 from Ottawa Hospital, Saint-Pierre 2015), and France (data from 1998-2016 from the French MESOBANK, Galateau Salle 2018). The statistics from these publications are summarized below and show the OS in months (m):

Reference	Number	Years	Epithelioid	Sarcomatoid	Biphasic	Non-epithelioid
US SEER	1183	2004-2010	69%	19%	12%	
Australian Median OS	910	2002-2009	60% 13.3 m	17% 5.4 m	13% 7.2 m	 6.2 m
UK-Scotland Median OS	114	2002-2012	56% 13.5 m	12% 4.1 m	16% 11.0 m	
UK-England +Wales Median OS	8740*	2008-2012	75% 13.1 m	14% 4 m	11% 8.4 m	
Canada Median OS	245	1991-2012	63% 12.5 m	14% 4.5 m	11% 8.1 m	
France Median OS	5726	1998-2016	91% 14 m	8% 4 m	1% 8 m	

*histology % noted only for specified types (N=3319)

Thus, these recent studies confirm further the poorer prognosis of nonepithelioid MPM ranging from 4.0 to 5.4 months for sarcomatoid and from 7.2 to 11.0 months for biphasic and are consistent with the 6.2 months for non-epithelioid histology noted in the Australian study (Linton 2014). The poor prognosis of sarcomatoid MPM has recently been reviewed (Galetta 2016).

Indeed, poor outcome of patients with non-epithelioid histologies has led to their exclusion from recent clinical trials (e.g., the anti-mesothelin [amatuximab] study: A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Amatuximab in Combination With Pemetrexed and Cisplatin in Subjects With Unresectable Malignant Pleural Mesothelioma, NCT02357147) (Amatuximab 2015). This underscores further the urgent need for development of effective therapy for non-epithelioid MPM.

The reason(s) for this poor prognosis for sarcomatoid histology has been attributed to expression of B7 homolog 1 (B7-H1; also known as programmed death ligand 1 [PD-L1]) which is expressed more frequently in sarcomatoid than epithelioid histologies (Mansfield & Roden 2014). Also, sarcomatoid and biphasic more frequently are deficient in expression of ASS1, the rate limiting enzyme in the urea cycle to form arginine. ASS1-deficiency is also associated with a poor prognosis in MPM and a variety of other cancers (Szlosarek 2006 & 2016, Delage 2008). The reason for this is not entirely clear, but appears due to rapidly expanding cancer cells preferentially using aspartate from the urea cycle to form nucleic acids and not arginine (Rabinovich 2015). ASS1 deficiency typically occurs through epigenetic modification (Phillips 2013).

2.1.1.2 Mesothelioma: Chemotherapy for MPM

The recommended treatment is dependent on both stage and histology. It is recommended that patients with operable clinical stage I-III epithelioid or mixed histology disease undergo multimodality therapy including surgery (Ettinger 2016). Current National Comprehensive Cancer Network (NCCN) guidelines (Mesothelioma NCCN 2015) recommend chemotherapy alone for all patients who have sarcomatoid histology, as well as for inoperable or clinical stage IV patients. Similar recommendations come from the European Society of Medical Oncology (ESMO) (Baas 2015). This underscores further the poor prognosis for sarcomatoid patients.

In MPM, both RR and PFS correlate with OS (Francart 2009, Blayney 2012, Hasan 2014). Thus RR and PFS serve as surrogate endpoints for OS in MPM.

Pemetrexed + Cisplatin/Carboplatin

The standard first-line chemotherapy treatment for MPM and advanced peritoneal mesothelioma is pemetrexed + cisplatin (Fennell 2008, Mirarabshahii 2012, Turner 2012, Kotova 2015). This is based on a phase 3 study for MPM comparing pemetrexed + cisplatin to cisplatin only (Vogelzang 2003) and open access data for peritoneal mesothelioma (Mirarabshahii 2012, Turner 2012). For MPM, median OS in the pemetrexed + cisplatin arm was 12.1 months (confidence interval [CI]: 10.0 to 14.4) vs. 9.3 in the control cisplatin arm, thus there was a 2.8 months survival advantage. Median time to progression (TTP) was 5.7 months in the study arm

vs. 3.9 months in the control arm. Response rates, determined by investigator assessment, were 41.3% (95% CI: 34.8 to 48.1) in the pemetrexed+cisplatin arm versus 16.7% in the control arm. The 1-year survival rate was 50.3% for pemetrexed + cisplatin arm. Change in disease was assessed by measuring the thickness of up to three involved areas of pleural rind at each of three separate levels at least 2 cm apart on computed tomography scan, at baseline, and every other cycle (at least one measurement was > 1.5 cm). Although the overall RR (ORR) was 41.3%, it was only 4/18 (22.2%) for sarcomatoid (Mansfield & Symanowski 2014), and this result was not noted in the primary publication (Vogelzang 2003). Indeed, in that summary review on MPM clinical trials focusing on sarcomatoid, the ORR for all subjects in the 30 studies that recorded data on survival and ORR in sarcomatoid, the ORR for all MPM was 21.9% in 1475 patients and only 19/137 (13.9%) in those with sarcomatoid disease (9.3% of total). As such, these results for sarcomatoid ORR to platinum based therapy may be an over estimate.

Further data on pemetrexed + cisplatin comes from expanded access programs that occurred after enrollment of the pivotal trial. In an expanded access program in the USA before regulatory approval (2002 to 2004), 728 chemotherapy naïve patients with MPM were enrolled and treated with pemetrexed + cisplatin (Obasaju 2007). The inclusion criteria were similar to the phase 3 study except that measurable lesions were not required, and RR could be assessed using RECIST, Southwest Oncology Group or World Health Organization criteria. Response data was available on 615 patients. Histologic subtype data was not reported. The ORR was 20.8% (95% CI: 17.7-24.3), the median survival was 10.9 (95% CI: 9.8-12.3) months, and the one year survival was 45.9%. Likewise, an expanded access program was initiated internationally (Santoro 2008). A total of 1704 chemo naïve patients were enrolled from 2002 to 2006, 843 received pemetrexed + cisplatin and 861 received pemetrexed + carboplatin (AUC of 5). The inclusion criteria were similar to the phase 3 study except that measurable lesions were not required, and the three different response criteria for assessment were allowed. The histologic breakdown for the pemetrexed + cisplatin group was as follows: epithelial 67.0%, sarcomatoid 6.3%, mixed 9.1%, and others 17.6%. Similar histologic breakdown occurred for the pemetrexed + carboplatin cohort. The ORR in 745 patients evaluable for response in the pemetrexed + cisplatin group was 26.3% (95% CI: 23.2-29.6), and was 21.7% (95% CI: 18.1-24.8) in the pemetrexed + carboplatin group. The median TTP was 7.0 months in the cisplatin cohort and 6.9 in the carboplatin cohort. The median survival was not estimated due to the high censoring rate. The 1-year survival rate was 63.1% in the cisplatin arm and 64% in the carboplatin arm. More grade 3/4 toxicity was noted in the carboplatin arm, as were more deaths.

The results of two phase 2 trials of pemetrexed + carboplatin in 178 patients from 11 Italian centers treated between 2002 and 2005 also were reported (Ceresoli 2008). Epithelioid represented 77%, mixed biphasic 12% and sarcomatoid 5%. The ORR was 23.8% (95% CI: 16.8-32.1). Therefore, these ORR results with pemetrexed + carboplatin in a heavily epithelioid population are similar to those observed in the international expanded access program with pemetrexed + cisplatin (Santoro 2008).

Thus the ORR in the expanded access programs with pemetrexed + cisplatin (Obasaju 2007, Santoro 2008) were approximately half of that observed in the phase 3 study of pemetrexed + cisplatin (20.8% and 26.3% vs. 41.3%) although measureable lesions were not required in the expanded access programs. Median TTP and median OS were only available for one expanded

access program, but these were similar to the phase 3 trial. The 1-year survival rates were 45.9 and 63.1% versus 50.3% in the phase 3 trial.

More recently, a randomized phase 2 study compared pemetrexed + cisplatin to that combination plus CBP501 in chemo naïve MPM (Krug 2014). Of the 23 in the pemetrexed + cisplatin arm, the histology was 70% epithelioid, 22% sarcomatoid and 9% mixed. For pemetrexed + cisplatin, the ORR, by modified RECIST (Byrne 2004), was 4/20 (20%) by investigator assessment and 2/20 (10%) by independent radiology assessment. For the doublet, the median PFS was 4.6 months by investigator and 3.4 by independent assessment, and the median OS was 12.8 (95% CI: 6.5-16.1) months by independent assessment.

In Japan, a retrospective analysis compared the results of 17 patients treated with pemetrexed + cisplatin to 13 with gemcitabine + cisplatin in MPM (Shukuya 2014). Overall, epithelioid accounted for 70%, sarcomatoid for 20% and not otherwise specified for 10%. The RR were 35% vs. 15%, the PFS were 215.5 days vs. 142.5 days and median OS was 597.5 days vs. 306.5 days, respectively, favoring the pemetrexed group. Hematologic AEs were more common in the gemcitabine group.

A French consortium (French Group of Onco-Pneumology) reported their data collected from medical files between 2005 and 2008 (Raynaud 2015). There were 406 patients from 37 sites, and 75% of patients received chemotherapy, primarily platinum + pemetrexed (91%). The ORR was 17.2%.

More recently, a French consortium of 73 hospitals added the anti-vascular endothelial growth factor (VEGF) bevacizumab to first-line pemetrexed + cisplatin in a randomized, open-label, phase 3 trial that enrolled 448 subjects aged 18-75 years (Zalcman 2016). Epithelioid accounted for 81% and sarcomatoid or mixed for 19%. ORR was not reported. The primary outcome measure was OS with an anticipated improvement of 33% (hazard ratio [HR] 0.75). The trial did not meet its primary outcome measure with HR = 0.77; the trial was stopped early by the independent data monitoring committee after assessment at 342 of the planned 397 deaths. Median OS for the doublet was 16.1 (95% CI: 14.1-17.9) months. Furthermore, the predictive analysis based on VEGF assessed as a continuous variable showed that the VEGF interaction between treatment group and VEGF concentration was not significant with bevacizumab treatment and OS or PFS. In addition, there were more serious cardiovascular adverse events as well as study discontinuation associated with the triplet therapy. Survival related to specific histologic subtypes was not shown. Another concern with the study was the exclusion of potential subjects older than 75 years, as they account for a significant percentage of MPM patients (Zauderer 2016). Indeed, in a review of 9014 patients with MPM from Belgium, the Netherlands and England collected between 2007 and 2011, 59% were 70 years or older (Damhuis 2015). Thus patients older than 75 years comprise a significant portion of MPM patients.

Cediranib or placebo was combined with cisplatin and pemetrexed in a randomized, phase 2 trial (Tsao 2019). The triplet did not improve OS. There were 12 patients with biphasic or sarcomatoid histology randomized to the placebo plus cisplatin and pemetrexed arm. Their median OS on cisplatin plus pemetrexed was 6.3 months. The ORR for these 12 was 8.3% (1/12) by both RECIST 1.1 and mRECIST criteria.

Other Chemotherapies

Similar data were obtained in MPM with another antifolate, raltirexed in combination with cisplatin vs. cisplatin monotherapy (Van Meerbeeck 2005). Among 213 patients with measurable disease (125 for combination vs. 122 for cisplatin), ORR by RECIST by investigator assessment was 23.6% (95% CI: 15.7-31.6) vs. 13.6%, PFS was 5.3 vs. 4.0 months, and median OS was 11.4 (95% CI: 11.1-15.0) vs. 8.8 months, respectively. For the combination arm, the histologies were: epithelioid 75%, mixed 14% and sarcomatoid 4%. A double-blind, phase 2 study compared gemcitabine + cisplatin with or without bevacizumab (Kindler 2012). Epithelioid accounted for 70.4% and non-epithelioid for 20.6%. The ORR was 24.5% in 53 patients treated with the 3 drug regimen vs. 21.8% in 55 treated with the two drug regimen. The median PFS was 6.9 vs. 6.0 months, and the median OS were 15.6 and 14.7 (95% CI: 10.3-20.0) months, respectively.

Summary

The prognosis for MPM is poor, with an overall median OS of ~ 1 year. The OS for epithelioid MPM is best followed by biphasic and then sarcomatoid. For the non-epithelioid, the median survival appears to be ~ 6 months. Regarding ORR, a variety of studies enriched for the epithelial subset, with best survival and response rate, more consistently show a rate of ~20-25% by investigator assessment in contrast to the 41% observed in the registration study, which also used investigator assessment (Vogelzang 2003). Thus it is also reasonable to believe the ORR assessed by BICR would be even lower, as was shown in a recent, albeit small study, where the ORR by BICR was half that compared to investigator assessment (Krug 2014).

It is generally considered that conventional cytotoxic chemotherapy has reached a therapeutic plateau and novel approaches are urgently needed (Fennell 2008, Mirarabshahii 2012, Turner 2012, Kotova 2015).

2.1.2 Amino Acid Deprivation Therapy

One established method for treating some malignancies is amino acid deprivation (Holcenberg 1977). This is based on the observation that some tumors are auxotrophic for otherwise non-essential amino acids. The best known example is the use of asparaginase (in the form of a polyethylene glycol conjugate, peg-asparaginase) in acute lymphoblastic leukemia (ALL) (Pasut 2008). Since most normal cells are able to synthesize asparagine, while the leukemia cells cannot due to lack of the enzyme asparagine synthetase, there is a selective effect on the growth of leukemia cells. Depletion of asparagine is relatively well tolerated and peg-asparaginase is part of standard therapeutic regimens for ALL (Zeidan 2009, van den Berg 2011).

2.1.3 Arginine Auxotrophy in Cancer Cells

Arginine is a non-essential amino acid that is, by definition, not required for the growth of most cells. The biochemical basis for this is synthesis of arginine from citrulline via the urea cycle (Husson 2003, Haines 2011). The ASS1 enzyme catalyzes the conversion of citrulline and aspartic acid into argininosuccinate, which is then converted into arginine and fumaric acid by argininosuccinate lyase (ASL). It has long been known that some tumor cells are auxotrophic for

arginine, based on the observation that normal cells derived from liver, kidney and testes could grow in medium depleted of arginine but supplemented with citrulline, while tumor cells from these organs could not (Tytell 1960). This implies that certain tumor cells could not re-synthesize arginine from citrulline. Other investigators also reported that certain tumor cell lines could not be maintained in medium contaminated with Mycoplasma species and that the killing of tumor cells under these conditions was associated with arginine depletion (Kenny 1963, Kraemer 1963 and 1964). Further studies showed that the depletion of arginine by Mycoplasma was due to the activity of the enzyme arginine deiminase (ADI), which is not present in mammalian cells (Schimke 1966). Thus, the understanding at that point was that some tumors were killed by arginine depletion mediated by Mycoplasma-produced ADI.

Depletion of available arginine however, should not lead to cell death in the presence of the ASS1 and ASL enzymes, which would replete arginine through conversion of citrulline. It was therefore hypothesized that cells auxotrophic for arginine might lack one of these enzymes and subsequently shown that certain cancer cell lines and human cancer tissue specimens lack significant expression of ASS1 (Sugimura 1992, Ensor 2002, Dillon 2004). The activity of ADI as an arginine-degrading drug is only apparent in cells that lack the ability to compensate by synthesizing endogenous arginine from citrulline.

In particular, methylation-dependent silencing of the *ASS1* promoter has been identified as a mechanism of gene repression in a subset of ASS1-deficient arginine auxotrophic solid and hematological tumors, including MPM (Szlosarek 2006, Nicholson 2009, Delage 2012). ASS1-deficiency is associated with a poor prognosis in MPM (Delage 2008) and a variety of other cancers including osteosarcoma (Kobayashi 2010), myxofibrosarcoma (Huang 2013), glioblastoma (Syed 2013), bladder cancer (Allen 2014), breast cancer (Qiu 2014) and pancreatic cancer (Liu 2014). The reason for this is not entirely clear, but may due to rapidly expanding cancer cells preferentially using aspartate from the urea cycle to form nucleic acids and not arginine (Rabinovich 2015). This ASS1 deficiency redirects aspartate to pyrimidine synthesis. In contrast, expressing ASS1 decreases cell proliferation by decreasing nucleotide synthesis, resulting in a less malignant phenotype. Therefore, the urea cycle enzymes are metabolically linked to pyrimidine synthesis and regulation of neoplastic growth. Another group has also shown that ASS1 is a tumor suppressor in renal cell carcinoma by modulating both the urea cycle and glycolytic flux (Simon 2015). Furthermore, they showed that re-expression of ASS1 retarded proliferation both in vitro and in vivo xenograft models.

2.1.4 Development of ADI-PEG 20

As a result of the above observations regarding the potential anti-cancer activity of arginine depletion, interest was focused on the development of ADI as a drug. The enzyme was cloned from *Mycoplasma hominis,* expressed in *E. coli* and subsequently conjugated to polyethylene glycol (PEG) (Takaku 1992 and 1993, Holtsberg 2002). The PEG conjugates were prepared to enhance *in vivo* stability, to increase the circulating half-life and decrease the immunogenicity of the recombinant Mycoplasma enzyme. It was determined that synthesis of ADI-PEG with PEG of 20,000 mw via a succinimidyl succinate linker (ADI-PEG 20) provided the optimal combination of enhanced half-life and diminished immunogenicity, as well as ease and yield of manufacture (Holtsberg 2002). Results of phase 1 and 2 ADI-PEG 20 treatment of subjects with HCC in the

USA, Italy and Taiwan have been reported (Curley 2003, Izzo 2004 and 2007, Yang 2010, Glazer 2010), as have similar phase 1 and 2 studies in metastatic melanoma (Ascierto 2005, Savaraj 2007, Feun 2008, 2012, Ott 2013). These studies demonstrated medical benefit.

2.1.5 Current ADI-PEG 20 Clinical Trials

The therapeutic applicability of targeting arginine deprivation therapy with ADI-PEG 20 in combination with systemic chemotherapy is only now being studied in the clinic. Recent preclinical studies have revealed that arginine deprivation may be combined successfully with cisplatin, docetaxel, gemcitabine, chloroquine and PI3K inhibitors to enhance the pro-apoptotic effect of ADI-PEG 20 in various arginine-dependent cancer xenograft models, including prostate cancer, pancreatic cancer, osteosarcoma and melanoma (Cheng 2007, Kim 2009, Daylami 2014, Tsai 2012). Clinically, the first combination phase 1 trial to assess the role of docetaxel with ADI-PEG 20 commenced in the US in 2011 (ClinicalTrials.gov Identifier: NCT01497925) and a second phase 1 is underway with cisplatin at the MD Anderson Cancer Center (Texas, US) (ClinicalTrials.gov Identifier: NCT01665183). Preliminary results show that the ADI-PEG 20-doublet chemotherapy regimens are well tolerated and have resulted in objective responses (Polaris-data on file). ADI-PEG 20 is currently being investigated in multiple clinical trials. Further information is available on these trials at ClinicalTrials.gov.

2.1.6 Cisplatin

Cisplatin is a heavy metal compound containing platinum (Rozencweig 1977, Prestayko 1979). Its mechanism of action involves covalent binding to purine DNA bases, this leads to cellular apoptosis (Kelland 2007). Side effects of cisplatin include nephrotoxicity, ototoxicity, gastrointestinal upset (including nausea and vomiting), neurotoxicity (especially peripheral neuropathy), electrolyte disturbances (hypomagnesaemia, hypokalemia and hypocalcaemia) and myelosuppression (Cisplatin 1999). The latter, depending on dosage regimen, typically has an onset of about 10 days with a nadir of about 14-23 days, with recovery by 39 days. Fever and infection may occur in those with neutropenia. Deaths due to infection, secondary to myelosuppression, may also occur. Myelosuppression appears to occur less frequently with lower doses (Rozencweig 1977).

2.1.7 Pemetrexed

Pemetrexed is a folate analog metabolic inhibitor (Pemetrexed 2013). In clinical trials, the most common adverse reactions (incidence ≥ 20%) during therapy as a single agent were fatigue, nausea, and anorexia. Additional common adverse reactions (incidence ≥ 20%) during therapy when used in combination with cisplatin included vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

2.1.7.1 ADI-PEG 20 plus Cisplatin in Melanoma: Preclinical Studies

Arginine is the substrate for nitric oxide (NO) synthase (Husson 2003, Haines 2011). Depletion of NO inhibited melanoma proliferation, and enhanced cisplatin-induced apoptosis in melanoma cells in tissue culture (Tang 2004, Sikora 2010). In addition, NO inhibition with the selective antagonist N^6-(1-iminoethyl) – L lysine dihydrochloride (L-NIL) synergized with cisplatin in xenograft models

without added toxicity (Sikora 2010). Interestingly, although the mice only received 3 doses of cisplatin every 3 days, continued dosing of L-NIL was sufficient to suppress tumor growth (Sikora 2010). These findings suggest that combination of NO inhibition with ADI-PEG 20 and cisplatin would be a reasonable approach to inhibiting melanoma, as ADI-PEG 20 has been shown to inhibit NO both in tissue culture, animals and humans with either melanoma or HCC (Thomas 2002, Dillon 2002, Ascierto 2005, Izzo 2007).

More recently, *in vitro* data has confirmed enhanced melanoma cell apoptosis with the combination of ADI-PEG20 and cisplatin and with the combination in xenograft models (Savaraj 2015). Treatment with ADI-PEG 20 and cisplatin combination showed significantly enhanced activity compared to either agent alone. The underlying mechanism is complex, but increased DNA damage upon arginine deprivation appears due to decreased DNA repair proteins which blunt the cancer cells' ability to respond to cisplatin induced DNA damage.

Thus both laboratory and xenograft data show that the combination of ADI-PEG 20 and cisplatin results in enhanced anti-tumor activity in ASS1-deficient melanoma cells, even when the cisplatin was administered over a limited period of time.

2.1.7.2 ADI-PEG 20 plus Cisplatin in Melanoma: Clinical Study

As noted, a phase 1 is underway with cisplatin at the MD Anderson Cancer Center (Texas, US) (ClinicalTrials.gov Identifier: NCT01665183). Preliminary results show that this doublet chemotherapy regimen (cisplatin 35 mg/m^2 weekly x weeks 1 - 3 of every 4 weeks [105 mg/m^2 every 4 weeks] and ADI-PEG 20 36 mg/m^2 weekly) is well tolerated and has resulted in objective responses (Fu 2014). This dose of ADI-PEG 20 is the same as that planned in this study, and the dose of cisplatin planned in this study (75 mg/m^2 every 3 weeks or 300 mg/m^2 planned for every 12 weeks [4 months]) is slightly less than that (315 mg/m^2 every 12 weeks) in the ongoing melanoma study.

2.1.8 Phase 2 Study of ADI-PEG 20 Monotherapy in ASS1-deficient MPM in the United Kingdom (ADAM Study)

The benefit of ADI-PEG 20 treatment in ASS1-deficient mesothelioma is supported strongly by a Phase 2 randomized study in ASS1-deficient MPM at 8 cancer centers in the United Kingdom (A Clinical Trial of ADI-PEG 20 in Patients with Malignant Pleural Mesothelioma [ADAM Study] [NCT01279967]), led by the principal investigator of the current study. This study compared ADI-PEG 20 monotherapy with best supportive care (BSC) (Szlosarek 2013, 2016). When this trial started, pemetrexed and cisplatin were not the approved first-line chemotherapy in the UK. Potential subjects had to have inoperable MPM, an ECOG performance status of 0-1, measurable disease by CT scan, and ASS1 deficiency (defined as ≤ 50% tumor cells with moderate and/or strong expression by IHC). ASS1 deficiency was found in 98 out of 214 subjects screened (46%). Sixty eight (68) patients were randomized 2:1 to ADI-PEG 20 (36 mg/m^2) + BSC (N=44) or BSC (N=24). CT scan was performed every 8 weeks. The primary endpoint was PFS, and the secondary endpoints were response rate, OS and toxicity. The study was powered for PFS with a target hazard ratio of 0.60. The study enrolled between March 2011 and May 2013. Epithelioid accounted for 96% of the enrolled subjects. Approximately half of the subjects were previously treated with a

platinum doublet. For ADI-PEG 20 + BSC, 17/44 (39%) were chemonaïve and 27/44 (61%) had been treated with prior chemotherapy.

ADI-PEG 20 + BSC prolonged PFS (3.2 months) compared with BSC alone (2.0 months) (hazard ratio 0.56, 95% CI [0.33-0.96], p=0.03).

Furthermore, although the study was not powered for OS, there was also a trend to improvement in OS with ADI-PEG 20 treatment. A test for proportional hazards produced p=0.02 for OS. Thus OS violated the proportional hazards assumption, so the restricted mean survival time, a measure of life expectancy, was also estimated. The restricted mean survival times (life expectancy) for OS are 15.7 (ADI-PEG 20) vs. 12.1 (BSC) months, a difference of 3.6 months (95% CI -1.0 to 8.1, p=0.13)

Note that the restricted mean survival of ADI-PEG 20 monotherapy treated subjects of 15.7 months compares favorably with the 12.1 months OS observed with the pemetrexed + cisplatin doublet (Vogelzang 2003).

There was no objective response on CT scan using modified RECIST criteria for MPM, although 18/39 (46%) of ADI-PEG 20 treated patients had a PR by FDG-PET.

ADI-PEG 20 was well tolerated as monotherapy in MPM patients, with no new adverse events compared with other ADI-PEG 20 monotherapy studies.

Given that PFS is a well-established surrogate for OS in MPM, the extended median PFS supports further exploration of the role of ADI-PEG 20 treatment in providing survival benefit.

ADI-PEG 20 was generally well tolerated and showed evidence of clinically significant activity in patients selected for arginine-dependent MPM (Szlosarek 2016). Thus arginine deprivation with ADI-PEG 20 may have a role in the future management of MPM either alone or in combination with selected therapies. One of the metabolically responding patients has already been reported (Szlosarek 2013). Furthermore, another patient with a prolonged response was on coexistent folate inhibition with methotrexate used to treat their rheumatoid arthritis. This suggests further that combination treatment with ADI-PEG 20 may be beneficial in MPM (see below).

2.1.9 Phase 1 Study of ADI-PEG 20 Plus Pemetrexed and Cisplatin in MPM and Non-squamous Non-Small Cell Lung Cancer (NSCLC) (TRAP Study)

Based on the success of ADAM study, a phase 1 study in ASS1-deficient patients with MPM or nonsquamous non-small cell lung carcinoma (NSCLC-nonsquamous) was undertaken (Phase 1 Study in Subjects with Tumors Requiring Arginine to Assess ADI-PEG 20 With Pemetrexed and Cisplatin [ADIPemCis] [TRAP Study]; NCT02029690). The TRAP study examines the standard regimen of pemetrexed + cisplatin (500 mg/m^2 and 75 mg/m^2 respectively, both given every 3 weeks) with escalating doses of ADI-PEG 20 (18, 27 and 36 mg/m^2). Subjects may receive a maximum of 6, 3-week cycles of three-drug treatment for a total of 18 weeks of treatment. Those subjects completing the three-drug regimen may continue on ADI-PEG 20 monotherapy if they have SD or better. Subjects must be chemotherapy naïve except for those with NSCLC and EGFR mutant or ALK positive disease, who must have had an EGFR tyrosine kinase inhibitor (TKI) or

ALK inhibitor (if available). Following the dose escalation portion, maximum tolerated dose (MTD) cohorts of up to 30 subjects each for MPM and NSCLC will be enrolled.

As of 20 March 2019, 36 MPM patients (12 epithelioid; 12 biphasic; and 12 sarcomatoid) were enrolled in the dose-escalation and dose expansion study at the MTD. The overall response rate was as follows: 15/36 (41.6%) PR and 19/36 (52.8%) SD for a DCR of 34/36 (94.4%); the PR rate in non-epithelioid disease was 8/24 (33.3%). Notably, the overall median OS in the expansion cohort was 10.1 months and 8.2 months in the non-epithelioid patient population, comparing favorably with the 22.2% of the pemetrexed + cisplatin phase 3 benchmark trial (Vogelzang 2003-quoted in Mansfield & Symanowski 2014) and known poorest prognosis of the MPM histologies (Mansfield & Symanowski 2014, Galetta 2016). The reason(s) for the higher than anticipated non-epithelioid enrollment are not clear, but appear due, at least in part, to enhanced referral of such patients to the lead investigator as this trial does not exclude such patients (see above) (Peter Szlosarek-personal communication).

Thus, for MPM with a high percentage of non-epithelioid, the ORR achieved with ADI-PEG 20 + pemetrexed + cisplatin is significantly higher than would be expected for the standard pemetrexed + cisplatin doublet.

In view of the poorer outcome for non-epithelioid MPM, it is remarkable that the median PFS for the sarcomatoid and biphasic subjects in the dose expansion TRAP study (20/31 enrolled) was 5.0 months, approaching the level of 5.7 months in a population containing 68% epithelioid in the pemetrexed + cisplatin treated group (Vogelzang 2003).

Note that response rate in the TRAP trial was determined using the modified RECIST criteria (Byrne 2004, Tsao 2011). Modified RECIST takes into account disease only in the thorax. In contrast, RECIST 1.1 takes into account disease in the thorax as well as in other body areas, although it does not assess pleural disease as well as modified RECIST does (Eisenhauer 2009, Tsao 2011). In the TRAP trial, tumor measurements using modified RECIST or RECIST 1.1 resulted in the same ORR (Peter Szlosarek, personal communication). However, as non-epithelioid tumors, especially sarcomatoid more frequently have more aggressive disease that may extend beyond the thorax (Klebe 2010, Galetta 2016), we will use modified RECIST response criteria for MPM for intra-thoracic disease (Appendix A) and RECIST 1.1 response criteria for extra-thoracic disease (Appendix B) for this current trial.

2.1.10 Rationale for Combining ADI-PEG 20 with Pemetrexed and Cisplatin

2.1.10.1 Rationale for Combining ADI-PEG 20 with Pemetrexed

ADI-PEG 20 inhibits intracellular levels of thymidine, and pemetrexed potentiates the anti-tumor activity of ADI-PEG 20. Treatment with ADI-PEG 20 was lethal in ASS1 negative bladder cancer cells and its exposure was associated with a marked reduction in intracellular levels of thymidine, due to suppression of both uptake and de novo synthesis (Allen 2014). Inhibition of de novo thymidine synthesis was linked to decreased expression of folate-dependent nucleotide synthesizing enzymes thymidylate synthase and dihydrofolate reductase. Notably, inhibition of de novo synthesis was associated with potentiation of ADI-PEG 20's anti-tumor activity by the antifolate drug

pemetrexed in a xenograft model. Similar data on thymidine salvage and de novo synthesis pathways were obtained in a panel of ADI-PEG 20 treated ASS1-negative mesothelioma cell lines. Taken together, these findings argue that arginine deprivation combined with antifolates warrants clinical investigation in cancers such as MPM and nonsquamous NSCLC where pemetrexed + cisplatin are first-line chemotherapy.

As noted above, there is a biochemical rationale for combining ADI-PEG 20 with pemetrexed in those tumors where standard treatment includes pemetrexed. Furthermore, there are biochemical rationales for combining ADI-PEG 20 with cisplatin, too.

2.1.10.2 Rationale for Combining ADI-PEG 20 with Cisplatin

Inhibition of nitric oxide synthesis by arginine depletion is enhanced by cisplatin, and ADI-PEG 20 inhibits synthesis of DNA repair enzymes required to repair cisplatin induced DNA damage. Arginine is the substrate for nitric oxide (NO) synthase (Husson 2003, Haines 2011). Depletion of NO inhibited melanoma proliferation, and enhanced cisplatin-induced apoptosis in melanoma cells in tissue culture (Sikora 2010). In addition, NO inhibition with the selective antagonist N6 (1 iminoethyl) – L lysine dihydrochloride (L NIL) synergized with cisplatin in xenograft models without added toxicity (Sikora 2010). These findings suggest that combination of ADI-PEG 20 and cisplatin would be a reasonable approach to inhibiting melanoma, as ADI-PEG 20 has been shown to inhibit NO in tissue culture, animal models and humans with either melanoma or HCC (see Investigator's Brochure).

Pre-clinical data have also been obtained with combination of cisplatin and ADI PEG 20 in treating melanoma (Savaraj 2015). Compared with either agent alone, treatment of ADI-PEG 20 + cisplatin caused significantly more growth inhibition as well as an increase in apoptosis in ASS1-negative melanoma cells. Tissue culture data shows that arginine deprivation with ADI-PEG 20 potentiates cisplatin sensitivity in ASS1-deficient tumor cells, and this effect is mediated by increased DNA damage and increased apoptosis, partly due to decreased DNA repair proteins. Thus tumor cells have increased difficulty in attempting to repair DNA damage caused by cisplatin in the presence of ADI-PEG 20. In addition, treatment with ADI-PEG 20 and cisplatin combination showed significantly enhanced anti-tumor activity compared with either agent alone in a xenograft model.

ADI-PEG 20 has also been tested in combination with cisplatin in a phase 1 trial (NCT01665183) (Fu 2014). The combination has been shown to be well-tolerated with no added toxicity with ADI-PEG 20 compared with those reported for cisplatin alone, except for injection site reactions that are consistent with the intramuscular injection mode of administration for ADI-PEG 20. In addition, objective responses have been observed.

2.2 Description of Investigational Product

Arginine deiminase (ADI) is a recombinant protein cloned from *M. hominis*, produced in *E. coli*, and conjugated with PEG of 20,000 mw using a succinimidyl succinate linker. Thus ADI-PEG 20 is an arginine degrading enzyme, ADI, coupled to PEG.

2.3 Summary of Findings to Date

2.3.1 Clinical Experience with Hepatocellular Carcinoma

ADI-PEG 20 has been found to be well tolerated and to result in apparent medical benefit in phase 1 and phase 2 studies. Some patients have been on ADI-PEG 20 weekly therapy for over 3 years. A global phase 3 trial has finished enrolling. For further information, see the Investigator's Brochure.

2.3.2 Clinical Experience with Metastatic Melanoma

ADI-PEG 20 has been found to be well tolerated and to result in apparent medical benefit in phase 1 and phase 2 studies (Phillips 2013). In particular, patients with metastatic uveal melanoma appeared to benefit with a significant prolongation of progression-free survival (Ott 2013). For further information, see the Investigator's Brochure.

2.3.3 Clinical Experience in MPM

The results of the phase 2 and phase 1 studies have been noted above.

2.3.4 Adverse Events

The toxicities expected from the use of ADI-PEG 20 are relatively mild based on the clinical experience to date detailed above. The most frequently reported physical symptom was mild, temporary tenderness at the injection site beginning 24 hours after the injection and lasting a total of 1 to 2 days. However, allergic reactions, including anaphylaxis have occurred. The most common laboratory toxicities, even at doses higher than those proposed here, were mild (Grade 1 to 2) and asymptomatic elevations of various serum chemistry values. Neutropenia also has been observed and has responded to growth factor support.

2.4 Study Rationale

The above background information provides the biochemical rationale for the use of ADI-PEG 20 in oncology studies. Tissue for ASS1 testing was initially required for study entry to support an adaptive biomarker-driven trial design. However, this design was amended prior to the interim analysis following objective responses in other clinical studies of ADI-PEG 20 combined with chemotherapeutic agents (FOLFOX and gemcitabine plus nab-paclitaxel; Harding 2018 and Lowery 2017) that did not correlate with ASS1 deficiency and were seen in both subjects with and without ASS deficiency. Pemetrexed and cisplatin are the first line chemotherapy in advanced MPM. Taken together, our preclinical and clinical data suggest that such a treatment combined with ADI-PEG 20 would be even more efficacious than standard pemetrexed plus cisplatin only.

In MPM, both RR and PFS correlate with OS (Francart 2009, Blayney 2012, Hasan 2014). Thus RR and PFS serve as surrogate endpoints for OS in MPM.

Clinical Experience

As noted above, a phase 1 combination study of ADI-PEG 20 plus pemetrexed and cisplatin is currently enrolling. The combination has been safe and well tolerated, with no more toxicity than with pemetrexed and cisplatin alone, except for injection site reactions consistent with the IM method of ADI-PEG 20 administration.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective of this study is:

- Determine efficacy as determined by RR, measured by modified RECIST criteria for unresectable MPM and RECIST 1.1 criteria (phase 2 portion) and OS (phase 3 portion)

3.2 Secondary Objectives

The key secondary objective of the phase 2 portion is:

- Determine the duration of response (DOR)

The key secondary objective of the phase 3 portion is:

- Assess progression free survival (PFS)

Other secondary 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

Objectives will be assessed according to the overall MPM population and according to each of the MPM subtypes.

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.

4 STUDY DESIGN

4.1 Design Summary

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 MPM of sarcomatoid or biphasic histologies.

The starting dose represents 100% of the recommended dose of cisplatin and pemetrexed and ADI-PEG 20 as determined in the phase 1 trial.

4.1.1 Continued Treatment after 6 Weeks of Treatment of ADIPemCis

Tumor assessment imaging will be performed at baseline (during screening) and at the end of week 6 for tumor response using modified RECIST for MPM for local pleural disease (Byrne 2004, Tsao 2011) and RECIST 1.1 for metastatic lesions (Eisenhauer 2009). The same imaging modality is to be used throughout the triplet treatment duration.

In the event of disease progression, the triplet chemotherapy will be stopped and the patient offered an alternative treatment plan.

In the absence of disease progression requiring other therapeutic interventions, patients 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 patient with tumor and stable disease or partial response should continue treatment until progression, unless Investigator thinks a better option is available. Thus, subjects completing ADIPemCis or PlaceboPemCis may continue to receive ADI-PEG 20 or placebo treatment. Any patient 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).

4.1.2 Blinded and Open-Label Extension at Study End

Subjects ongoing at study end (once the required number of events have been observed for the final analysis) may continue to receive weekly 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. A local laboratory may be used instead of a central laboratory for the extension phase of the study.

Subjects wishing to continue study treatment will follow the Schedule of Assessments in Table 4.1.2.1

Blinded and Open-Label Extension Schedule of Assessments and Procedures

Table 4.1.2.1 Study Assessments and Procedures

	Study Week																		
Study Procedure	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**EOT**
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE assessment[b]	X			X			X			X			X			X			X
Concomitant medications	X			X			X			X			X			X			X
Study drug administration[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Note: All study evaluations and related procedures may occur ± 3 days of the planned date.

Subjects who remain on treatment after 18 weeks will continue following the schedule in Table 4.1.2.1. For example, week 19 would follow the schedule for week 1, week 20 would follow the schedule for week 2 and so on.

a. Vital signs to be obtained before and 1 hour ± 15 minutes after ADI-PEG 20 or placebo treatment.

b. Adverse events, including serious adverse events will be assessed at each of the indicated visits. Ongoing adverse events will be followed until resolution or stabilization. New AEs will be recorded until 30 days after last drug administration. Adverse events will be reported to Polaris monthly. SAEs will be reported within 24 hours of awareness to Polaris or designee.

c. During blinded extension, visits will be registered in IWRS. During Open-Label Extension, Polaris will provide a list of vial numbers to be pulled from inventory and given to subjects at each visit. ADI-PEG 20 will be administered weekly. Cisplatin and pemetrexed will be administered every 3 weeks up to the planned 18 weeks duration of these agents.

Note: CT/MRI scans during the extension will be standard of care in the opinion of the investigator.

4.1.3 Anticipated Number of Subjects and Target Accrual

See Section 11.

4.2 Criteria for Study Termination

The study may be terminated at any time by Sponsor for the following reasons: 1) the Investigator does not adhere to the protocol, i.e. commits significant protocol violations, 2) in Sponsor's judgment, there are no further benefits to be achieved from the study, or 3) the clinical development of the investigational product in this study is discontinued. If this study is discontinued, Sponsor will inform all study investigators/institutions, the IRB/IEC and regulatory authorities.

The Investigator and Sponsor have the right to close a study, at any time; however, this should occur only after consultation between the parties. If the study is closed, the IRB/IEC must be

informed. If the study is closed prematurely, all study materials, except documentation that has to remain stored at the center site, must be returned to Sponsor. The Investigator will retain all other documents until notification given by the Sponsor for destruction. Events that may trigger premature termination of a study or closure of a center include, but are not limited to:

- New toxicity finding
- Non-compliance with the protocol
- Change in development plans for the drug
- Slow recruitment
- Poor quality data
- Regulatory authority mandate

5 STUDY POPULATION

5.1 Inclusion Criteria

A subject will be eligible for study participation if they meet the following criteria prior to the first dose:

1. Histologically proven unresectable MPM of biphasic or sarcomatoid histology. Biphasic MPM is defined using the World Health Organization's international histological classification of tumors as containing an epithelial and a sarcomatoid component with each component comprising at least 10% of the tumor (Corson 2004, Allen 2005).
2. Naïve to prior chemotherapy or immunotherapy (i.e., this is a first-line systemic therapy study).
3. Measurable disease as assessed by modified RECIST for MPM local pleural disease (Appendix A) and RECIST 1.1 for metastatic lesions (Appendix B).
4. ECOG performance status of 0 – 1 (Appendix C).
5. Predicted life expectancy of at least 12 weeks.
6. Age ≥ 18 years (there is no upper age limit).
7. Fully recovered from any prior surgery and no major surgery within 4 weeks. Surgery for placement of vascular access devices is acceptable.
8. Subjects and their partners must be asked to use appropriate contraception. They must agree to use two forms of contraception or agree to refrain from intercourse for the duration of the study and for 35 days after last dose of ADI-PEG 20 or for at least six months after treatment with pemetrexed and cisplatin whichever is the longer duration. Females must not be pregnant at the start of the study, and a serum human chorionic gonadotropin (HCG) pregnancy test must be negative before entry into the study. If positive HCG pregnancy test, further evaluation to rule out pregnancy must be performed according to GCP before this patient is claimed eligible.
9. Informed consent must be obtained prior to study initiation.
10. Hemoglobin (HB) > 9.0 g/dL.
11. Absolute neutrophil count (ANC) > 1,500/μL.

12. Platelets > 75,000/μL.
13. Either: (i) serum bilirubin ≤ 1.5 x upper limit of normal (ULN) or
    (ii) alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or alkaline phosphatase (ALP) ≤ 3 x (ULN) unless raised due to tumor in which case up to 5 x ULN is permissible
14. Serum uric acid ≤ 10 mg/dL (595 μmol/L) (with or without medication control).
15. Creatinine clearance ≥ 45 mL/min (estimated, using Cockcroft and Gault formula). Cisplatin dose adjustment is recommended for subjects with a creatinine clearance between 45 and 59 mL/min (Bennis 2014) as follows: reduce cisplatin dose by 25% for clearance between 50-59.9 mL/min and by 50% for clearance between 45 – 49.9 mL/min.

5.2 **Exclusion Criteria**

A subject will not be eligible for study participation if s/he meets any of the exclusion criteria before first dose:

1. Radiotherapy (except for palliative reasons) the previous two weeks before.
2. Ongoing toxic manifestations of previous treatments.
3. Symptomatic brain or spinal cord metastases (patients must be stable for > 1 month post radiotherapy or surgery).
4. Major thoracic or abdominal surgery from which the patient has not yet recovered.
5. Serious infection requiring treatment with intravenous antibiotics at the time of study entrance, or an infection requiring intravenous therapy within 7 days prior.
6. Known to be serologically positive for human immunodeficiency virus (HIV). Testing to determine possible infection status is not required.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (New York Heart Association Class III or IV), symptomatic cardiac arrhythmia, previous history of myocardial infarction (unless stable and good ejection fraction on echocardiogram) or psychiatric illness and social situations that would limit compliance with study requirements.
8. Is a participant of, or plans to participate in, another interventional clinical study whilst taking part in this study. Participation in an observational or biomarker study would be acceptable, with prior Sponsor approval.
9. Subjects with history of another primary cancer, including co-existent second malignancy, with the exception of: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary malignancy with no known active disease present in the opinion of the Investigator will not affect patient outcome.
10. Allergy to cisplatin or other platinum-containing compounds.
11. Pregnancy or lactation.
12. Expected non-compliance.
13. Subjects who had been treated with ADI-PEG 20 previously.
14. History of uncontrolled seizure disorder not related to underlying cancer.
15. ECOG performance status ≥ 2.

16. Allergy to pegylated compounds.
17. Allergy to E. coli drug products (such as GMCSF).
18. Allergy to pemetrexed or to any other ingredient used in the formulation.

5.3 Criteria for Subject Withdrawal

Subjects are free to discontinue the study treatment at any time, for any reason, and without prejudice to further treatment.

A subject experiencing any of the following will be withdrawn from the study treatment:

1. Significant noncompliance on the part of the subject.
2. Refusal of the subject to continue treatment or observations.
3. Adverse Event. Laboratory abnormalities that can be corrected with interventions (e.g., hyperuricemia with allopurinol and/or urate oxidase, and neutropenia with growth factor support) do not require subject withdrawal.
4. Decision by the Investigator that termination is in the subject's best medical interest.
5. Unrelated medical illness or complication.
6. Death.
7. Lost to follow-up.
8. Progressive Disease according to modified RECIST or RECIST1.1 as appropriate for the disease under study, or clinical progression in the opinion of the Investigator. BICR results will be used for decisions on the discontinuation of or continued treatment during the phase 2 portion.

5.4 Withdrawal Procedures

In the event of a subject's withdrawal, the investigator will promptly notify the study monitor and will make every effort to complete the EOT assessments (see Table 1.4.2).

Subjects withdrawn from treatment for reasons other than PD may continue to receive scans every 8 weeks until PD.

After discontinuation/withdrawal from treatment, a subject must be entered into the follow-up period, and contacted regularly (every 3 months) for survival status until study closure. If a subject decides not to continue to receive study drug, they will be removed from the study treatment portion and the investigator will request the subject to provide follow up information on the study. If a subject withdraws from the study treatment, every effort will be made to complete EOT, Follow-Up Visit, and End of Study eCRFs.

If a subject should die during treatment or within 30 days of stopping treatment, the investigator will inform Sponsor's representative. The cause of death should be reported in detail, within 24 hours, on an SAE form and reported to Sponsor's representative/designee (see Section 9).

Subjects that have signed informed consent for treatment, and undergo at least some of the screening procedures, but fail to meet eligibility criteria will be considered screening failures. The reason for failure will be recorded on the screening log provided by Polaris. A record of such subjects will be maintained in the Trial Master File (TMF) at the study site and will be retained for the required period of time in compliance with the Code of Federal Regulations (CFR) 21, Sec.312.57, part (c) and Good Clinical Practice (GCP). Subjects that are "screen failures" may be rescreened at the discretion of the investigator.

All withdrawn subjects will be followed until resolution of any ADI-PEG 20 related AEs, or until these unresolved AEs are judged by the investigator to have stabilized.

6 STUDY PROCEDURES

The procedures for each visit are listed in Section 1.4 SCHEDULE OF ASSESSMENTS AND PROCEDURES.

Results of all assessments will be recorded on the appropriate eCRF.

6.1 Screening Procedures

The investigator will inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject prior to performing any study-related procedures and prior to the administration of study drug.

The results of the screening evaluation must meet the inclusion/exclusion criteria for the subject to be entered into the study. Thus the investigator must review the results of histology determination, diagnostic testing (CT scan or MRI, serum pregnancy test [if appropriate], and clinical laboratory tests), and the results of that screening testing must meet the inclusion/exclusion criteria for the subject to be enrolled into the study. BICR results will be used for eligibility determination in the phase 2 portion.

Study Informed Consent Form

There will be one main consent form for this study.

6.1.1 ASS1 Expression Screening

ASS1 expression testing was initially required but the protocol was amended to remove this requirement.

6.1.2 Study Screening

6.1.2.1 Screening Procedures within 4 weeks (28 days) of Start of Treatment

The following must be performed/ obtained within the four weeks before the patient receives the first dose of ADI-PEG 20:

- Upon determination that a patient has a biphasic or sarcomatoid tumor, the patient will then undergo further screening procedures, as follows
- Demographic details
- Medical History including prior diagnosis, prior treatment, concomitant diseases, concomitant treatment and baseline signs and symptoms
- Disease Assessments: Radiological measurements (chest, abdominal and pelvis computerized tomography (CT) scan, as appropriate), ideally within 2 weeks of study drug administration but 28 days is acceptable.

6.1.2.2 Screening Procedures within 1 week (7 days) of Start of Treatment

The following must be performed within one week before the patient receiving the first dose of ADI-PEG 20:

- ECOG performance status
- Complete physical examination
- Height, weight, temperature, blood pressure (BP), respiratory rate and heart rate
- Laboratory Tests: Samples to be obtained for clinical laboratory tests as outlined in Table 9.2. Serum human chorionic gonadotropin (HCG) test to rule out pregnancy at study entry; results must be obtained and reviewed before the first dose of ADI-PEG 20 is administered, if applicable (i.e., females).
- Creatinine clearance ≥ 45 mL/min (estimated, using Cockcroft and Gault formula). Creatinine clearance = {(l 40–age[yr]) x weight[kg])/(72xSerum creatinine[mg/dL])}x 0.85 (if female).
- 12 lead electrocardiogram (ECG)

6.2 Clinic Visits

There are no fasting or food restrictions for the clinic visits. The visit frequency is described in Section 1.4 SCHEDULE OF ASSESSMENTS AND PROCEDURES. Selected weekly clinic visits may be conducted in the home setting by home cancer care staff rather than in the clinic. If home care is to be used the process must be documented and approved by the Sponsor.

6.2.1 End of Treatment

At the time of discontinuation of treatment for any reason, subjects will be asked to report to the study site for EOT assessments. This assessment is to be completed 7-30 days after last dose administered (preferably 30 days after last dose administration but may be performed earlier if necessary).

6.2.2 Follow-up Period

The subject will be contacted every 3 months post EOT assessment until study closure to determine survival status. In addition, a current survival status is required prior to the interim and final analysis. Any ongoing AEs related to ADI-PEG 20 when subject stops the study treatment will be followed by the Investigator until the event resolves, stabilizes, or returns to baseline status (see Follow-up Period Table, Table 1.4.3).

7 STUDY DRUGS

7.1 Identity of Investigational Product and Standard, Background Chemotherapies

7.1.1 Drug Name(s)

7.1.1.1 ADI-PEG 20 - Investigational Product

For further information, see the Investigator's Brochure. Arginine deiminase (ADI) is a recombinant protein cloned from *M. hominis*, produced in *E. coli*, and conjugated with polyethylene glycol (PEG) of 20,000 mw. Thus, ADI-PEG 20 is an arginine degrading enzyme, ADI, coupled to PEG. ADI-PEG 20 is the investigational product in the study.

7.1.1.2 Pemetrexed – Standard, Background Chemotherapy

This is an approved medication that is considered in the study as background therapy to be provided through the local pharmacy. The brand name Alimta® (Lilly-name used in the USA) should be used for this study unless use of an alternative generic version has been approved in advance by the Sponsor.

7.1.1.3 Cisplatin – Standard, Background Chemotherapy

This is an approved medication that is considered in the study as background therapy to be provided through the local pharmacy.

7.1.2 Storage Conditions

The investigator will ensure that all the study drugs are stored and dispensed in accordance with US Food and Drug Administration (FDA) regulations and other country specific health authority regulations concerning the storage and administration of investigational drugs.

ADI-PEG 20 and placebo will be stored frozen at the temperature indicated on the product label. The drug product is stable for 24 hours once it is thawed after taking it out from frozen storage.

Pemetrexed and cisplatin are to be stored per institutional standards.

7.2 Blinding of Investigational Product

Subjects will be randomly assigned to receive ADI-PEG 20 drug product or matching placebo in a double-blind fashion. Thus, neither the investigator, nor the subject will know which study

treatment is being administered. The randomization number will be assigned based on information obtained from an IWRS. ADI-PEG 20 drug product and placebo will be identical in appearance in order to preserve the blinding. In order to maintain this blind, study medication (ADI-PEG 20 or placebo) will be labeled with a unique "medication number", which will be assigned to a subject by an IWRS. Note that SAS programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes. In such an event, arbitrary treatment group assignments must be randomly linked to subjects, effectively rendering any output of programs meaningless. The complete random lists will be archived with the IWRS. Should a medical emergency arise that requires identification of the study medication administered, in order to manage the acute situation of the subject, the blind can be broken. The investigator should treat the subject as if the subject were on the active drug product. The study medication can be unblinded by the investigator via the IWRS if needed.

Unblinding may occur for emergency purposes only. Investigators should note that the occurrence of an SAE should not routinely precipitate the immediate unblinding of the label. If unblinding is necessary for the treatment of a subject for an SAE, the investigator should promptly document and explain any unblinding to Polaris, or their designee within 24 hours of unblinding. The medical monitor must also be promptly notified that the blind has been broken. If unblinding occurs, the study medication (ADI-PEG 20 or placebo) must be discontinued. Subjects that have discontinued study drug/placebo may not re-start treatment.

7.3 Study Treatment

7.3.1 Dose and Administration

ADI-PEG 20 or placebo will be administered by intramuscular (IM) injection to subjects once weekly. Subjects will remain in the treatment area for 1 hour ± 15 minutes after the injection. At the end of this post injection period, subjects will be assessed for safety and tolerability, including obtaining vital signs. ADI-PEG 20 or placebo is to be administered before pemetrexed + cisplatin. Pemetrexed + cisplatin administration is to begin at least 60 minutes after ADI-PEG 20 or placebo administration on the same day, except during cycle 1 when the chemotherapy is administered on Day 3.

Pemetrexed + cisplatin are to be administered per institutional standards (this may include capping of BSA for dosing, banding, rounding, prefilled products, or logistical requirements for prehydration, etc.).

7.3.2 Rationale and Dose Selection

7.3.2.1 ADI-PEG 20

ADI-PEG 20 (at dose of 36 mg/m^2) or placebo is to be given via the IM route of administration. This is the dose that has been used successfully in the current phase 1 study of ADI-PEG 20 plus pemetrexed plus cisplatin in MPM and NSCLC. Subjects will receive one injection of ADI-PEG 20 or placebo intramuscularly into the deltoid, gluteal or quadriceps muscles (Note: this will total approximately 6 mL for a larger subject, if this volume is a problem from an institutional nursing

perspective, it may be given as 2 injections in different body locations) weekly. To limit the volume administered for a larger subject there will be dose capping at 74.8 mg which is the equivalent of 6.5 mL. The injections may be given ± 3 days from the scheduled weekly dosing, except for the first dose, which is fixed. Subjects will be observed in the clinic for 1 hour ± 15 minutes following each ADI-PEG 20 or placebo injection. ADI-PEG 20 or placebo is to be administered before pemetrexed and cisplatin. Pemetrexed and cisplatin administration is to begin at least 60 minutes after ADI-PEG 20 or placebo administration on the same day, except for the first cycle where the doublet chemotherapy will be administered on day 3. Treatments shall not be interrupted due to either scheduling for CT (or MRI) scans or delays in the assessment of scan results.

7.3.2.2 Pemetrexed and Cisplatin

Treatment with pemetrexed and cisplatin is as per institutional guidelines, including infusion protocols.

The dosages of pemetrexed and cisplatin are those used to treat unresectable MPM. The dose of pemetrexed is 500 mg/m^2 every 3 weeks given by IV. The dose of cisplatin is 75 mg/m^2 every 3 weeks given by IV.

7.3.3 Dose Adjustments

Treatment may be withheld for up to 2 weeks in any subject that demonstrates Grade 3 non-hematologic toxicity or hematologic toxicity, as defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE version 4.03, or approved version). If the toxicity is no longer Grade 3, treatment may be resumed; treatment does not have to wait for the next scheduled dose visit. Use of hematopoietic growth factors is allowed to treat hematologic toxicity at the discretion of the investigator. Grade 3 or 4 laboratory abnormalities (e.g., hyperuricemia) that can be corrected with interventions do not require cessation of therapy. If treatment is withheld for more than 2 weeks (or more than 2 missed doses of ADI-PEG 20/placebo), the subject should be discontinued from treatment, unless it is approved by Polaris in certain situations for the subject to continue.

ADI-PEG 20 or Placebo

ADI-PEG 20 or placebo will be given on days 1 (week 1), 8 (week 2), and 15 (week 3) of a cycle. Toxicity which is attributable to either cisplatin or pemetrexed will not mandate withholding the dose of ADI-PEG 20 or placebo for that cycle. Dose reduction of ADI-PEG 20 or placebo is not allowed.

Investigators retain the discretion to withhold ADI-PEG 20 or placebo dose on the grounds of patient safety.

For patients to receive Day 15 ADI-PEG 20 or placebo the following parameter is required during the chemotherapy treatment period (Cycles 1-6):

1. Platelets ≥ 50 x 10^9/L – on day 8

Patients who do not meet this criterion should have the dose of ADI-PEG 20 or placebo withheld. Specific toxicity resulting from ADI-PEG 20 or placebo administration should be managed as follows:

- Local injection site reactions to date have been self-limiting and typically resolve within 48 hrs.
- Anaphylaxis should be managed in line with local policy for anaphylaxis. In the event of Grade 2 or lower anaphylaxis re-challenge with ADI-PEG 20 or placebo may be considered and pre-medication with hydrocortisone and cholorpheniramine may be used. Grade 3 or greater anaphylaxis will result in the patient being withdrawn from study treatment.
- Hyperuricemia is to be monitored. Any clinically relevant elevation should be treated with allopurinol or urate oxidase, or sites may choose appropriate substitutions according to local policy.
- Epilepsy/fits should be managed according to local policy and with benzodiazepines as necessary. Once stabilized and dependent on the type and severity of reaction re-challenge with ADI-PEG 20 or placebo may be considered. If further seizures occur, despite prophylactic measures, the patient should be withdrawn from study treatment.

Pemetrexed and Cisplatin:

Cisplatin dose adjustment is recommended for subjects with a creatinine clearance between 45 and 59 mL/min (e.g., Bennis 2015).

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be re-treated using the guidelines in Table 7.3.3:

Table 7.3.3: Management of Drug Related Toxicity

	Cisplatin	**Pemetrexed**
Hematological:		
Nadir ANC <500/mm^3 & nadir platelets ≥50,000/mm^3	75% previous dose	75% previous dose
Nadir platelets <50,000/mm^3 regardless of nadir ANC	75% previous dose	75% previous dose
Nadir platelets <50,000/mm^3 with bleeding regardless of nadir ANC	50% previous dose	50% previous dose
Non-Haematological:		
Any Grade 3 or 4 toxicities except mucositis	75% previous dose	75% previous dose
Any diarrhea requiring hospitalisation (irrespective of grade) or Grade 3 or 4 diarrhoea	75% previous dose	75% previous dose
Grade 3 or 4 mucositis	100% previous dose	50% previous dose

	Cisplatin	**Pemetrexed**
Neurotoxicity Grade 1	100% previous dose	100% previous dose
Neurotoxicity Grade 2	50% previous dose	100% previous dose
Creatinine clearance 50-59.9 mL/min	75% previous dose	Not applicable
Creatinine clearance 45-49.9 mL/min	50% previous dose	Not applicable

If a subject develops non-hematologic toxicities ≥ Grade 3 (excluding neurotoxicity), pemetrexed should be withheld until resolution to less than or equal to the subject's pre-therapy value. Treatment should be resumed according to the guidelines in Table 7.3.3.

Treatment with pemetrexed and cisplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

The first occurrence of toxicity which leads to a dose reduction of pemetrexed and / or cisplatin will not mandate a dose reduction in ADI-PEG 20 or placebo so long as the toxicity is attributable to the cytotoxic agent(s).

Either pemetrexed and / or cisplatin may be discontinued due to toxicity, and the continued single chemotherapy agent may be given with ADI-PEG 20 or placebo.

7.3.4 Switching from Cisplatin to Carboplatin

Cisplatin is the recommended chemotherapy for use in the initial and subsequent cycles. However, subjects who do not tolerate cisplatin or who would not be expected to tolerate cisplatin may have carboplatin substituted for cisplatin at any cycle including the initial cycle at the discretion of the investigator. The dose of carboplatin is area under the plasma concentration–time curve (AUC) 5 mg per ml per minute. This may be modified at investigator discretion.

7.3.5 Missed Doses

An ADI-PEG 20 or placebo dose that is administered within the +3 days from the projected day will be considered delayed but not a deviation. Beyond the +3 days, the dose would be considered missed for that week. Missed doses of ADI-PEG 20 or placebo will not be made up.

A pemetrexed and/or cisplatin/carboplatin (or carboplatin) dose that is not administered on Cycle X/Day 1 will be considered delayed if given within 2 weeks of that cycle. Subsequent dosing schedule would need to be adjusted so that the chemotherapy is given in 3 weeks' time. Beyond this, the doses would be considered missed.

7.3.6 Subject Replacement

Only screening failure subjects will be replaced. All patients who receive any dose of study drug will be evaluable for safety.

7.3.7 Optional Single Agent Treatment

Subjects that have completed 18 weekly treatments (ADI-PEG 20 or placebo plus pemetrexed and cisplatin/carboplatin) may continue ADI-PEG 20 or placebo if they have stable disease or better for up to 2 years.

7.3.8 Data Safety and Monitoring Board (DSMB)

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 (2) 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.

7.3.9 Duration of the Study

Anticipated Duration of Treatment: 18 weeks - with possible extension for responding or stable disease, and stopping for progressive disease

Anticipated Enrollment Period: Approximately 24 months

Anticipated Follow-up Period: Approximately 12 months. Thus the study is anticipated to take 36 months to complete.

7.3.10 Estimated Study Drug Requirements

Study drug is as follows: ADI-PEG 20, in the histidine-buffered formulation, will be provided as a sterile solution in single-dose glass vials.

Placebo is as follows: Placebo will be provided as a sterile solution in single-dose glass vials. Each vial delivers 3.5 mL of solution containing low viscosity sodium carboxymethylcellulose, PEG 3350, propylene glycol, and Tween 80. The placebo will not contain ADI, PEG 20 or succinimidyl linker.

It is assumed that each subject will be treated with approximately 18 doses of either study drug or placebo. Some subjects will be treated for shorter duration and some for longer duration.

Thus the approximate number of vials required for the phase 2 portion of the study is: 88 subjects per study arm x 2 vials per week x 18 weeks = 3168 vials of ADI-PEG 20 and an equivalent number of vials of placebo.

7.3.11 Study Drug Dispensing

To prepare the test article for intramuscular use, first allow the frozen vial to warm to room temperature and then gently swirl the solution. Remove flip-off cap and using clean technique, withdraw an appropriate volume of solution into a syringe. Vials are designed for single-use only. Any test material remaining in an opened vial must not be used.

Clinical trial material	Preparation	Administration
Test Article	Once the agent has been thawed and warmed to room temperature, the appropriate amount of agent for the individual subject is to be drawn into a syringe and injected intramuscularly.	Inject intramuscularly

7.3.12 Packaging and Labeling

Label text will be approved according to Polaris or their designee's procedures. The drug product and placebo labels will comply with local legal and regulatory requirements and will be multi-language where appropriate. The proper storage conditions of the study drug and placebo will also be described on the medication labels.

The following clinical trial materials (CTM) will be used:

- ADI-PEG 20 for IM injection
- Placebo for IM injection

ADI-PEG 20 is produced by DesigneRx Pharmaceuticals, Inc. (DesigneRx), a subsidiary of Polaris. Placebo will be identical in appearance to the active study drug. Placebo will also be supplied by DesigneRx. The CTM is blinded.

Pemetrexed, cisplatin, and carboplatin are available through the study site pharmacy.

7.3.13 Study Drug Handling

Participating countries and sites will be provided with the CTM according to the number of patients assigned, and labeled according to local law. Once the CTM has been received, it should be kept in a safe place as directed on label. Study drug supplies must be used only for the investigation specified in this protocol, and study drug supplies must be accessible only to authorized staff. The investigator, or responsible person or pharmacist, as appropriate at each site must confirm the receipt of the drug supplies by signing the order form. Study drug supplies may only be administered by the investigator or the investigator's designate. Study drug accountability must be performed every day study drug is dispensed. Used or partially used vials should be retained until use has been verified by Polaris or their designee. Documented destruction of partially used drugs and disposal of drug containers must be performed by each site. One copy of the destruction certificate must be kept by the investigator, or responsible person or pharmacist, as appropriate at each site, and the other copy must be sent to the Polaris representative.

7.3.14 Study Drug Storage

CTM will be stored until use at conditions described on the label.

7.3.15 Study Drug Accountability and Return

The investigator must ensure that all drug supplies are kept in a secure locked area with access limited to those authorized by the investigator. The investigators or appropriate designee will maintain a record of all study medications received and dispensed. Records must include but not be limited to the date received, lot number, expiration date, amount received, and the disposition of all study drug. Current dispensing records will also be maintained including the date and amount of drug dispensed and the subject receiving the drug. All remaining drug not required by regulations to be held by the clinical facility must be returned to Sponsor or its representative immediately after the study is completed. Study drug shipments will be addressed to the Investigator's authorized designee, preferably, the site's pharmacy. The recipient will verify the amount and condition of the drug and will return a signed Acknowledgment of Receipt and the temperature profile from the temperature monitor to the Sponsor. A drug dispensing log (inventory) will be kept by the study site, containing at least the following:

- The subject's identification (subject number and initials)
- Date and quantity of drug dispensed
- Date and quantity of drug returned to the investigator/pharmacy (if applicable)
- Date and quantity of accidental loss of drug (if any)

These inventories must be made available for inspection by the study monitor. The Investigator should have access to the study drug dispensing record. At the end of the study, the study monitor will also collect the original study drug dispensing records.

At the end of the study or as directed by Sponsor, all used and unused supplies, including partially used or empty containers, will be disposed of or transferred as instructed by Polaris, and in accordance with local written procedures, if applicable. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log and signed-off by a second person. At the end of the study, the monitor will collect the original drug disposition logs.

7.3.16 Cross-Over

No crossover will be permitted.

7.3.17 Compliance

This study will be conducted in accordance with the provisions of the Declaration of Helsinki, the FDA Code of Federal Regulations, the ICH Guidelines on GCP, and local regulations as applicable. Before initiating the trial, the Investigator/institution should have written and dated approval from the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) for the trial protocol, written informed consent documents, and any written information to be provided to subjects. The

investigator or appropriate designee will maintain a record of all study medications received and dispensed and also source documents for each subject in the study, consisting of case and visit notes.

7.4 Prior and Concomitant Therapy

A concomitant therapy is any drug or substance administered from administration of first dose of study drug until the last dose of study drug administered. A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment performed from administration of first dose of study drug until the last dose of study drug administered. No new concomitant therapies or procedures will be collected after the administration of last dose of study drug. If the subject is being followed for study drug related toxicity the corresponding concomitant therapy or procedure will be followed until the event is resolved or stabilized.

The use of concomitant therapies or procedures defined above must be recorded on the subject's eCRF, according to instructions for eCRF completion. AEs related to administration of these therapies or procedures must be documented on the appropriate eCRF.

All medications (prescription and non-prescription), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication eCRF and will include generic (preferably) or brand name, start and stop date, dose and route of administration, and indication. Medications taken for a procedure should also be included. All non-drug therapies must be recorded in the respective sections of the eCRF.

Subjects who require oral anticoagulation with warfarin (or other substitutions) may continue provided there is increased vigilance with local INR monitoring.

7.4.1 Non-Permitted Concomitant Therapies

Subjects **may not** receive chemotherapy, radiation therapy (palliative radiation therapy to sites not representing PD is acceptable), or immunotherapy during the study. Subjects may not receive interferon or the vaccine for yellow fever.

7.4.2 Permitted Concomitant Therapies

At the discretion of the investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, except another systemic therapy (chemotherapy) and/or radiation therapy, and/or immunotherapy.

Non-steroidal anti-inflammatory drugs (NSAIDs) will be avoided where possible. Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) should avoid taking, medications such as ibuprofen and aspirin (>1.3 g daily), where possible. If necessary, they should be omitted for 2 days before, on the day of, and 2 days following pemetrexed and cisplatin administration.

7.4.2.1 ADI-PEG 20

Routine treatment with antihistamines or corticosteroids is not recommended before ADI-PEG 20 treatment, but may be instituted at the discretion of the treating physician if clinically necessary in a patient that has experienced an allergic reaction while on ADI-PEG 20 treatment. Investigators may prescribe all other concomitant medications or treatments deemed necessary to provide adequate patient care. Thus corticosteroid may be given prior to pemetrexed administration (see below).

For management of Grade 3 or greater hyperuricemia, allopurinol therapy will be administered to subjects until serum uric acid levels have normalized and symptoms have resolved. If the hyperuricemia does not respond to allopurinol therapy, uricase (rasburicase) therapy may be administered.

7.4.2.2 Pemetrexed and Cisplatin

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day.

To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation. Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1,000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an IM injection of vitamin B_{12} (1,000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.

Supportive and pre-medications to include the following (or equivalent substitutions) or as per local policy:

- Folic acid 400 mcg daily, oral
- Hydroxycobalamin 1000 mcg IM injection
- Dexamethasone 4 mg bd (3 doses) preceding hospital visit. Dexamethasone may also be administered i.v. and at a dose per local policy.
- Anti-emetic e.g. 5HT3 antagonist, domperidone and dexamethasone 8 mg
- Furosemide 40 mg oral once

8 EFFICACY ASSESSMENTS

8.1 Efficacy Parameters

See Section 3.

8.1.1 Timing and Methods of Efficacy Assessments

Overall survival will be assessed by the time from randomization until death or censoring. PFS will be assessed as the time from randomization until objective tumor progression or death.

The Schedule of Assessments (Section 1.4) lists the timing of imaging studies.

Subjects that miss a scheduled efficacy assessment, whether a laboratory test, clinic visit procedure or CT/MRI, should be contacted by study site personnel with the request that the subject have the missed assessment performed.

If clinical progression is suspected, an efficacy assessment (i.e. CT/MRI scan) should be performed at that time and results obtained prior to removing a subject from study treatment.

A blinded independent central review (BICR) of the CT/MRI scans will be established, and details will be provided in a separate document to describe the imaging requirements and BICR process.

8.2 Appropriateness of Efficacy Assessments

The measures of efficacy to be used in this study reflect accepted standard of care, i.e., should be widely used and generally recognized as reliable, accurate, relevant and able to discriminate between effective and ineffective treatment agents.

9 SAFETY ASSESSMENTS

Laboratory tests, vital sign measurements, physical examinations and subject medical history will be performed to detect new abnormalities and any deterioration in pre-existing conditions. All clinically significant abnormalities and deteriorations should be recorded in the eCRFs as AEs and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Safety monitoring will be performed by the Sponsor and the CRO, if applicable, on a regular basis.

9.1 Vital Signs

- Systolic and diastolic blood pressure using an appropriate cuff size
- Respiration rate
- Heart rate
- Body temperature

Note that any clinically significant abnormalities should be noted in the eCRFs as AEs.

9.2 Laboratory Tests

Samples will be obtained for the clinical laboratory tests outlined in Table 9.2 and as per Section 1.4 SCHEDULE OF ASSESSMENTS AND PROCEDURES.

A central laboratory will be utilized to process and provide results for the clinical laboratory tests. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

However, a local laboratory may be used as well on days of chemotherapy administration to determine whether or not to give the chemotherapy. Central laboratory samples are to be collected at the same time as local samples and sent in for testing.

Hematology and Chemistry sampling from Cycle X/Day 1 should follow the chemotherapy administration day in case of a chemotherapy dosing delay. Clinically significant local laboratory findings that directly inform a dosing decision will be recorded as an adverse event.

A central laboratory will be utilized to process and provide results of blood sampling for special tests (pharmacodynamics [peripheral blood arginine and citrulline levels], immunogenicity [anti-ADI-PEG 20 antibodies], and pharmacokinetics [peripheral blood ADI-PEG 20 levels]).

Table 9.2 Clinical Laboratory Tests

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

For any laboratory test value outside the reference range that the investigator considers clinically significant:

- The investigator may repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution or stabilization.
- A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an AE.

Special Blood Sampling

Arginine, citrulline, anti-ADI-PEG 20 antibody, and ADI-PEG 20 levels, as well as future research will be obtained at the times (before ADI-PEG 20 injection) noted in Section 1.4.

Special blood sampling should follow calendar days; do not adjust for changes in dosing schedule.

9.3 ECG

ECG and QTcF collection will also be determined. If the week 4 or week 12 ECG collection timepoint is missed due to dosing being delayed or withheld, the ECG should be collected at the next visit.

9.4 Physical Examination

A comprehensive physical examination, including height and weight, will be performed at the screening visit. Physical examination will be performed on Day 1 of every cycle and at other times as clinically indicated. If weight varies by >10%, the BSA and doses should be recalculated. Any clinically significant findings or absence of findings relative to each subject's physical examination will be carefully documented in the subject's AE eCRF. Symptom directed examinations may be performed more frequently at the discretion of the investigator.

9.5 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.

Subjects will be monitored throughout the study for AEs and every effort must be made to remain alert to possible AEs. At the signing of the ICF, each subject should be given the names and contact information of appropriate study site staff for the reporting of AEs and medical emergencies.

For description of a Serious Adverse Event (SAE), see Section 9.5.7.

9.5.1 Assessment of Adverse Events – Relationship to Study Drug

The relationship of all serious and non-serious adverse events to the investigational agent(s) will be determined by the Investigator on the basis of their clinical judgment, using 1 of the following terms

(in accordance with FDA Guidance for Industry and Investigators, "**Safety Reporting Requirements for INDs and BA/BE Studies"** released December 2012):

- Definitely related (There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.)
- Probably related (There is evidence to suggest a causal relationship and the influence of other factors is unlikely.)
- Possibly related (There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).)
- Unlikely related (There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).)
- Unrelated (There is no evidence of any causal relationship)

The Investigator must assess the causality of all serious adverse events/reactions to ADI-PEG 20, or to pemetrexed or to cisplatin, or to a combination of any or all three in relation to the trial treatment according to the definition given.

Note: Information provided in the Investigator's Brochure may support these evaluations.

9.5.2 Recording of Adverse Events

Any medical sign or symptom a subject may experience post ICF and before first administration of study treatment should be recorded as part of patient medical history. Assessment of progressive disease is an endpoint of the study and would not typically be recorded as an AE.

Adverse events are to be recorded on the AE page of the eCRF. Severity of all AEs will be graded according to the CTCAE scale (Version 4.03). Disease progression is to be recorded on specific tumor assessment pages rather than the AE page of the eCRF.

Adverse events will be recorded from administration of first dose of study drug until 30 days after last study drug administration. If any toxicity or medical sign or symptom a subject may experience post signing of ICF meets the definition of Serious Adverse Event (SAE) per Section 9.5.7 they must be reported as an SAE per Section 9.5.8

Action taken with study treatment (study drugs) as a result of the AE will be categorized as dose increased, dose not changed, dose reduced, drug interrupted, and drug withdrawn, not applicable, and unknown.

Action taken to treat the event will be categorized as none, medication, surgical/diagnostic procedure, hospitalization, other, and withdrawal from study.

Event outcome at resolution or time of last follow-up will be recorded as event resolved, resolved with sequelae, resolving, not resolved, fatal, and unknown.

9.5.3 Following Adverse Events

Adverse events related to ADI-PEG 20 that were still ongoing at End-of-Treatment visit should be followed up until resolution or stabilization or until all attempts to determine resolution of the event are exhausted.

The investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

Note: All follow-up information pertaining to SAEs must be forwarded to Polaris designee within 24 hours of receipt.

9.5.4 Discontinuation due to Adverse Events

Subjects may be withdrawn from the study at any time. Subjects withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the Investigator until the clinical outcome from the AE is determined. Any subject who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. The AE(s) should be noted on the appropriate eCRFs and the subject's progress should be followed until the AE is resolved. The Polaris medical monitor must be notified. If the AE may relate to overdose of study treatment, the Investigator Brochure should be consulted for details of any specific actions to be taken.

9.5.5 Pregnancy

Although pregnancy itself is not considered an adverse event or a serious adverse event, pregnancy should be reported as "Information" (not as an "Adverse Event" or "Other Problem or Event").

Pregnancy does not have to be reported if the subject has entered study follow-up period and *conception* occurred 30 days after the final dose of study drug administration.

Pregnancy Notification and Outcome Form will be provided to the investigational site to assist in reporting of the pregnancy and follow-up information to Polaris.

A subject that becomes pregnant will be discontinued from the study.

The pregnant subject or the partner of a male subject should be followed until termination or to partum to ensure absence of congenital anomaly or birth defect that may have resulted from maternal exposure or transmission of the study drug via semen following paternal exposure.

A congenital anomaly or birth defect should be promptly reported as a SAE per Sections 9.5.7 and 9.5.8.

Investigators should advise all subjects to use a highly effective method of birth control to protect the health and safety of the mother and/or child. Investigators should report the pregnancy of a subject or a subject's partner to their IRB/IEC per IRB/IEC guidelines. In addition, Investigators should follow IRB/IEC guidelines for consenting pregnant partners of study subjects in order to obtain pregnancy follow up information.

9.5.6 Post-treatment Adverse Events

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted. AEs that are related to ADI-PEG 20 should be followed until resolution or deemed stable by the investigator. All events that are ongoing at this time will be recorded as ongoing on the eCRF. Serious adverse events will follow the SAE procedures specified.

9.5.7 Serious Adverse Events

Subjects will be monitored throughout the study for SAEs.

An SAE is any untoward medical occurrence that at any dose:

1. Results in death,
2. Is life-threatening*,
3. Requires inpatient hospitalization or prolongation of existing hospitalization**,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly/birth defect,
6. Is another medically important condition***.

*The term "life-threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

**The following are not considered SAEs in this Polaris sponsored clinical study:

- A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered "important medical event" or event life-threatening).
- Elective surgery, planned prior to signing study consent.
- Medical/surgical hospital admission for purpose other than remedying an ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Routine health assessment requiring hospital admission for baseline/trending of health status (e.g., routine colonoscopy).
- Hospital admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

- Hospital admission or other medical occurrences (such as prolonged hospitalization or death) for adverse events due to the malignant disease under study (including associated signs and symptoms of disease progression). Changes in disease are reported separately.
- Hospital admission for study biopsies.

***Medically important conditions that may not result in death, be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Note: The term "severe" is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject's life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed is the applicable product information, and meets one of the above listed serious criteria.

9.5.8 Reporting Serious Adverse Events

Any Serious Event that is reported or observed that occurs from the time that the subject has signed informed consent form until 30 days after the final dose of study treatment regardless of the severity of the event or its relationship to study treatment must be reported to the Polaris designee within 24 hours of the study site staff becoming aware of the event. Thereafter, serious events should only be reported if the Investigator considers it possibly related or related to study treatment.

A report must be submitted to the Polaris designee regardless of the following:

- whether or not the subject has undergone study-related procedures
- whether or not subject has received study treatment
- the severity of the event
- the relationship of the event to study treatment

A serious pre-treatment event is any event that occurs post ICF and prior to first administration of study treatment that meets the criteria for SAE. A serious pre-treatment event should be recorded as medical history and the study site needs to contact Polaris designee within 24 hours of site study becoming aware of serious pre-treatment event.

All initial and follow-up information pertaining to SAEs must be forwarded to Polaris designee within 24 hours of study site staff becoming aware of serious adverse event. SAEs will be reported

using either paper or electronic forms and the sites will be provided with instructions at the time of study initiation.

SAE Reporting guidelines will be provided to the investigational site to assist in collecting, organizing, and reporting SAEs and follow-up information.

All SAEs should be followed to their resolution, with all SAE related documentation such as doctor's notes, hospital discharge summary, etc. provided to Polaris designee in a timely manner.

SAEs will be reported to all applicable Regulatory Authorities as noted in 21 CFR 312.32(c).

The Sponsor will also comply with responsibilities and requirements concerning SAE/SUSAR reporting established in the European Directive 2001/20/EC.

9.6 Appropriateness of Safety Assessments

Safety evaluations selected for this study are typical of those for this subject population and utilize widely accepted measures.

10 PHARMACODYNAMIC, PHARMACOKINETIC, IMMUNOGENICITY AND OTHER ASSESSMENTS

10.1 Pharmacodynamic Parameters

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.

Pharmacodynamics will be assessed by measurement of peripheral blood levels of arginine and citrulline by LCMS.

10.2 Immunogenicity Parameters

Immunogenicity will be assessed for all patients from the ADIPemCis arm by measurement of peripheral blood antibodies to ADI-PEG 20. Blood will also be available for testing for anti-PEG antibodies.

10.3 Pharmacokinetics

Pharmacokinetics will also be determined for all patients from the ADIPemCis arm.

10.4 Exploratory Research

Additional translational research, including pharmacogenomics and profiling the inflammatory and metabolomic effects of ADI-PEG 20 in combination with pemetrexed and cisplatin is now planned. This research will be conducted on existing plasma samples from subjects in the US and UK who

have consented to their blood samples being used in future research. Also, research will be conducted on archival tissue from subjects at selected sites in the UK who have consented to their tissue samples being used in future research.

11 STATISTICAL CONSIDERATIONS

Detailed procedures for statistical analyses to be performed for this study will be provided in a separate Statistical Analysis Plan that will be finalized prior to the final database lock. Any changes to the protocol-specified or SAP-specified planned analyses that are made after the database lock will be described in the clinical study report.

This study will employ an adaptive design with two interim analyses to be conducted at the end of the Phase 2 portion and when 50% of planned OS events for phase 3 have occurred. These two interim analyses will be performed by an Independent Analysis Group. The decision rules and analysis strategies that will be applied at the interim and final analyses are described in the SAP.

11.1 Statistics and Sample Size Considerations

The sample size calculation for the efficacy 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 approximately 87% power to detect an improvement in the RR from 15% to 35% at the interim analysis.

The sample size calculation for the phase-3 primary endpoint (OS) assumed that the median OS was 6 months in the PlaceboPemCis arm. Assuming a median OS of 8.4 months in the ADIPemCis 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 patients.

11.2 Analysis Populations

The following patient populations will be used in the analysis of efficacy and safety data:

The Intent-to-Treat (ITT) population will contain all randomized patients. All analyses using the ITT population will group patients according to the randomized treatment, regardless of the treatment received during the course of the study. The ITT population will be used in the analysis of the efficacy endpoints.

The Per-Protocol (PP) population will include 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. The major protocol deviation criteria will be specified in the SAP and finalized as part of the blinded data review prior to the final database lock. Assignment of subjects to treatment group is based on the randomized treatment assignment.

The Safety Analysis (SA) population will contain all patients who received at least one dose of the study medication. All analyses using the SA population will group patients according to the treatment actually received. All safety analyses will be based on this population.

11.3 Demographics and Baseline Characteristics

The number of patients who have been randomized, have received at least one dose of the study medication and have completed the clinical trial according to the protocol will be summarized. The number of patients that discontinue the treatment or the study, as well as the reasons for discontinuation, will be summarized. In addition, summary tables with descriptive statistics will be generated for demographics, baseline characteristics and relevant disease characteristics and history by the treatment arm in the ITT population.

11.4 Safety Analysis

11.4.1 Adverse Events

Adverse events will be graded using the NCI CTCAE (version 4.03), which provides a mechanism for grading the severity of the adverse event. Treatment Emergent Adverse Events (TEAEs) include all adverse events that start on or after the first dose of study medication, or adverse events that are present prior to the first dose of study medication, but their severity or relationship increases after the first dose of study medication up to and including 30 days after the final study medication dosing date.

The number and percent of subjects with any TEAEs will be displayed by system organ class and preferred term for each treatment group. Within each preferred term, subjects will be counted only once if they had more than one event reported during the treatment period. The same summary will be performed for all serious TEAEs and all TEAEs causing discontinuation of study drug.

TEAEs will also be summarized by greatest reported severity grade (Grades 1-5) for each event preferred term. Counts indicate subjects reporting one or more TEAEs that map to the severity grade classification for each preferred term. At each level of summarization (system organ class or event preferred term) subjects are only counted once. TEAEs will be summarized by greatest reported relationship in a similar manner.

A listing will be produced for all subjects who reported serious TEAEs or who discontinued study medication due to TEAEs.

All TEAEs will be listed individually by subject.

Formal toxicity monitoring will occur, as described in Section 9, Safety Assessments. Laboratory tests, ECGs, vital sign measurements, physical exams and patient interviews will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. All clinically significant abnormalities and deteriorations should be recorded in the Case Report Forms as Adverse Events and graded according to the NCI CTCAE v4.03. All subjects who received at least one dose of

ADI-PEG 20 will be evaluated for safety and tolerability. Appropriate summaries of AEs, and laboratory data. AEs will be listed individually per patient according to CTCAE version 4.03, and the number of patients experiencing each AE will be summarized using descriptive statistics.

11.5 Efficacy Analysis

11.5.1 Primary Efficacy Endpoints

The number and percent of patients responding, measured by modified RECIST for MPM and RECIST 1.1 criteria, as applicable, will be summarized by treatment group. The analysis of RR will be conducted at the end of the phase 2 portion, after adequate response assessment of the first176 subjects enrolled. The treatment groups will be compared using the Cochran-Mantel-Haenszel (CMH) test, stratified by tumor histology (biphasic versus sarcomatoid). 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 of OS will be performed at the final analysis. The treatment effect on OS will be evaluated using the stratified log-rank test (stratified by tumor histology). The significance levels to be used in the OS analysis at the final analyses will be based on α=0.05 (two-sided).

11.5.2 Key Secondary Efficacy Endpoints

The key secondary objective of the phase 2 portion (DOR) will be analyzed at the end of the phase 2 portion.

The key secondary endpoint for the phase 3 portion 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.

11.6 Multiplicity Adjustment

Details are described in the SAP.

11.7 Interim Analysis

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 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.

The decision-making rules associated with these decisions are described in the SAP.

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.

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 patients may be adjusted in a blinded manner to achieve the desired number of OS events. This will be accomplished using standard event forecasting methods (see, for example, Anisimov 2011).

11.8 **Pharmacodynamics**

Blood levels of arginine and citrulline will be summarized descriptively for each group and for all subjects by time point for the observed value.

11.9 **Immunogenicity**

Blood levels of antibodies to ADI-PEG 20 will be summarized descriptively for each treatment group and for all subjects by time point for the observed value as well as for the change from baseline value.

11.10 **Pharmacokinetics**

Pharmacokinetics will also be summarized descriptively for each group and for all subjects by time by time point for the observed value.

12 ETHICS

12.1 **Institutional Review Board / Independent Ethics Committee**

The investigator will ensure that the protocol and consent form are reviewed and approved by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) prior to the start of any study procedures. The IRB/IEC will be appropriately constituted and will perform its functions in accordance with Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) good clinical practice (GCP) guidelines, and applicable local regulatory requirements as applicable.

In addition, the IRB/IEC will approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB/IEC and regulatory authority as applicable.

12.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Declaration of Helsinki and GCP according to ICH guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by an IRB or IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

12.3 Informed Consent

The nature and purpose of the study will be fully explained to each subject. Written informed consent must be obtained from each subject prior to any study procedures being performed. The consent documents to be used for the study will include all the required elements of informed consent per regulatory requirements and will be reviewed and approved by the appropriate IRB/IEC before use.

12.4 Changes to Protocol

Only Polaris may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between Polaris and the investigator. The only exception is when the investigator assesses a subject's safety will be compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC must be sought, and the investigator should inform Polaris and the full IRB/IEC within 5 working days after the emergency occurred. All amendments that have a significant impact on subject risk or the study objectives, or require revision of the informed consent forms, must receive approval from the IRB/IEC prior to their implementation.

13 STUDY MONITORING

13.1 Data Reporting and Electronic Case Report Forms

The investigator will permit the site monitor to review study data as frequently as is deemed necessary to ensure data is being recorded in an adequate manner and protocol adherence is satisfactory. The investigator will access medical records for the monitor to verify eCRF entries. The investigator, as part of his or her responsibilities, is expected to cooperate with the Sponsor/designee in ensuring the study adheres to GCP requirements. The investigator may not

recruit subjects into the study until an initial visit, or, with the agreement of Sponsor, attendance at a site initiation visit has been made by the Sponsor/designee to conduct a detailed review of the protocol and eCRFs.

13.1.1 Pre-Study Requirements

The following is required before study drug can be shipped to the study site:

- Signed Statement of Investigator
- Regulatory Approval (e.g., active IND or IMPD)
- Ethics Committee approval of Protocol and Informed Consent Forms
- Executed Clinical Trial Agreement (if applicable)

13.1.2 Study Master Files

The Investigator must retain a Sponsor-specified comprehensive and centralized filing system ("Study Master File") of all study-related documentation that is suitable for inspection by Polaris and regulatory authorities. Upon completion of the study, the Investigator is required to submit a summary report to Sponsor at the discretion of the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time determined by Sponsor. No part of the Study Master File shall be destroyed or relocated without prior written agreement between Sponsor and the Investigator.

13.1.3 Study Records

The study documents must be maintained as specified in the ICH guidelines for GCP and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Sponsor. It is the responsibility of Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

13.1.4 Electronic Case Report Forms (eCRFs)

An electronic data capture system will be used for this trial. Instructional materials will be provided to the sites as appropriate. The investigator and site staff will ensure all data from subject visits are promptly entered into the electronic Case Report Forms (eCRFs) in accordance with study specific eCRF completion guidelines. The investigator must approve the eCRFs within the electronic system to verify the integrity of the data recorded.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to trial start. If a central laboratory has been selected to conduct any or all tests, it is essential all samples be analyzed at that laboratory. The investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

13.2 **Access to Source Data/Documents**

The investigator will provide direct access to source data and documents to individuals conducting study-related monitoring, audits, IRB/IEC review, and regulatory review. The investigator must inform the study subject that his/her study-related records may be reviewed by the above individuals without violating the subject's privacy of personal health information.

13.3 **Confidentiality**

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and IRBs/IECs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IRB/IEC. By signing this protocol, the investigator affirms to Sponsor that the investigator will maintain, in confidence, information furnished to him by Sponsor and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

13.4 **Retention of Data**

All records and documents pertaining to the study will be maintained by the investigator for a period of: (a) 2 years after approval of the drug; (b) 5 years after non-approval of the NDA or ANDA; or (c) 2 years after withdrawal of the IND under which this study was conducted. In order to avoid any possible errors, the investigator will contact Sponsor prior to the destruction of any study records. The investigator will promptly notify Sponsor in the event of accidental loss or destruction of any study records.

13.5 **Quality Control and Quality Assurance**

Sponsor/designee will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with the FDA Code of Federal Regulations (CFR §312.50 and §312.56) and the ICH (E6) Guidelines on GCP (CPMP/ICH/135/95and the provisions of the EU Clinical Trial Directives 2001/20/EC and 2002/20/EC.

14 ADMINISTRATIVE INFORMATION

14.1 **Financing and Insurance**

These issues will be addressed in a separate agreement between Sponsor and the investigator.

14.2 **Publication Policy**

Sponsor will retain ownership of all data. All proposed publications based on this study will be subject to Polaris's approval requirements.

Any and all data and results and intellectual property rights in the data and results derived from this study are the property of Sponsor. Sponsor may utilize the data in a variety of ways, including but not limited to submission to government regulatory agencies/authorities or disclosure to other investigators. An investigator in this study, while free to utilize data derived from the study for scientific purposes, must discuss any publication with Sponsor prior to release and obtain written consent of Sponsor on and for the intended publication. Sponsor recognizes the right of the investigators to publish the results upon the completion of the study. However, the investigator(s) must send a draft manuscript of the intended publication or abstract to Sponsor thirty (30) days in advance of submission in order to obtain the approval of Sponsor prior to submission of the final version for intended publication. This draft will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Sponsor and the investigator(s), the contents of the draft will be discussed in order to find a solution which satisfies both parties.

14.3 **Protocol Amendments**

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, IRB/IEC and, if required, the regulatory authorities. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to such approvals. However, in this case, approval must be obtained as soon as possible after implementation. Implementation of administrative amendments that do not affect the safety of the subjects do usually not require prior IRB/IEC approval, just notification, unless otherwise required by local ethics committees.

14.4 **Premature Trial Termination**

Sponsor and Investigator have the right to prematurely terminate the study. In such case, one party must notify the other in advance in writing about the intent of and the reasons for the termination. The investigator must also notify the appropriate IRB/IEC accordingly.

14.5 **Language**

The protocol is written in English. All correspondence between the study site and Sponsor should be maintained in English. Case Report Forms must be completed in English. All written material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

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16 APPENDIX A: MODIFIED RECIST CRITERIA FOR MALIGNANT PLEURAL MESOTHELIOMA

Tumour thickness perpendicular to the chest wall or mediastinum was measured in two positions at three separate levels on transverse cuts of CT scan. The sum of the six measurements defined a pleural unidimensional measure. Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax were chosen to allow reproducible assessment at later time points. If measureable tumour was present, transverse cuts in the upper thorax, above the level of division of the main bronchi were preferred. At reassessment, pleural thickness was measured at the same position at the same level and by the same observer. This was not necessarily the greatest tumour thickness at that level. Nodal, subcutaneous and other bidimensionally measurable lesions were measured unidimensionally as per the RECIST criteria. Unidimensional measurements were added to obtain the total tumour measurement.

Response Criteria	**Definition**
CR	disappearance of all target lesions with no evidence of tumour elsewhere
PR	at least a 30% reduction from baseline in the total tumour measurement
PD	an increase of at least 20% in the total tumour 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

A confirmed response required a repeat observation on two occasions 4 weeks apart.
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A practical guide to modified RECIST for MPM also has been published: Tsao AS, Garland L, Redman M, Kernstine K, Gandara D, Marom EM. 2011. A practical guide of the Southwest Oncology Group to measure malignant pleural mesothelioma tumors by RECIST and modified RECIST criteria. J Thorac Oncol 6:598-601.

17 APPENDIX B: RECIST 1.1 CRITERIA

Category	RECIST 1.1
Minimum size measurable lesions	• CT 10 mm; delete reference to spiral scan • Clinical: 10 mm (must be measurable with calipers) Lymph Node • CT: ≥15 mm short axis for target ≥10–<15 mm for non-target <10 mm is non-pathological
Special considerations on lesion measurability	Notes included on bone lesions, cystic lesions
Overall tumor burden	5 lesions (2 per organ)
Response criteria target disease	• CR lymph nodes must be <10 mm short axis • PR at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters • PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions
Response criteria non-target disease	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase
New lesions	New section on New lesions
Overall response	• Two tables: one integrating target and non-target and the other of non-target only • Special notes: -How to assess and measure lymph nodes -CR in face of residual tissue -Discussion of 'equivocal' progression
Confirmatory measure	Retain this requirement ONLY for non-randomized trials with primary endpoint of response
Progression-free survival	-More specific comments on use of PFS (or proportion progression-free) as phase II endpoint -Greater detail on PFS assessment in phase III trials
Reporting of response results	-Divided into phase II and phase III -9 categories collapsed into 5 -In phase III, guidance given about reporting response
Response in phase III trials	This section removed and referenced in section above: no need to have different criteria for phase II and III

Imaging appendix	- Appendix II: updated with detailed guidance on use of MRI, PET/CT (Note that for this study, non-CT/MRI scanning are not required and but may be completed as standard of care) - Other practical guidance included
New appendices	- Appendix I: comparison of RECIST 1.0 and 1.1 - Appendix III: frequently asked questions

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1 in E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). EUROPEAN JOURNAL OF CANCER 45 (2009) 228-247.

Response Evaluation Criteria in Solid Tumors - Quick Reference

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease is defined by the presence of at least one measurable lesion.

In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are eligible.

Measurement of Tumors at Baseline: Measurable vs. Non-Measurable Lesions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

Tumor lesions: measure at least longest diameter with a minimum size of:
10 mm using CT scan (CT scan thickness no greater than 5 mm), or
10 mm caliper measurements on clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable, or

20 mm by chest x-ray

Malignant lymph nodes: measure at short axis with a minimum size of ≥ 15 mm

Non-measurable lesions - all other lesions, including small lesions (longest diameter <10 mm) or pathological lymph nodes with ≥ 10 to ≤ 15 mm (short axis). Lesions considered truly non-measureable: leptomeningeal disease, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and also abdominal masses/organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

Special considerations

Bone lesions

Bone scan, PET scan or plain films are not considered adequate imaging techniques, however, these lesions can be used to confirm the presence or disappearance of bone lesions

Cystic lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions

"Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they met the definition of measurability described above

Lesions with prior local treatment

Lesions in a previously irradiated area or in an area subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the area

Measurement of Lesions

- All measurements should be taken and recorded in metric notation, using calipers if clinically assessed.
- All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Methods of Measurement

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

CT and MRI – CT is the best currently available and reproducible methods to measure target lesions selected for response assessment. CT should be performed with cuts of 5 mm or less in slice thickness contiguously. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations.

Chest x-ray – chest CT is preferred over chest x-ray. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Ultrasound – is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, laparoscopy – utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers – *alone* cannot be used to assess *objective* tumor response. If markers are initially above the upper limit of normal, however, they must normalize for a patient to be considered in complete response.

Cytology, histology – can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors where know residual benign disease can remain). When effusions are known to be potential adverse effect of treatment (e.g., with certain taxanes or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

Baseline Documentation of "Target" and "Non-Target" Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and lend themselves to reproducible repeated measurements.

Lymph nodes are normal anatomic structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes are defined as measurable and may be identified as target lesions if the short axis is $\geq$ 15 mm.

A sum of the diameters (longest diameter [LD] for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize any objective tumor regression.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions:

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

Special notes on assessment of target lesions:

- Lymph nodes
- The short axis should be measured. Thus, the "sum" of lesions may not be zero even if CR response criteria are met, since a normal lymph node is defined as having a short axis < 10 mm.
- Target lesions that have become "too small to measure"
- A number should be recorded. If, in the opinion of the radiologist, that the lesion has disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (5 mm is derived from the 5 mm CT slice thickness).
- Lesions that split or coalesce
- The longest diameters of the fragmented portions should be added together to calculate the target lesion sum. If the lesions have truly coalesced, the vector of the longest diameter should be the maximal longest diameter for the "coalesced lesion."

Evaluation of non-target lesions:

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

- When the patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression.
- When the patient has only non-measureable disease, the same general concepts apply.

New Lesions

The appearance of new malignant lesions denotes progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions).

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease.

It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). FDG-PET scanning is not specifically required by the protocol but may be considered as part of standard of care. New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline with a positive ("positive" FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image) FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow up:
    i) If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
    ii) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET).
    iii) If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

- The best overall response is the best response recorded from the start of the treatment until the end of treatment taking into account any requirement for confirmation.
- When no imaging/measurement is done at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is considered NE at that time point, unless a convincing argument can be made that the contribution of the missing lesion(s) would not change the assigned time point 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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status. FDG-PET may be used to upgrade a lesion to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Confirmation

In non-randomized studies where response is the primary end-point, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. In randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results.

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial therapy is not known, follow-up every 6-8 weeks (timed to coincide with the end of a cycle) is

reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances.

At the end of treatment, the need for repetitive tumor evaluations depends on whether the trial has a goal the response rate or the time to an event (progression/death). If "time to an event" (e.g., time to progression, disease-free survival, progression-free survival) is the main endpoint, then routine scheduled re-evaluation of protocol specified sites of disease is warranted.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded on study.

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

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for disease progression are met, taking as reference the smallest sum on study measurements recorded since the treatment started.

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval requited between two measurements for determination of SD.

Progression-Free Survival/Proportion Progression-Free

Phase II trials

- In some circumstances, "response rate" may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases "progression-free survival" (PFS) or the "proportion progression-free" at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilizing these endpoints are best designed with randomized control.

Phase III trials

- Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to

criticism: it may result in a trial where the results are less likely to be generalizable if, in the disease under study, a substantial proportion of patients would be excluded.

Response Review

For trials were objective response (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiographical images is the best approach.

Reporting of Results

Phase II Trials

- When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or they are not evaluable. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) unevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumor assessments not repeated/incomplete; other [specify]). Normally, all eligible patients should be included in the denominator for the calculation of the response rate for phase ii trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate.
- Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should not be based on a selected "evaluable" subset.

Phase III trials

- Response evaluation in phase III trials may be an indicator of the relative anti-tumor activity of the treatments evaluated and is almost always a secondary endpoint. Observed differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied.

18 APPENDIX C: PERFORMANCE STATUS PERFORMANCE SCALES (KARNOFSKY, ECOG-WHO-ZUBROD)

These scales are used by practicing oncologists and researchers to assess how a patient's disease is progressing, to assess how the disease affects the daily life, and to determine appropriate treatment and prognosis.

Status	Karnofsky	Grade	ECOG
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

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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 Principals 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 α=0.00001 will be paid for second interim analysis, and the allocated α=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^2 (or placebo) will be combined with pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 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^2 (or placebo) will be administered weekly by intramuscular (IM) injection. Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 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

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 *unequivocal progression* 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

Hematology (CBC)	Serum Chemistry
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Absolute Neutrophil Count (ANC) Lymphocytes (Absolute values) Monocytes (Absolute values) Basophils (Absolute values) Eosinophils (Absolute values) Platelet count (estimate not acceptable)	Albumin Alkaline phosphatase Blood urea nitrogen (BUN) Calcium Chloride Creatinine Glucose (non-fasting) HCG (at screening only) Potassium 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 (± 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 (± 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: $QTcF = QT/R\text{-}R^{0.33}$.

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 ≤10 μM and citrulline increase will be defined as increase from baseline ≥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 α=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, 25th and 75th 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 α=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 α=0.00001 will be paid for this interim analysis, and the allocated α=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 α=0.00001 will be paid for second interim analysis, and the allocated α=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 ≥ 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 ≥ Grade 3 TEAEs related to ADI-PEG 20/Placebo by MedDRA system organ class and preferred term;
- Subject incidence of ≥ Grade 3 TEAEs related to Pemetrexed by MedDRA system organ class and preferred term;
- Subject incidence of ≥ 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.

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