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)

Indication Studied:	Unresectable malignant pleural mesothelioma (MPM)
Developmental Phase of Study:	Phase 2/3
First Subject Randomized:	01Aug2017
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Company/Sponsor Signatory: John S. Bomalaski, MD
Executive Vice-President,
Medical Affairs
Polaris Group
10675 Sorrento Valley Road,
Suite 200
San Diego, CA 92121 US
Phone: (858) 452-6688

2. SYNOPSIS

The synopsis is provided in a separate document.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialized terms are used in this CSR.

Table 1: Abbreviations and Specialized Terms

Abbreviation or Specialized Term	Explanation
$5HT_3$	5-hydroxytryptamine (also known as serotonin)
Abs	Antibodies
ADA	Anti-drug antibody
ADI	Arginine deiminase
ADI-PEG 20	ADI-PEG with PEG of 20,000 mw via a succinimidyl succinate linker
ADIPemPlatinum	Treatment arm in which weekly ADI-PEG 20 was combined with pemetrexed and a platinum agent, both given every 3 weeks
AE	Adverse event
ALL	Acute lymphocytic leukemia
ALT	Alanine transaminase (also known as SGPT)
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
ANDA	Abbreviated New Drug Application
ASL	Argininosuccinate lyase
ASS1	Argininosuccinate synthetase (also known as ASS)
AST	Aspartate transaminase (also known as SGOT)
ATC	Anatomic Therapeutic Chemical
AUC	Area under the plasma concentration–time curve
BA	Bioavailability
bd	Twice daily (bis in die)
BE	Bioequivalence
BICR	Blinded independent central review
BQL	Below quantification limit
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle
CA	California
CBC	Complete blood count

Abbreviation or Specialized Term	Explanation
CCP	Confirmation cut-point
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CP	Conditional power
CPMP	Committee for Proprietary Medicinal Products
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
D	Day
DCR	Disease control rate
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECL	Electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
E. coli	Escherichia coli
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunoassay
EOT	End of Treatment
ESMO	European Society of Medical Oncology
EU	European Union
FDA	US Food and Drug Administration
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin
GCP	Good Clinical Practice
GMCSF	Granulocyte-macrophage colony-stimulating factor
HB	Hemoglobin
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin

Abbreviation or Specialized Term	Explanation
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous(ly)
IWRS	Interactive Web Response System
KS	Kansas
LCMS	Liquid chromatography mass spectrometry
LLOQ	Lower limit of quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
M. hominis	Mycoplasma hominis
MHRA	Medicines and Healthcare Products Regulatory Agency
Min	Minimum
MPM	Malignant pleural mesothelioma
MRD	Minimum required dilution
MRI	Magnetic resonance imaging
N	Population sample size
n	Number of subjects with available data
NA	Not applicable
NC	North Carolina
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NSCLC	Non-small cell lung carcinoma
NSW	New South Wales

Abbreviation or Specialized Term	Explanation
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PEG	Polyethylene glycol
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic(s)
PlaceboPemPlatinum	Treatment arm in which weekly placebo (volume matched to ADI-PEG 20) was combined with pemetrexed and a platinum agent, both given every 3 weeks
PP	Per-Protocol
PR	Partial response
PSCP	Plate specific cut-point
Q1	Quartile 1
Q3	Quartile 3
QTcF	QT corrected using Fridericia's correction formula
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROC	Republic of China
RR	Response rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (software)
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SI	Système International
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TMF	Trial Master File
TX	Texas
UK	United Kingdom

Abbreviation or Specialized Term	Explanation
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
US	United States
WBC	White blood cell
WHO	World Health Organization

5. ETHICS

5.1. Independent Ethics Committee or Institutional Review Board

The Investigator was to ensure that the protocol and consent form were reviewed and approved by the appropriate IRB/IEC prior to the start of any protocol-specific screening procedures. The IRB/IEC was appropriately constituted and performed its functions in accordance with FDA regulations, ICH GCP guidelines, and applicable local regulatory requirements, as applicable.

In addition, the IRB/IEC approved 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.

Only Polaris was allowed to modify the protocol. Amendments to the protocol were made only after consultation and agreement between Polaris and the Investigator. The only exception was to be if the Investigator assessed a subject's safety would be compromised without immediate action; however, this did not occur during the study. All amendments that had a significant impact on subject risk or the study objectives, or required revision of the ICFs, had to receive approval from the IRB/IEC prior to their implementation.

The IRB/IECs are listed in Appendix 16.1.3.

5.2. Ethical Conduct of the Study

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

5.3. Subject Information and Consent

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

A sample ICF is included in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Study Sponsor was Polaris Group (San Diego, CA, US). A list of all investigators is provided in Appendix 16.1.4. The signatures of the lead investigator and Sponsor's responsible medical officer are provided in Appendix 16.1.5.

Additional organizations involved in the conduct of the study are listed below.

Function	**Organization**
Sponsor:	Polaris Group 10675 Sorrento Valley Road, Suite 200 San Diego, CA 92121 US
Lead Investigator and Lead Clinical Study Center:	Peter Szlosarek, MD PhD Centre for Experimental Cancer Medicine Barts Cancer Institute Queen Mary University of London Lower Ground Floor Old Anatomy Building Charterhouse Square London, EC1M 6BQ, UK Telephone: 020 7882 3559 Fax: 020 7882 8490 Email: p.w.szlosarek@qmul.ac.uk
Study Monitoring:	Polaris Group 10675 Sorrento Valley Road, Suite 200 San Diego, CA 92121 US Chiltern 4000 Centre Green Way Suite 300 Cary, NC 27513 US Karma Oncology De Cuserstraat 93 1081 Cn. Amsterdam, The Netherlands Novotech Novotech (Australia) Pty Ltd Level 3, 235 Pyrmont Street Pyrmont, Sydney, NSW 2009 Australia

Function	Organization
Clinical Laboratory:	Clinical Reference Laboratory 8433 Quivira Road Lenexa, KS 66215 US Icon Laboratory Services South County Business Park Leopardstown Dublin 18, Ireland
Pharmacodynamic, Immunogenicity, and PK Analytical Laboratory:	Covance/LabCorp Building #9, No. 338 Galileo (Jialilue) Road Zhangjiang Hi-Tech Park, Pudong, Shanghai 201203 China
Diagnostic Imaging Review:	Icon Imaging South County Business Park Leopardstown Dublin 18 Ireland
Data Management, Biostatistics, CSR Authoring, and Pharmacovigilance and Regulatory Submission Collaboration:	Precision for Medicine, Oncology and Rare Disease (Previously Agility Clinical, Inc.) 6005 Hidden Valley Road, Suite 170 Carlsbad, CA 92011, US
Drug and Clinical Supply Depots:	Zuellig Pharma (Taiwan sites) No. 91, Kaihe Rd., Heping Village 1st Neighborhood Dayuan District, Taoyuan City 33742, Taiwan ROC Catalent (UK and Italy sites) Lancaster Way, Wingates Industrial Estate Westhoughton, Bolton, Lancashire, BL5 3XX, UK 1 Inchwood Park, Bathgate West Lothian EH48 2FY, UK Design RX (part of Polaris group) (US and Australia sites) 4941 Allison Parkway, Suite B Vacaville, CA 95688 US

7. INTRODUCTION

Mesotheliomas are neoplasms arising from mesothelial cells lining the pleura, peritoneum, tunica vaginalis testis and pericardium (Kao 2010, Mirarabshahii 2012). Approximately 80 to 85% are MPM, 15 to 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).

Malignant mesothelioma has three histologic subtypes, epithelioid, sarcomatoid, and biphasic. Recent studies confirm a poor prognosis for nonepithelioid MPM. For details on these studies and the prognosis for each of the histologic subtypes of mesothelioma, see Section 2.1.1.1 of the protocol (Appendix 16.1.1).

The recommended treatment for MPM 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). At the time this study started enrollment, NCCN guidelines (Mesothelioma NCCN 2015) recommended chemotherapy alone for all patients who have sarcomatoid histology, as well as for inoperable or clinical stage IV patients. Similar recommendations came from the ESMO (Baas 2015). This underscores the poor prognosis for sarcomatoid patients.

At the time this study started enrollment, the standard first-line chemotherapy treatment for MPM was pemetrexed + cisplatin (Fennell 2008, Mirarabshahii 2012, Turner 2012, Kotova 2015). For details on the clinical studies supporting the rational for this first-line therapy, see Section 2.1.1.2 of the protocol (Appendix 16.1.1).

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. A variety of studies enriched for the epithelial subset consistently show an ORR of ~ 20% to 25% by investigator assessment, in contrast to the 41% ORR by investigator assessment observed in the pivotal study that led to the approval of pemetrexed and cisplatin (Vogelzang 2003). Thus, it is 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).

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 PEG conjugate, peg-asparaginase) in 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).

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 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 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. For details on arginine auxotrophy in cancer cells, see Section 2.1.3 of the protocol (Appendix 16.1.1).

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 PEG (Takaku 1992 and 1993, Holtsberg 2002). The PEG conjugates were prepared to enhance *in vivo* stability, to increase the circulating half-life, and to decrease the immunogenicity of the recombinant Mycoplasma enzyme. It was determined that synthesis of ADI-PEG 20 (pegargiminase) 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 US, 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 and a randomized phase 2 in subjects with MPM (Ascierto 2005, Savaraj 2007, Feun 2008 and 2012, Ott 2013, Szlosarek 2017). These studies demonstrated medical benefit.

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, Allen 2014, 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 has been completed with cisplatin at the MD Anderson Cancer Center (TX, 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). Furthermore, ADI-PEG 20 has been investigated as part of triplet drug regimens, including with cisplatin and pemetrexed in the context of thoracic cancers. High rates of disease control and acceptable safety were demonstrated for ADI-PEG 20 plus pemetrexed and cisplatin in subjects with MPM and non-squamous non-small cell lung cancer (Beddowes 2017, Szlosarek 2020 and 2021). ADI-PEG 20 is currently being investigated in multiple clinical trials. Additionally, patients with metastatic uveal melanoma appeared to

benefit with a significant prolongation of PFS (Ott 2013). Further information is available on these trials at ClinicalTrials.gov. See Section 2.1.6, Section 2.1.7, Section 2.1.8, Section 2.1.9, Section 2.1.10, and Section 2.3 of the protocol (Appendix 16.1.1) for details. Taken together, 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).

The present study was a randomized, double-blind, multi-center, phase 2/3 trial of ADI-PEG 20 in combination with pemetrexed and a platinum agent in subjects with unresectable MPM of sarcomatoid or biphasic histologies that aims to determine the efficacy of ADI-PEG 20 in combination with pemetrexed and a platinum agent as determined by RR and OS. Secondary objectives included determining the DOR in the phase 2 portion of the study and PFS in the phase 3 portion of the study and assessing safety and tolerability, pharmacodynamics, immunogenicity, and PK in both portions. After the second interim analysis, the DSMB recommended stopping enrollment for this study due to positive results and because of slow study enrollment related to an evolving treatment landscape for MPM and the COVID-19 pandemic. This strategy was discussed with the FDA. Enrollment was subsequently stopped in August 2021 and follow up was continued until August 2022.

8. STUDY OBJECTIVES

8.1. Objectives and Endpoints

8.1.1. Objectives

8.1.1.1. Primary Objective

The primary objective of this study was:

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

8.1.1.2. Secondary Objectives

The key secondary objective of the phase 2 portion was:

- To determine the DOR

The key secondary objective of the phase 3 portion was:

- To assess PFS

Other secondary objectives of this study were:

- To assess safety and tolerability of ADI-PEG 20 in combination with pemetrexed and cisplatin
- To determine the pharmacodynamics of ADI-PEG 20 in combination with pemetrexed and cisplatin
- To determine the immunogenicity of ADI-PEG 20 in combination with pemetrexed and cisplatin
- To determine the PK of ADI-PEG 20 in combination with pemetrexed and cisplatin

(Note: The protocol was amended to allow subjects to start on carboplatin without first starting on cisplatin; see Appendix 16.1.1.)

Objectives were 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 was to provide data to support accelerated approval by the FDA, and the goal of the phase 3 portion of the trial was to provide a confirmatory study that would be ongoing at the time of the marketing application.

8.1.2. Endpoints

8.1.2.1. Primary Endpoints

8.1.2.1.1. Primary Efficacy Endpoints

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

- Objective RR: calculated as the proportion of subjects whose best tumor response from all post-baseline tumor assessments was CR or PR.

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

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

8.1.2.2. Secondary Endpoints

8.1.2.2.1. Secondary Efficacy Endpoints

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

- DOR: calculated for subjects who had 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 EOT were 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 was:

- PFS: calculated as the time from randomization until date of tumor progression or death. In the event that no tumor progression or death was documented prior to EOT, analysis cutoff, or the start of confounding anticancer therapy, PFS was to be censored at the date of the last tumor assessment demonstrating no tumor progression.

8.1.2.2.2. Safety Endpoints

Safety endpoints included AEs, laboratory tests, ECGs, vital signs, physical examinations, and subject interviews to review possible AEs with the subject.

8.1.2.2.3. Pharmacodynamic Endpoints

Pharmacodynamic endpoints included peripheral blood (plasma) levels of arginine and citrulline by LCMS.

8.1.2.2.4. Immunogenicity Endpoint

The immunogenicity endpoint was the peripheral blood (plasma) antibodies to ADI-PEG 20. Blood was also available for testing for anti-PEG antibodies.

8.1.2.2.5. Pharmacokinetic Endpoint

The PK endpoint was ADI-PEG 20 plasma levels throughout the study.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

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

The starting doses represented 100% of the recommended doses of the platinum agent, pemetrexed, and ADI-PEG 20 as determined in the phase 1 trial (Beddowes 2017).

The duration of treatment was 18 weeks, with possible extension for responding or stable disease, and stopping for PD. The follow-up period continued for survival or until the end of the study in August 2022. After the second interim analysis, the DSMB recommended stopping enrollment for this study due to positive results and because of slow study enrollment related to an evolving treatment landscape for MPM and the COVID-19 pandemic. This strategy was discussed with the FDA. Enrollment was subsequently stopped in August 2021 and follow up was continued until August 2022.

The protocol and amendments are provided in Appendix 16.1.1, and detailed study procedures are provided in Section 6 of the protocol.

9.1.1. Continued Treatment after 6 Weeks of Treatment of ADIPemPlatinum

Tumor assessment imaging was 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 was to be used throughout the triplet treatment duration.

In the event of disease progression, the triplet chemotherapy was to be stopped and the subject offered an alternative treatment plan.

In the absence of disease progression requiring other therapeutic interventions, subjects may have received additional cycles of ADIPemPlatinum or PlaceboPemPlatinum treatment following the same procedures and schedule as Week 7 and onward for up to 18 weeks.

Subjects were allowed to continue to receive treatments unless one of the following occurred at any time during the course of therapy: (1) unacceptable AEs, (2) death, (3) PD, (4) significant noncompliance on the part of the subject, (5) refusal of the subject to continue treatment or observations, (6) decision by the Investigator that termination was in the subject's best medical interest, (7) unrelated medical illness or complication, or (8) lost to follow-up. Any subject with tumor and stable disease or PR was to continue treatment until progression, unless the Investigator determined a better option was available. Thus, subjects completing ADIPemPlatinum or PlaceboPemPlatinum were allowed to continue to receive ADI-PEG 20 or placebo treatment. Any subject with a CR was allowed to receive 4 more weekly treatments of ADI-PEG 20 or placebo. The maximum number of cycles of pemetrexed + platinum agent was 6 (18 weeks at every 3 weeks cycle).

9.1.2. Blinded and Open-Label Extension at Study End

Subjects ongoing at the study end (once the required number of events had been observed for the final analysis) were allowed to continue to receive study treatment until the study was unblinded. Once the study treatment assignments were known, the subjects receiving ADI-PEG 20 were allowed to continue to receive ADIPemPlatinum (or ADI-PEG 20 alone) until 1 of the following occurred: (1) unacceptable AEs, (2) death, (3) PD, or (4) decision by the Sponsor. Subjects receiving placebo were to be consulted regarding alternative treatment options. A local laboratory was allowed to be used instead of a central laboratory for the extension phase of the study.

Subjects wishing to continue study treatment followed the Blinded and Open-Label Extension Schedule of Events as shown in Table 5. Note: CT/MRI scans during the extension were standard of care in the opinion of the Investigator.

9.1.3. End of Treatment

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

9.1.4. Follow-up Period

The subject was to be contacted every 3 months post EOT assessment until study closure to determine survival status. In addition, a current survival status was required prior to the interim and final analysis. Any ongoing AEs related to ADI-PEG 20 when a subject stopped the study treatment were to be followed by the Investigator until the event resolved, stabilized, or returned to baseline status.

9.1.5. Criteria for Study Termination

The study could have been terminated at any time by the Sponsor for the following reasons:

1. The Investigator did not adhere to the protocol, ie, committed significant protocol violations,
2. In the Sponsor's judgment, there were no further benefits to be achieved from the study, or
3. The clinical development of the IP in this study was discontinued.

If this study was to be discontinued, the Sponsor was to inform all study investigators/institutions, the IRB/IEC, and regulatory authorities.

The Investigator and Sponsor had the right to close the study at any time; however, this was to occur only after consultation between the parties. If the study was to be closed, the IRB/IEC was to be informed. If the study was to be closed prematurely, all study materials, except documentation that had to remain stored at the center site, were to be returned to the Sponsor. The Investigator was to retain all other documents until notification was given by the Sponsor for

destruction. Events that could have triggered premature termination of the study or closure of a center included, but were 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

9.1.6. Data Safety and Monitoring Board

A DSMB was instituted for this study to ensure the safety of the subjects. Recommendations for continuation of the study were guided by safety evaluations at safety data reviews. The committee included two independent oncologists with experience in thoracic oncology and an independent statistician. Safety meetings were 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, were made after recommendations from the DSMB had been assessed by Polaris. The DSMB was not expected to conduct the key efficacy analyses at the interim or final analysis.

9.2. Discussion of Study Design, Including the Choice of Control Groups

The background information provided in Section 2.1 of the protocol (Appendix 16.1.1) 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 + nab-paclitaxel; Harding 2018 and Lowery 2017) that did not correlate with ASS1 deficiency. Pemetrexed and cisplatin were the first-line chemotherapy in advanced MPM at the time this study started enrollment. 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 + cisplatin only.

In MPM, both RR and PFS correlate with OS (Blayney 2012, Hasan 2014). Thus, RR and PFS serve as surrogate endpoints for OS in MPM (Allen 2014, Beddowes 2017, Szlosarek 2020).

9.3. Selection of Study Population

9.3.1. Inclusion Criteria

A subject was eligible for study participation if they met the following criteria prior to the first dose:

1. Histologically proven unresectable MPM of biphasic or sarcomatoid histology. Biphasic MPM was defined using the WHO'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 (ie, this was a first-line systemic therapy study).
3. Measurable disease as assessed by modified RECIST for MPM for local pleural disease (Appendix A of the protocol [Appendix 16.1.1]) and RECIST 1.1 for metastatic lesions (Appendix B of the protocol [Appendix 16.1.1]).
4. ECOG performance status of 0 – 1 (Appendix C of the protocol [Appendix 16.1.1]).
5. Predicted life expectancy of at least 12 weeks.
6. Age ≥ 18 years (there was 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 was acceptable.
8. Subjects and their partners must have been asked to use appropriate contraception. They must have agreed to use two forms of contraception or have agreed 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 platinum agent whichever was the longer duration. Females must not have been pregnant at the start of the study, and a serum HCG pregnancy test was to be negative before entry into the study. If there was a positive HCG pregnancy test, further evaluation to rule out pregnancy must have been performed according to GCP before this subject was claimed eligible.
9. Informed consent must have been obtained prior to study initiation.
10. HB > 9.0 g/dL.
11. ANC > 1500/µL.
12. Platelets > 75000/µL.
13. Either: (i) serum bilirubin ≤ 1.5 x ULN or (ii) ALT, AST, and/or ALP ≤ 3 x ULN unless raised due to tumor in which case up to 5 x ULN was 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 was 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 and 59.9 mL/min and by 50% for clearance between 45 and 49.9 mL/min.

9.3.2. Exclusion Criteria

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

1. Radiotherapy (except for palliative reasons) the previous 2 weeks before.
2. Ongoing toxic manifestations of previous treatments.

3. Symptomatic brain or spinal cord metastases (subjects must have been stable for > 1 month post radiotherapy or surgery).
4. Major thoracic or abdominal surgery from which the subject had not yet recovered.
5. Serious infection requiring treatment with IV antibiotics at the time of study entrance, or an infection requiring IV therapy within 7 days prior.
6. Known to be serologically positive for HIV. Testing to determine possible infection status was 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 have limited compliance with study requirements.
8. Was a participant of, or planned to participate in, another interventional clinical study whilst taking part in this study. Participation in an observational or biomarker study was 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 that would not affect subject 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.

9.3.3. Removal of Subjects from Therapy or Assessment

Subjects were 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 was to 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. AE. Laboratory abnormalities that could be corrected with interventions (eg, hyperuricemia with allopurinol and/or urate oxidase, and neutropenia with growth factor support) did not require subject withdrawal.
4. Decision by the Investigator that termination was in the subject's best medical interest.
5. Unrelated medical illness or complication.
6. Death.
7. Lost to follow-up.
8. PD 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 were to be used for decisions on the discontinuation of or continued treatment during the phase 2 portion.

In the event of a subject's withdrawal, the Investigator was to promptly notify the study monitor and to make every effort to complete the EOT assessments (see Table 4).

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

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

If a subject died during treatment or within 30 days of stopping treatment, the Investigator was to inform the Sponsor's representative. The cause of death was to be reported in detail, within 24 hours, on an SAE form and reported to the Sponsor's representative/designee (see Section 9.5.8 of the protocol [Appendix 16.1.1]).

Subjects who signed informed consent for treatment and underwent at least some of the screening procedures, but failed to meet eligibility criteria, were to be considered screening failures. The reason for failure was to be recorded on the screening log provided by Polaris. A record of such subjects was to be maintained in the TMF at the study site and was to be retained for the required period of time in compliance with CFR 21, Sec.312.57, part (c) and GCP. Subjects who were "screen failures" may have been rescreened at the discretion of the Investigator. Only screening failure subjects were to be replaced. All subjects who received any dose of study drug were evaluable for safety.

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

9.4. Treatments

9.4.1. Treatments Administered

ADI-PEG 20 or placebo was administered by IM injection to subjects once weekly. Subjects were to remain in the treatment area for 1 hour ± 15 minutes after the injection. At the end of this

post-injection period, subjects were to be assessed for safety and tolerability, including obtaining vital signs.

As previously mentioned, the standard first-line chemotherapy treatment for MPM at the time this study started enrollment was pemetrexed + cisplatin. Therefore, cisplatin was the recommended chemotherapy for use in the initial and subsequent cycles. However, subjects who did not tolerate cisplatin or who were not expected to tolerate cisplatin were allowed to have carboplatin substituted for cisplatin at any cycle, including the initial cycle, at the discretion of the Investigator (see Appendix 16.1.1 for protocol amendments and details). The dose of carboplatin was AUC 5 mg/mL/m^2. This was allowed to be modified at the Investigator's discretion.

ADI-PEG 20 or placebo was to be administered before pemetrexed + platinum agent. Pemetrexed + platinum agent administration was to begin at least 60 minutes after ADI-PEG 20 or placebo administration on the same day, except during cycle 1 when the chemotherapy was administered on Day 3.

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

For details regarding study drug dispensing, packaging and labeling, handling, storage, storage conditions, and drug accountability and return, refer to Section 7.3.11, Section 7.3.12, Section 7.3.13, Section 7.3.14, Section 7.1.2, and Section 7.3.15 of the protocol, respectively (Appendix 16.1.1).

9.4.2. Identity of Investigational Products

A list of subjects receiving each study drug batch number is provided in Appendix 16.1.6.

The Investigator was to ensure that all study drugs were stored and dispensed in accordance with FDA regulations and other country specific health authority regulations concerning the storage and administration of investigational drugs.

9.4.2.1. ADI-PEG 20

ADI is a recombinant protein cloned from *M. hominis*, produced in *E. coli*, and conjugated with PEG of 20,000 mw. Thus, ADI-PEG 20 is an arginine degrading enzyme, ADI, coupled to PEG. ADI-PEG 20 was the IP in the study.

ADI-PEG 20, in the histidine-buffered formulation, was provided as a sterile solution in single-dose glass vials containing 3.5 mL of solution with a concentration of 11.5 mg/mL. ADI-PEG 20 was stored frozen at the temperature indicated on the product label. The drug product was stable for 24 hours once it was thawed.

9.4.2.2. Placebo

Placebo was provided as a sterile solution in single-dose glass vials that were identical in appearance to the ADI-PEG 20 vials. The volume of placebo given was calculated based on a 36 mg/m^2 dose of ADI-PEG 20. The solution in each vial contained low viscosity sodium

carboxymethylcellulose, PEG 3350, propylene glycol, and Tween 80. The placebo did not contain ADI, PEG 20, or succinimidyl linker.

Placebo was stored frozen at the same temperature indicated on the ADI-PEG 20 product label.

9.4.2.3. Pemetrexed – Standard, Background Chemotherapy

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

Pemetrexed was to be stored per institutional standards.

9.4.2.4. Platinum Agents – Standard, Background Chemotherapy

The platinum agents in this study (cisplatin and carboplatin) are approved medications that were considered in the study as background therapy to be provided through the local pharmacy.

The platinum agents were to be stored per institutional standards.

9.4.3. Method of Assigning Subjects to Treatment Groups

Eligible subjects were randomized in a 1:1 ratio to ADIPemPlatinum or PlaceboPemPlatinum. The randomization was stratified by histology (biphasic or sarcomatoid).

The randomization scheme is provided in Appendix 16.1.7.

9.4.4. Selection of Doses in the Study

9.4.4.1. ADI-PEG 20 Dose Selection

ADI-PEG 20 (at dose of 36 mg/m^2) or placebo was to be given via the IM route of administration. This was the dose that was used successfully in the phase 1 study of ADI-PEG 20 + pemetrexed + cisplatin in MPM and NSCLC.

9.4.4.2. Pemetrexed and Platinum Agent Dose Selection

Treatment with pemetrexed and a platinum agent was as per institutional guidelines, including infusion protocols.

The dosages of pemetrexed and the platinum agents were those used to treat unresectable MPM. The dose of pemetrexed was 500 mg/m^2 every 3 weeks given by IV, the dose of cisplatin was 75 mg/m^2 every 3 weeks given by IV, and the dose of carboplatin was AUC 5 mg/mL/m^2 every 3 weeks (given by IV).

9.4.5. Selection and Timing of Dose for Each Subject

9.4.5.1. ADI-PEG 20 Timing of Dose Selection

Subjects received one injection of ADI-PEG 20 or placebo IM into the deltoid, gluteal, or quadriceps muscles (Note: this totaled approximately 6 mL for a larger subject, if this volume was a problem from an institutional nursing perspective, it was allowed to be given as

2 injections in different body locations) weekly. To limit the volume administered for a larger subject, there was dose capping at 74.8 mg, which was the equivalent of 6.5 mL. The injections were allowed to be given ± 3 days from the scheduled weekly dosing, except for the first dose, which was fixed. Subjects were observed in the clinic for 1 hour ± 15 minutes following each ADI-PEG 20 or placebo injection. ADI-PEG 20 or placebo was to be administered before pemetrexed and a platinum agent. Pemetrexed and platinum agent administration was 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 was administered on Day 3. Treatments were not to be interrupted due to either scheduling for CT (or MRI) scans or delays in the assessment of scan results.

9.4.5.2. Pemetrexed and Platinum Agent Timing of Dose Selection

Treatment with pemetrexed and a platinum agent was as per institutional guidelines, including infusion protocols.

The dosages of pemetrexed and the platinum agent were those used to treat unresectable MPM, as described in Section 9.4.4.2.

9.4.5.3. Dose Adjustments

Treatment was allowed to be withheld for up to 2 weeks in any subject who demonstrated Grade 3 non-hematologic toxicity or hematologic toxicity, as defined by the NCI CTCAE version 4.03, or approved version. If the toxicity was no longer Grade 3, treatment may have been resumed; treatment did not have to wait for the next scheduled dose visit. Use of hematopoietic growth factors was allowed to treat hematologic toxicity at the discretion of the Investigator. Grade 3 or 4 laboratory abnormalities (eg, hyperuricemia) that could be corrected with interventions did not require cessation of therapy. If treatment was withheld for more than 2 weeks (or more than 2 missed doses of ADI-PEG 20/placebo), the subject was to be discontinued from treatment, unless it was approved by Polaris in certain situations for the subject to continue.

9.4.5.3.1. ADI-PEG 20 or Placebo Dose Adjustments

ADI-PEG 20 or placebo was to be given on Days 1 (Week 1), 8 (Week 2), and 15 (Week 3) of a cycle. Toxicity that was attributable to either a platinum agent or pemetrexed did not mandate withholding the dose of ADI-PEG 20 or placebo for that cycle. Dose reduction of ADI-PEG 20 or placebo was not allowed.

Investigators retained the discretion to withhold ADI-PEG 20 or placebo dose for subject safety.

For subjects to receive Day 15 ADI-PEG 20 or placebo, the following parameter was required during the chemotherapy treatment period (Cycles 1 to 6): Platelets $\geq 50 \times 10^9$/L on Day 8.

Subjects who did not meet this criterion were to have the dose of ADI-PEG 20 or placebo withheld. Specific toxicity resulting from ADI-PEG 20 or placebo administration was to be managed as follows:

- Local injection site reactions to date were self-limiting and typically resolved within 48 hours.

- Anaphylaxis was to 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 was allowed to be considered and pre-medication with hydrocortisone and cholorpheniramine was allowed to be used. Grade 3 or greater anaphylaxis resulted in the subject being withdrawn from study treatment.
- Hyperuricemia was to be monitored. Any clinically relevant elevation was to be treated with allopurinol or urate oxidase, or sites were allowed to choose appropriate substitutions according to local policy.
- Epilepsy/fits were to be managed according to local policy and with benzodiazepines as necessary. Once stabilized, and depending on the type and severity of reaction, re-challenge with ADI-PEG 20 or placebo was allowed to be considered. If further seizures occurred, despite prophylactic measures, the subject was to be withdrawn from study treatment.

9.4.5.3.2. Pemetrexed and Platinum Agent Dose Adjustments

Platinum agent dose adjustment was recommended for subjects with a creatinine clearance between 45 and 59 mL/min (eg, Bennis 2014).

Dose adjustments at the start of a subsequent cycle were to be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Treatment was allowed to be delayed to allow sufficient time for recovery. Upon recovery, subjects were to be re-treated using the guidelines in Table 7.3.3 of the protocol (Appendix 16.1.1).

If a subject developed non-hematologic toxicities ≥ Grade 3 (excluding neurotoxicity), pemetrexed was to be withheld until resolution to less than or equal to the subject's pre-therapy value. Treatment was to be resumed according to the guidelines in Table 7.3.3 of the protocol (Appendix 16.1.1).

Treatment with pemetrexed and a platinum agent was to be discontinued if a subject experienced any hematologic or non-hematologic Grade 3 or 4 toxicity after 2 dose reductions, or immediately if Grade 3 or 4 neurotoxicity was observed.

The first occurrence of toxicity that led to a dose reduction of pemetrexed and/or platinum agent did not mandate a dose reduction in ADI-PEG 20 or placebo as long as the toxicity was attributable to the cytotoxic agent(s).

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

9.4.5.4. Missed Doses

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

A pemetrexed and/or platinum agent dose that was not administered on Day 1 of a cycle was considered delayed if given within 2 weeks of the start of the cycle. The subsequent dosing schedule needed to be adjusted so that the chemotherapy was given in 3 weeks' time. Beyond this, the doses were considered missed.

9.4.5.5. Optional Single Agent Treatment

Subjects who completed 18 weekly treatments (ADI-PEG 20 or placebo + pemetrexed and a platinum agent) were allowed to continue ADI-PEG 20 or placebo, if they had stable disease or better, for up to 2 years.

9.4.6. Blinding

Subjects were randomly assigned to receive ADI-PEG 20 drug product or matching placebo in a double-blind fashion. Thus, neither the Investigator, nor the subject knew which study treatment was being administered. The randomization number was assigned based on information obtained from an IWRS. ADI-PEG 20 drug product and placebo were identical in appearance in order to preserve the blinding. In order to maintain this blind, study medication (ADI-PEG 20 or placebo) was labeled with a unique "medication number", which was assigned to a subject by an IWRS. Note that SAS programming occurred as study data accumulated in order to have analysis programs ready at the time the study finished. Arbitrary treatment group assignments were randomly linked to subjects, effectively rendering any output of programs meaningless. The complete random lists were archived with the IWRS. When a medical emergency arose that required identification of the study medication administered, in order to manage the acute situation of the subject, the blind was allowed to be broken. The Investigator treated the subject as if the subject were on the active drug product. The study medication was unblinded by the Investigator via the IWRS as needed.

Unblinding was to occur for emergency purposes, for DSMB purposes, and to report SUSARs to regulatory authorities. Investigators were to note that the occurrence of an SAE was not to routinely precipitate the immediate unblinding of the label. When unblinding was necessary for the treatment of a subject for an SAE, the Investigator promptly documented and explained any unblinding to Polaris or their designee within 24 hours of unblinding. The medical monitor was also promptly notified that the blind was broken. When unblinding occurred, the study medication (ADI-PEG 20 or placebo) was discontinued. Subjects who discontinued study drug/placebo did not re-start treatment. Six subjects were unblinded by Precision Safety for regulatory reporting purposes (SUSAR reporting), and 2 subjects were reported by the site Investigator as detailed below:

- Subject 0201-0048 by Precision Safety for SUSAR reporting for an event of gout
- Subject 0202-0005 by Precision Safety for SUSAR reporting for an event of pulmonary embolism
- Subject 0218-0002 by Precision Safety for SUSAR reporting for an event of sudden death
- Subject 0303-0001 by Precision Safety for SUSAR reporting for an event of lung infection
- Subject 0211-0006 by Precision Safety for SUSAR reporting for an event of neutropenic sepsis
- Subject 0305-0005 by Precision Safety for SUSAR reporting for an event of enterocolitis

- Subject 0101-0008 by the site Investigator for an event of anaphylactic reaction
- Subject 0203-0018 by the site Investigator for an event of stroke resulting in death, and MHRA performed an audit focusing of this case. The coroner requested the unblinding.

9.4.7. Prior and Concomitant Therapy

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

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

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

Subjects who required oral anticoagulation with warfarin (or other substitutions) were allowed to continue, provided there was increased vigilance with local INR monitoring.

9.4.7.1. Non-permitted Concomitant Therapies

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

9.4.7.2. Permitted Concomitant Therapies

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

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

9.4.7.2.1. ADI-PEG 20

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

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

9.4.7.2.2. Pemetrexed and Platinum Agent

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

To reduce toxicity, subjects treated with pemetrexed were to also receive vitamin supplementation. Subjects were to take oral folic acid or a multivitamin containing folic acid (350 to 1000 µg) on a daily basis. At least five doses of folic acid were to be taken during the seven days preceding the first dose of pemetrexed, and dosing was to continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Subjects were to also receive an IM injection of vitamin B12 (1000 µg) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections were allowed to be given on the same day as pemetrexed.

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

- Folic acid 400 µg daily, oral
- Hydroxycobalamin 1000 µg IM injection
- Dexamethasone 4 mg bd (3 doses) preceding the hospital visit. Dexamethasone was also allowed to be administered IV and at a dose per local policy.
- Anti-emetic, eg, $5HT_3$ antagonist, domperidone, and dexamethasone 8 mg
- Furosemide 40 mg oral once

9.4.8. Treatment Compliance

ADI-PEG 20 or placebo was administered by study staff via IM injection to subjects once weekly. ADI-PEG 20 or placebo was to be administered before pemetrexed + platinum agent. Pemetrexed + platinum agent administration was to begin at least 60 minutes after ADI-PEG 20 or placebo administration on the same day, except during Cycle 1 when the chemotherapy was administered on Day 3.

The Investigator or appropriate designee maintained a record of all study medications received and dispensed and source documents for each subject in the study, consisting of case and visit notes.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

9.5.1.1. Efficacy Measurements

Overall survival was assessed as the time from randomization until death or censoring. Progression-free survival was assessed as the time from randomization until objective tumor progression or death.

The schedules of assessments (Section 9.5.1.3) list the timing of imaging studies.

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

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

A BICR of the CT/MRI scans was established, and details were provided in a document to describe the imaging requirements and BICR process.

9.5.1.2. Safety Measurements

Laboratory tests, vital sign measurements, physical examinations, and subject medical history were performed to detect new abnormalities and any deterioration in pre-existing conditions. All clinically significant abnormalities and deteriorations were to be recorded in the eCRFs as AEs and graded according to the NCI CTCAE version 4.03.

Safety monitoring was performed by the Sponsor and Precision, on a regular basis.

9.5.1.2.1. Vital Signs

Vital signs for this study included:

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

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

9.5.1.2.2. Laboratory Tests

Samples were obtained for the clinical laboratory tests outlined in Table 2 as per the schedules of assessments (Section 9.5.1.3).

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

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

Hematology and chemistry sampling from Day 1 of a cycle were to follow the chemotherapy administration day in case of a chemotherapy dosing delay. Clinically significant local laboratory findings that directly informed a dosing decision were recorded as an AE.

A central laboratory was 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 PK [peripheral blood ADI-PEG 20 levels]).

Table 2: Clinical Laboratory Tests

Hematology (CBC)	**Serum Chemistry**
Hematocrit	Albumin
HB	ALP
RBC count	BUN
WBC count	Calcium
ANC	Chloride
Lymphocytes (Absolute Values)	Creatinine
Monocytes (Absolute Values)	Glucose (Nonfasting)
Basophils (Absolute Values)	HCG (At Screening Only)
Eosinophils (Absolute Values)	Potassium
Platelet count (Estimate Not Acceptable)	SGOT/AST
	SGPT/ALT
	Sodium
	Total bilirubin
	Total protein
	Uric acid

For any laboratory test value outside the reference range that the Investigator considered clinically significant:

- The Investigator was allowed to repeat the test to verify the out-of-range value.
- The Investigator followed the out-of-range value to a satisfactory clinical resolution or stabilization.
- A laboratory test value that required a subject to be discontinued from the study or required a subject to receive treatment was recorded as an AE.

Special blood samples for arginine, citrulline, anti-ADI-PEG 20 antibody levels, and ADI-PEG 20 levels, as well as for future research, were obtained at the times (before ADI-PEG 20 injection) noted in the schedules of assessments (Section 9.5.1.3).

9.5.1.2.3. Electrocardiograms

Electrocardiogram was performed, and QTcF was determined. If the Week 4 or Week 12 ECG collection time point was missed due to dosing being delayed or withheld, the ECG was to be collected at the next visit.

9.5.1.2.4. Physical Examination

A comprehensive physical examination, including height and weight, was performed at the Screening Visit. Physical examination was performed on Day 1 of every cycle and at other times as clinically indicated. If weight varied by ≥ 10%, the BSA and doses were to be recalculated. Any clinically significant findings or absence of findings relative to each subject's physical examination were carefully documented in the subject's AE eCRF. Symptom directed examinations were allowed to be performed more frequently at the discretion of the Investigator.

9.5.1.2.5. Adverse Events

9.5.1.2.5.1. Definition of Adverse Event

An AE was any untoward medical occurrence or clinical investigation in a subject administered a pharmaceutical product and that did not necessarily have a causal relationship with the treatment. An AE could 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, was extended for the purpose of Polaris studies to include any events, intercurrent diseases, and accidents observed while the subject was on study, ie, during the actual treatment period, as well as during drug-free, pre- and post-treatment periods.

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

Treatment-emergent AEs included all AEs that started on or after the first dose of study medication, or a condition that was present prior to the first dose of study medication, but the severity or relationship of which increased (exacerbated) after the first dose of study medication, up to and including 30 days after the final study medication dosing date.

Adverse events that were identified at the last assessment visit (or the Early Termination Visit) were to be recorded on the AE eCRF with the status of the AE noted. AEs that were related to ADI-PEG 20 were to be followed until resolution or deemed stable by the Investigator. All events that were ongoing at this time were to be recorded as ongoing on the eCRF.

For description of SAEs, see Section 9.5.1.2.5.5.

For details regarding recording of AEs, see Section 9.5.2 of the protocol (Appendix 16.1.1).

9.5.1.2.5.2.Assessment of Adverse Events – Relationship to Study Drug

The relationship of all serious and non-serious AEs to the investigational agent(s) was determined by the Investigator on the basis of their clinical judgment, using one of the following terms (in accordance with FDA 2012):

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

The Investigator was to assess the causality of all SAEs/reactions to ADI-PEG 20, to pemetrexed, to a platinum agent, 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 have also supported these evaluations.

9.5.1.2.5.3.Following Adverse Events

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

The Investigator used his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

Note: SAE updates made in the EDC came as email alerts to Polaris and Precision. Initial SAEs were processed and triaged by Precision. Follow-up information pertaining to SAEs was reviewed by Polaris within 24 hours of receipt and forwarded to Precision for entry into the safety database.

9.5.1.2.5.4.Discontinuation due to Adverse Events

Subjects were allowed to be withdrawn from the study at any time. Subjects withdrawn from the study due to an AE, whether serious or non-serious, were to be followed by the Investigator until the clinical outcome from the AE was determined. Any subject who experienced an AE was allowed to be withdrawn at any time from the study at the discretion of the Investigator. The AE(s) was (were) to be noted on the appropriate eCRFs, and the subject's progress was to be followed until the AE was resolved. The Polaris medical monitor was to be notified. If the AE

was related to overdose of study treatment, the Investigator's Brochure was to be consulted as well for details of any specific actions to be taken.

9.5.1.2.5.5.Serious Adverse Events

Subjects were monitored throughout the study for SAEs. An SAE was any untoward medical occurrence that at any dose:

1. Resulted in death,
2. Was life-threatening,

   The term "life-threatening" in the definition of "serious" referred to an event in which the subject was at risk of death at the time of the event; it did not refer to an event, which hypothetically might have caused death if it were more severe.
3. Required inpatient hospitalization or prolongation of existing hospitalization,

   The following were not considered SAEs in this Polaris-sponsored clinical study:

   - A visit to the emergency room or other hospital department < 24 hours that did not result in admission (unless considered "important medical event" or the event was life-threatening).
   - Elective surgery, planned prior to signing study consent.
   - Medical/surgical hospital admission for purposes other than remedying an ill health state and was planned prior to entry into the study. Appropriate documentation was required in these cases.
   - Routine health assessment requiring hospital admission for baseline/trending of health status (eg, routine colonoscopy).
   - Hospital admission encountered for another life circumstance that carried no bearing on health status and required no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
   - Hospital admission or other medical occurrences (such as prolonged hospitalization or death) for AEs due to the malignant disease under study (including associated signs and symptoms of disease progression). Changes in disease were reported separately.
   - Hospital admission for study biopsies.
4. Resulted in persistent or significant disability or incapacity,
5. Was a congenital anomaly/birth defect, or
6. Was another medically important condition.

   Medically important conditions that may not have resulted in death, been immediately life-threatening, or required hospitalization may have been considered as an SAE when, based upon appropriate medical judgment, they may have jeopardized the subject or may have required intervention to prevent one of the outcomes listed in the definition above. Examples of such events were intensive treatment in an emergency room or at home for

allergic bronchospasm; blood dyscrasias, or convulsions that did not result in hospitalization; or development of drug dependency or drug abuse.

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

A SUSAR was defined as an untoward and unintended response to a study drug, which was not listed in the applicable product information, and met one of the above listed serious criteria.

See Section 9.5.8 of the protocol (Appendix 16.1.1) for details about reporting SAEs.

9.5.1.2.5.6.Pregnancy

Although pregnancy itself was not considered an AE or an SAE, pregnancy was to be reported as "Information" (not as an "Adverse Event" or "Other Problem or Event"). Details regarding pregnancy are available in Section 9.5.5 of the protocol (Appendix 16.1.1). No pregnancies were reported during the study.

9.5.1.3. Schedule of Events

Table 3 presents the schedule of events for Pre-Study (Screening) and Cycles 1 to 4, Table 4 presents the schedule of events for Cycles 5, 6, 7, and beyond, and Table 5 presents study assessments and procedures for the blinded and open-label extension for subjects wishing to continue study treatment after the end of the study.

In addition to the events presented in Table 3, Table 4, and Table 5, beginning 30 days (± 7 days) after the EOT Visit, survival status was followed via telephone, email, or clinic visit for each subject every 3 months (± 1 week) until the end of the study.

Table 3: Schedule of Events: Study Assessments and Procedures: Pre-Study (Screening) and Cycles 1 to 4

Study Procedure	Screening Assessments		Cycle 1			Cycle 2			Cycle 3			Cycle 4		
			Day of Cycle (Week of Treatment)											
	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/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	
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		
Platinum Agent Administration[k, p]			X[l]			X			X			X		

Note: Visits were allowed to occur ± 3 days of the planned date except for PemPlatinum administration on Cycle 1 Day 3. All study evaluations and related procedures were allowed to occur 3 days prior to dosing except for CT or MRI, which was allowed to occur ± 7 days of the planned date. See Appendices of the protocol (Appendix 16.1.1) for more on modified RECIST response criteria for MPM for 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 was extended to -42 days without requiring a reconsent.

b. Physical examination was to be performed on Day 1 of each cycle and was symptom directed as clinically indicated.

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

d. Subjects were assessed for AEs on Day 1 of each cycle and weekly thereafter or as clinically indicated. AEs, including SAEs and toxicities, were recorded after the first administration of study treatment until 30 days after last study drug administration. AEs related to ADI-PEG 20 that were still ongoing at the EOT Visit were to be followed up until resolution or stabilization. Any medical sign or symptom a subject may have experienced post signing of the ICF and before the first administration of study treatment were to be recorded as part of medical history. If any toxicity or medical sign or symptom a subject may have experienced post signing of the ICF met the definition of an SAE per Section 9.5.1.2.5.5, they were to be reported as an SAE per Section 9.5.8 of the protocol (Appendix 16.1.1).

e. Baseline CT with contrast or MRI of the involved organs was to be conducted within 28 days prior to subject receiving the first ADI-PEG 20 or placebo dose (this was allowed to be conducted prior to signing informed consent if part of standard of care). Scans were to be performed every 6 weeks (preferably in the week after 2 cycles of ADIPemPlatinum or PlaceboPemPlatinum dosing) and after every 8th weekly dose of ADI-PEG 20 or placebo during ADI-PEG 20 or placebo only treatment. Tumor measurements had to be noted. CT with contrast had to be used unless the subject was allergic to IV contrast despite use of diphenhydramine and corticosteroids, in this case, CT without contrast (if borders were distinct) was the second choice and MRI was a third choice if borders were not well-defined on CT. The same imaging modality was to be used throughout the study. Details were provided in the Imaging Manual. For subjects with tumor responses (CR and PR), scans continued according to the regular schedule. Imaging was to follow calendar days and was not to be adjusted for changes in dosing schedule. Subjects withdrawn from treatment for reasons other than PD were allowed to continue to receive regular scans until PD.

f. Female subjects only, serum HCG.

g. Blood samples were to be collected before ADI-PEG 20 or placebo administration. Hematology and chemistry sampling from Day 1 of a cycle was to follow the chemotherapy administration day in case of a chemotherapy dosing delay. Local blood samples were allowed to 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 were also collected at the same time and sent in for testing. Clinically significant local laboratory findings that directly informed a dosing decision were recorded as an AE. See Section 9.5.1.2.2 for details.

h. Creatinine clearance ≥ 45 mL/min (estimated, using Cockcroft and Gault formula).

i. Blood samples were to be collected before ADI-PEG 20 or placebo administration for arginine and citrulline (pharmacodynamics), ADI-PEG 20 antibody levels (immunogenicity), and ADI-PEG 20 levels (PK). Special blood sampling was to follow calendar days and not adjusted for changes in dosing schedule. See Section 9.5.4, Section 9.5.5, and Section 9.5.6 for details.
j. ADI-PEG 20 or placebo was to be administered before pemetrexed and a platinum agent on days when all 3 drugs were given, except during Cycle 1 where the chemotherapy was administered on Day 3. Pemetrexed and platinum agent administration was to begin at least 60 minutes after ADI-PEG 20 or placebo administration on the same day.
k. Supportive and pre-medications were to include the following or as per local policy (see Section 9.4.7.2.2 for further details):

- Folic acid 400 µg daily, oral
- Hydroxycobalamin 1000 µg IM injection
- Dexamethasone 4 mg bd (3 doses) preceded the hospital visit by 24 hours. Dexamethasone was also allowed to be administered IV and at a dose per local policy.
- Anti-emetic, eg, $5HT_3$ antagonist, domperidone, and dexamethasone 8 mg
- Furosemide 40 mg oral once

l. PemPlatinum was to be administered on Day 3 of Cycle 1
m. These assessments at Week 1 were allowed to be omitted if performed within 72 hours of the first dose.
n. ECG was to be performed 1 hour ± 15 minutes after ADI-PEG 20 or placebo treatment. This assessment was to include the QT/QTcF: QTc = QT/RR0.33
o. During the chemotherapy treatment period (Cycles 1 to 6), a cycle was 3 weeks. During the single agent period, beginning on Week 19, a cycle was defined as every 4 weeks.
p. Cisplatin was the recommended chemotherapy for use in the initial and subsequent cycles. However, subjects who did not tolerate cisplatin or who were not expected to tolerate cisplatin may have had carboplatin substituted for cisplatin at any cycle including the initial cycle at the discretion of the Investigator.

Table 4: Schedule of Events: 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								EOT[a]
	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]	
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/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											
Platinum Agent Administration[i,l]	X			X											

Note: Visits were allowed to occur ± 3 days of the planned date. All study evaluations and related procedures were allowed to occur 3 days prior to dosing except for CT or MRI which was allowed to occur ± 7 days of the planned date, but preferably after every 2 cycles of ADIPemPlatinum or PlaceboPemPlatinum and after every 8th weekly dose of ADI-PEG 20 or placebo during ADI-PEG 20 or placebo only treatment.

See appendices of the protocol (Appendix 16.1.1) for more on modified RECIST response criteria for MPM for local pleural disease (Appendix A), RECIST 1.1 response criteria for metastatic lesions (Appendix B), and performance status (Appendix C).

a. The EOT Visit was to occur 7 to 30 days (preferably 30 days) after the last dose of treatment.

b. Physical examination was to be performed on Day 1 of each cycle and was symptom directed as clinically indicated.

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

d. Subjects were assessed for AEs on Day 1 of each cycle and weekly thereafter or as clinically indicated. AEs, including SAEs and toxicities, and baseline toxicities/symptoms were recorded starting with the signing of the ICF. These were recorded until 30 days after last study drug administration. AEs related to

ADI-PEG 20 or placebo that were still ongoing at the EOT Visit were to be followed up until resolution or stabilization. Any medical sign or symptom a subject may have experienced post signing of ICF and before first administration of study treatment were to be recorded as part of the medical history. If any toxicity or medical sign or symptom a subject may have experienced post signing of ICF met the definition of an SAE per Section 9.5.1.2.5.5, they were to be reported as an SAE per Section 9.5.8 of the protocol (Appendix 16.1.1).

e. Scans were to be performed every 6 weeks (preferably in the week after 2 cycles of ADIPemPlatinum or PlaceboPemPlatinum dosing) and after every 8th weekly dose of ADI-PEG 20 or placebo during ADI-PEG 20 or placebo only treatment. Tumor measurements had to be noted. The same imaging modality was to be used throughout the study. For subjects with tumor responses (CR and PR), scans continued according to the regular schedule. Imaging was to follow calendar days and was not to be adjusted for changes in dosing schedule. Subjects withdrawn from treatment for reasons other than PD were allowed to continue to receive regular scans until PD.

f. Blood samples were to be collected before ADI-PEG 20 or placebo administration. Hematology and chemistry sampling from Day 1 of a cycle was to follow the chemotherapy administration day in case of a chemotherapy dosing delay. Local blood samples were allowed to 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 were also collected at the same time and sent in for testing. Clinically significant local laboratory findings that directly informed a dosing decision were to be recorded as an AE. See Section 9.5.1.2.2 for details.

g. Blood samples were to be collected before ADI-PEG 20 or placebo administration for arginine and citrulline (pharmacodynamics), ADI-PEG 20 antibody levels (immunogenicity), and ADI-PEG 20 levels (PK). Special blood sampling was to follow calendar days and not adjusted for changes in dosing schedule. See Section 9.5.4, Section 9.5.5, and Section 9.5.6 for details. Special blood sampling was not required during ADI- PEG 20 or placebo only treatment after 25 weeks.

h. ADI-PEG 20 or placebo was to be administered before pemetrexed and a platinum agent on days when all 3 drugs were given. Pemetrexed and platinum agent administration was to begin at least 60 minutes after ADI-PEG 20 or placebo administration on the same day.

i. Supportive and pre-medications were to include the following or as per local policy (see Section 9.4.7.2.2 for further details):

- Folic acid 400 µg daily, oral
- Hydroxycobalamin 1000 µg IM injection
- Dexamethasone 4 mg bd (3 doses) preceded the hospital visit by 24 hours. Dexamethasone was also allowed to be administered IV and at a dose per local policy.
- Anti-emetic, eg, $5HT_3$ antagonist, domperidone, and dexamethasone 8 mg
- Furosemide 40 mg oral once

j. Subjects who remained on treatment after 26 weeks and up to 2 years of study treatment continued to follow the schedule in this table. For example, Week 27 was to follow visit assessments for Week 19; Week 28 was to follow Week 20, and so on. Therefore, CT scans were obtained every 8 weeks for those still on treatment.

k. During the chemotherapy treatment period (Cycles 1 to 6), a cycle was 3 weeks. During the single agent period, beginning on Week 19, a cycle was defined as every 4 weeks.

l. Cisplatin was the recommended chemotherapy for use in the initial and subsequent cycles. However, subjects who did not tolerate cisplatin or who were not expected to tolerate cisplatin may have had carboplatin substituted for cisplatin at any cycle including the initial cycle at the discretion of the Investigator.

Table 5: Schedule of Events: Blinded and Open-Label Extension Schedule of 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 were allowed to occur ± 3 days of the planned date.

Subjects who remained on treatment after 18 weeks were to continue following the schedule in this table. For example, Week 19 was to follow the schedule for Week 1, Week 20 was to follow the schedule for Week 2, and so on.

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

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

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

9.5.2. Appropriateness of Measurements

The measures of efficacy used in this study reflected accepted standard of care, ie, are widely used and are generally recognized as reliable, accurate, relevant, and able to discriminate between effective and ineffective treatment agents.

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

9.5.3. Primary Efficacy Variables

See Section 8.1.2 for the study endpoints, including the primary efficacy endpoints in Section 8.1.2.1.1.

9.5.4. Drug Concentration Measurements

Pharmacokinetics were determined for all subjects from the ADIPemPlatinum arm.

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

ADI-PEG 20 concentration was measured in plasma using a fluorogenic assay that measures the release of ammonia from arginine by the enzyme (Covance study 8353-406). This assay has a range of 800 ng/mL to 10000 ng/mL.

Approximately 10 mL of peripheral blood was collected prior to ADI-PEG 20 or placebo dosing and used for pharmacodynamics, PK, and immunogenicity studies.

Analysis of derived PK parameters by age, sex, and BSA will be reported in a separate report. Additional analysis of derived PK parameters or correlation to efficacy endpoints may be performed and summarized in a separate report outside of this CSR.

9.5.5. Pharmacodynamic Measurements

Pharmacodynamics were assessed by measurement of peripheral blood (plasma) levels of arginine and citrulline by LCMS.

ADI-PEG 20 is an enzyme that catabolizes one mole of arginine into one mole of ammonia and one mole of citrulline. Arginine and citrulline levels were measured by LCMS (Covance study 8353-402) with an arginine range of 0.75 nmol/mL to 750 nmol/mL and a citrulline range of 1.5 nmol/mL to 1500 nmol/mL.

9.5.6. Immunogenicity Measurements

Immunogenicity was assessed for all subjects from the ADIPemPlatinum arm by measurement of peripheral blood (plasma) antibodies to ADI-PEG 20. ADI is a foreign protein, and as such, it was expected that anti-ADI-PEG 20 antibodies would develop after repeat dosing. A newly developed assay, Mesoscale ECL assay (Covance report 8396-848), was used for the first time in this study. The ECL assay is more sensitive (15.9 ng/mL at the PSCP and 19.1 ng/mL at the CCP), at an MRD of 1:5, than previously used ELISA assays. Previous ELISA assays used in

clinical trials for ADI-PEG 20 (Covance report 8246-509) were less sensitive (1 µg/mL undiluted), at an MRD of 1:10. Titers from the two assays could not be directly compared but the trends could be.

Blood was also available for testing for anti-PEG antibodies. The ECL assay was developed for testing anti-PEG antibodies in subjects for the present study (Covance study 8396-850) and was used for the first time in this study, so there were no other data reports to compare. The assay has a sensitivity of 95.6 ng/mL, with a MRD of 1:50. It is known in the literature that anti-PEG antibodies exist in the general population due to the widespread use of PEG in many products used, both topical and oral.

9.5.7. Exploratory Assessments

Additional translational research, including pharmacogenomics and profiling of the inflammatory and metabolomic effects of ADI-PEG 20 in combination with pemetrexed and a platinum agent, is 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. The results will be presented outside of this CSR.

9.6. Data Quality Assurance

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

Pre-study requirements before the study drug was allowed to be shipped to a study site are detailed in Section 13.1.1 of the protocol (Appendix 16.1.1).

Details regarding confidentiality measures are presented in Section 13.3 of the protocol (Appendix 16.1.1).

9.6.1. Study Administration and Conduct

9.6.1.1. Study Monitoring

An EDC system was used for this trial. Instructional materials were provided to the sites as appropriate. The Investigator and site staff ensured all data from subject visits were promptly entered into the eCRFs in accordance with study-specific eCRF completion guidelines. The Investigator approved 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 was part of the documentation collated prior to trial start. If a central laboratory was selected to conduct any or all tests, it was essential that all samples were analyzed at that laboratory. The Investigator was

to maintain source documents such as laboratory reports and complete history and physical examination reports.

The Investigator permitted the site monitor to review study data as frequently as was deemed necessary to ensure data were being recorded in an adequate manner and protocol adherence was satisfactory. The Investigator granted access to the medical records for the monitor to verify eCRF entries. The Investigator, as part of his or her responsibilities, was expected to cooperate with the Sponsor/designee in ensuring the study adhered to GCP requirements. The Investigator was not permitted to recruit subjects into the study until an initial visit, or, with the agreement of Sponsor, attendance at a site initiation visit had been made by the Sponsor/designee to conduct a detailed review of the protocol and eCRFs.

The sample eCRF is provided in Appendix 16.1.2.

9.6.1.2. Audits and Inspections

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

Audit certificates are provided in Appendix 16.1.8.

9.6.2. Data Handling and Recordkeeping

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.

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.

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 IP. 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.

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 the Sponsor at the discretion of the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time in alignment with the local authority's regulations. No part of the Study Master File shall be destroyed or relocated without prior written agreement between the Sponsor and the Investigator.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

9.7.1.1. General Methodology

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

9.7.1.1.1. Reporting Conventions

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

In general, continuous variables were summarized to indicate the N, n, mean, SD, median, minimum, and maximum values. Categorical variables were 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 was based on the number of subjects with available data.

Rounding conventions are detailed in Section 7.1.1 of the SAP (Appendix 16.1.9).

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

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

9.7.1.1.2. Summarization by Visit

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

9.7.1.1.3. Standard Calculations

Standard calculation information for study day, and calculation of days, months, years, change from baseline, and percent change from baseline is presented in Section 7.1.3 of the SAP (Appendix 16.1.9).

9.7.1.2. Analysis Populations

The analysis populations were defined as follows:

- Safety Population: included all randomized subjects who received at least one dose of the study medication. Assignment of subjects to treatment group was based on the treatment actually received.
- ITT Population: included all randomized subjects. Assignment of subjects to treatment group was based on the randomized treatment assignment.
- PP Population: included all ITT subjects who had no major protocol violations that may have potentially affected the primary and secondary efficacy measures (eg, no MPM, no measurable disease). Subjects to be excluded from the PP Population were determined prior to database lock and prior to breaking the blind of the treatment group assignments. Assignment of subjects to treatment group was based on the randomized treatment assignment.

Data summaries to be presented on multiple populations (ie, the Safety Population and the ITT Population) were only to be produced on multiple analysis sets if there was a difference in the population groups (eg, at least one subject receives a different treatment than they were originally assigned). However, all subjects enrolled in the study were included in the Safety, ITT, and PP Populations; therefore, duplicative data summaries were not produced.

9.7.1.3. Study Subjects

9.7.1.3.1. Disposition of Subjects

Subject disposition was summarized for all randomized subjects by treatment group and over all subjects combined. Summaries included 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 was also summarized separately for each study center.

9.7.1.3.2. Protocol Deviations

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

All major protocol deviations were 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 were presented.

9.7.1.4. Efficacy Analyses

9.7.1.4.1. Datasets Analyzed

All efficacy summaries were based on the ITT Population. All subjects enrolled in the study were included in the Safety, ITT, and PP Populations; therefore, duplicative data summaries for the PP Population were not produced.

9.7.1.4.2. Demographic and Other Baseline Characteristics

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

- If the month and day portion of the informed consent date was prior to the month and day portion of the birth date, age was 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 was on or after the month and day portion of the birth date, age was calculated as the year of informed consent minus the year of birth.
- For the calculation of age, if only year was given, the birth day was assumed to be Jan 1 of the given year. If a year and month were given, but no day, the first of the month was assumed.

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

Baseline characteristics included medical history, disease history (type of histology, stage of MPM, any radiation or surgery treatment for actual cancer), height, weight, BSA, and ECOG performance status. Height, weight, and BSA at baseline were summarized using descriptive statistics. ECOG performance status and disease history were summarized using frequency counts and percentages. Subjects reporting abnormal medical history were presented only in subject data listings by subject and body system. All other baseline characteristics were summarized by treatment group and over all subjects combined for the Safety Population.

9.7.1.4.3. Primary Efficacy Endpoint Analysis Methods

9.7.1.4.3.1.Objective Response Rate

The analysis of RR was 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, stable disease, PD, missing, or not evaluable) were summarized by treatment group. The objective RR was compared between treatment groups using the CMH test, stratified by tumor histology (biphasic vs sarcomatoid). The point estimate of the relative risk ratio and the corresponding two-sided CI were provided. The significance level and coverage probability to be used in the RR analysis was based on $\alpha = 0.05$ (two-sided). The RR was only tested once at the end of the phase 2 regardless of its significance. The analysis was based on the ITT Population.

9.7.1.4.3.2.Overall Survival

The primary analysis of OS was performed at the final analysis. Results were presented by treatment group. The Kaplan-Meier method was used to provide estimates of the OS curves, including the median, 25^{th} and 75^{th} percentiles, and their corresponding 95% CIs. The number and percentage of subjects with an OS event and those who were censored were presented along with minimum and maximum survival times. The Kaplan-Meier curves were also plotted. A Cox proportional hazard model with an adjustment for tumor histology (biphasic vs sarcomatoid) was

used to compute the estimated hazard ratio and two-sided 95% CI. The treatment effect on OS was 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 was based on $\alpha = 0.04999$ (two-sided). The analysis was based on the ITT Population.

There was an interim analysis of OS once 50% of the planned OS events for phase 3 occurred that was used to determine whether to possibly terminate the study for futility or for possible sample size re-estimation for the phase 3 portion of the trial as described in Section 11.4.2.3. An administrative penalty of $\alpha = 0.00001$ was paid for this interim analysis, and the allocated $\alpha = 0.04999$ was used for the final analysis. Based on DSMB recommendations, the deaths for the original planned final analysis of OS were changed from 338 to the actual number of deaths occurring by 14Aug2022.

9.7.1.4.4. Secondary Efficacy Endpoint Analysis Methods

The secondary efficacy endpoint for phase 2 at the first interim analysis was DOR. DOR was analyzed using the Kaplan-Meier curves to estimate its median and 95% CIs.

The secondary efficacy endpoint for phase 3 at the final analysis was PFS, which was analyzed only if the analysis of OS was 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 9.7.1.4.3.2.

Summaries of secondary efficacy endpoints were provided for the ITT Population.

9.7.1.4.5. Pharmacodynamics

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

9.7.1.4.6. Immunogenicity

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

9.7.1.4.7. Pharmacokinetics

Pharmacokinetic analyses are described in Section 9.5.4.

9.7.1.5. Safety Analyses

Safety analyses were carried out for the Safety Population, including all subjects who received at least one dose of study drug. Subjects who did not complete the study, for whatever reason, but had all available data up until the time of termination were included in the analysis. For safety

analyses presented by study visit, the baseline value was defined as the last value reported prior to the first study drug administration.

9.7.1.5.1. Extent of Exposure and Treatment Compliance

Extent of exposure to study treatment was summarized for the Safety Population by treatment group. The number of doses administered and the total dose administered were 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, were summarized.

Compliance was not evaluated as the study drug was administered by staff in the clinic.

9.7.1.5.2. Adverse Events

Treatment-emergent AEs were 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 were summarized by treatment group. Events reported with a partial onset date (eg, month and year were reported but the day was missing) were considered to be treatment-emergent if it could not be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on eCRFs were mapped to preferred terms and system organ classes using the MedDRA version 19.1.

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

- Overall summary of number of unique TEAEs and TESAEs 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 (eg, TEAEs occurring in ≥ 10% of the Safety Population) by MedDRA preferred term;
- Subject incidence of TEAEs by CTCAE grade, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to ADI-PEG 20/placebo, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to pemetrexed, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to 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 TESAEs by MedDRA system organ class and preferred term.

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

Adverse event data were 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 were presented in separate data listings.

9.7.1.5.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post treatment follow-up period, were 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, were provided in separate subject data listings.

9.7.1.5.4. Clinical Laboratory Evaluation

All descriptive summaries of laboratory results were based on data analyzed by the central laboratory and presented in 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 (October 2013). All data were included in by-subject data listings. Laboratory measurements identified as abnormal (ie, outside the normal range) were also listed separately by subject, laboratory test, and unit.

Clinical laboratory measurements, including serum chemistry and hematology, were summarized by treatment group. Descriptive statistics were presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the protocol (Appendix 16.1.1).

Where applicable, hematology and chemistry results for select parameters were assigned a toxicity grade based on the US Department of Health and Human Services CTCAE, version 4.03 (June 2010). Five-by-five contingency tables were presented for laboratory tests where toxicity grading could be applied to summarize the shift from the baseline grade to the worst

post-baseline grade. Grades were presented as none (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Death related to an AE (ie, Grade 5) could not be determined with available laboratory-based data collection and, thus, was not summarized as a category. Summary results included the count and percentage of subjects within each shift category.

Where applicable, laboratory results were classified as "low," "normal," or "high" with respect to the parameter-specific reference ranges (ie, below the lower limit of the normal range, within the normal range, or above the ULN range). Three-by-three contingency tables were presented for laboratory parameters that could not 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 included the count and percentage of subjects within each shift category and treatment group.

9.7.1.5.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

9.7.1.5.5.1.Vital Signs

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

9.7.1.5.5.2.12-lead Electrocardiogram

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

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

Prolonged QT intervals were summarized as QTcF measurements that were > 450, > 470, and > 500 msec at each visit where ECG was routinely collected per the protocol (Appendix 16.1.1). Change from baseline categories were also summarized for measurements that represented a change > 30 or > 60 msec relative to the baseline value. Summary results included the percentage of subjects within each category and treatment group.

9.7.1.5.5.3.Physical Examination

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

9.7.1.5.5.4.Prior and Concomitant Medications

Medications were coded using the WHO Drug 01Mar2018 enhanced dictionary. Medications entered on the eCRF were mapped to ATC drug class (level 4) and drug name.

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

9.7.2. Determination of Sample Size

The sample size calculation for the phase 2 primary endpoint (RR) assumed that the objective RR in the PlaceboPemPlatinum arm was 15%. A total sample size of 176 subjects (88 per arm) in the phase 2 portion of the study provided 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 hazard ratio of 0.714), 338 OS events provided 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 second interim analysis included an option to increase the target number of events, which would have affected the target total number of subjects; however, it was not increased.

The study included an unblinded interim analysis once 50% of the planned OS events for phase 3 had occurred, which was performed by an Independent Analysis Group. The DSMB reviewed the interim analysis report and provided 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 11.4.2.3.

Based on DSMB recommendations, the original planned sample size was changed from 386 subjects to all enrolled up to 15Aug2021 (249 subjects); and the deaths for the original planned final analysis of OS were changed from 338 to the actual number of deaths occurring by 14Aug2022. The estimated power with 249 subjects was predicted to be in a range of 73% to 80% if the true hazard ratio was in a range of 0.71 to 0.68.

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

The original protocol (version 1.0) was dated 10Dec2015. While 5 protocol amendments were issued, no subjects were enrolled until version 4.0 of the protocol, dated 05Dec2016. Versions 4.0, 5.0, and 6.0 of the protocol are provided in Appendix 16.1.1. Details of key changes in these versions of the protocol are described below.

9.8.1.1. Protocol Amendment 3, Protocol Version 4.0

Version 4.0 of the protocol was dated 05Dec2016.

Key revisions within this protocol amendment included the following (see the summary of changes document in Appendix 16.1.1 for details and rationale for each change):

- Removed references that the interim analysis would support "a number of" adaptive decisions. It was the intent to only analyze the adaptive decisions that had previously been listed.
- For the blinded and open-label extension portion of the study, a separate and truncated schedule of assessments was added.
- Revised the eligibility criteria relating to cisplatin and pemetrexed to include some applicable contraindications.
- In the unblinding section, the requirement for Sponsor involvement in the decision-making process for unblinding was removed.
- Added a definition for end of trial as the required number of events (target number of events) being reached in the survival analysis.
- A definition was added for a SUSAR, in addition to a declaration that the Sponsor was to comply with the responsibilities and requirements concerning SAE/SUSAR set forth in the European Directive 2001/20/EC.

9.8.1.2. Protocol Amendment 4, Protocol Version 5.0

Version 5.0 of the protocol was dated 12Nov2019.

Key revisions within this protocol amendment included the following (see the summary of changes document in Appendix 16.1.1 for details and rationale for each change):

- Removed "with Low Argininosuccinate Synthetase 1 Expression" from the protocol title.
- Removed requirement for tumor samples for ASS1 testing as an eligibility criterion and other study-specific sections and references related to tumor sample collection and ASS1 testing.
- Removed RR, DOR, and DCR as secondary efficacy endpoints for the phase 3 portion
- Removed requirement for confirmation of measurable disease by BICR
- Removed requirement for confirmational scans 4 weeks after the scheduled scans showing tumor response (PR and CR)
- Removed requirement for BICR to determine PFS in the phase 3 portion
- Clarified language for the exclusion of subjects who had a history of uncontrolled seizure disorder not related to underlying cancer.
- Updated language for switching from cisplatin to carboplatin to allow more discretion by the Investigators.

- Added hematology, chemistry, and special blood sampling instructions.
- Made the following changes related to the SAP:
  - Included 2 interim analyses: the first one was the RR analysis (at the end of the phase 2 portion) and the second one was the interim OS analysis for futility stopping and sample size re-estimation.
  - Removed sections related to analyses driven by ASS1 expression and adaptive design decisions based on such analyses.
  - Modified methods for addressing multiplicity analyses.
- Administrative changes and other minor editorial corrections, clarifications, and formatting changes were made. Additional supportive and referenced texts were added as background information.

9.8.1.3. Protocol Amendment 5, Protocol Version 6.0

Version 6.0 of the protocol was dated 21Sep2021.

Key revisions within this protocol amendment included the following:

- Added Exploratory research.
- Additional translational research, including pharmacogenomics and profiling of the inflammatory and metabolomic effects of ADI-PEG 20 in combination with pemetrexed and a platinum agent was planned. This research was to be conducted on existing plasma samples from subjects in the US and UK who had consented to their blood samples being used in future research. Also, research was to be conducted on archival tissue from subjects at selected sites in the UK who had consented to their tissue samples being used in future research.

9.8.2. Changes in the Planned Analyses

Version 1.0 of the SAP, dated 02Mar2017, and 3 SAP Amendments are provided in Appendix 16.1.9.

Version 2.0 of the SAP was dated 06Nov2019. Notable changes from version 1.0 to version 2.0 of the SAP corresponded to similar changes from version 4 to version 5 of the protocol and included:

- Removal of secondary endpoints of objective RR and DOR in phase 3. Both endpoints remained 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 OS events had 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, dated 06Nov2019, to version 3.0, dated 07Sep2021, of the SAP were based on DSMB recommendations as follows:

- On 26Apr2021, based on the second interim analysis, the DSMB recommended that Polaris contact regulatory authorities to consider ending enrollment within the next 3 months and continuing follow-up so that all subjects had at least 1 one year of follow-up.
- The original planned sample size was to be changed from 386 subjects to all enrolled up to 15Aug2021 (249 subjects); and the deaths for the original planned final analysis of OS were to be changed from 338 to the actual number of deaths occurring on 14Aug2022. Also, an administrative penalty of $\alpha = 0.00001$ was paid for the second interim analysis, and the allocated $\alpha = 0.04999$ was used for the final analysis.

Changes from version 3.0, dated 07Sep2021, to version 4.0, dated 04Jan2022, of the SAP included only minor clarifications.

9.8.2.1. Changes to Protocol-Defined Analyses

There were no changes to the study conduct or planned analyses identified within the development of version 4.0 of the SAP (Appendix 16.1.9), relative to the descriptions provided within version 6.0 of the protocol (Appendix 16.1.1).

9.8.2.2. Changes to SAP-Defined Analyses

For informative purposes, post-hoc analyses were conducted for OS and PFS by tumor histology type. These analyses were not predefined analyses in the SAP and were not statistically powered.

The SAP states that arginine and citrulline results may have also been correlated with efficacy endpoints, similar to PK; however, correlations are not currently planned.

The sensitivity analysis using rank preserving structural failure time models described in the SAP was not performed.

Graphical analysis for anti-PEG antibodies described in the SAP was removed due to too few responses at each time point. Percent of subjects with positive titer results and range were presented in the tables.

The sensitivity analysis to evaluate the possible impacts introduced by the receipt of therapies for MPM after the end of study treatment was not conducted. The rationale for this omission was that Table 14.3.7.5 (Therapeutic Procedures After the EOT) showed that the percentage of subjects who received any post-treatment therapeutic procedures was similar among the two treatment groups so there was not likely to be a bias regarding an effect of post-treatment procedures.

No other changes to the SAP-defined analyses occurred.

10. STUDY SUBJECTS

10.1. Disposition of Subjects

A summary of the disposition of subjects is presented in Table 6 and in Figure 1. Subject disposition was similar between groups.

Overall, the most common reason for discontinuing ADI-PEG 20 or placebo was PD (67.9% of subjects), followed by AE (13.3% of subjects), withdrawal by subject (8.0% of subjects), and death (6.0% of subjects). The most common reason for study termination was death (88.8% of subjects), followed by "other" (10.4% of subjects, which included study completion for the majority of subjects with a reason of "other", 1 subject with study termination, 2 subjects moving away, 1 subject with an unknown reason, and 1 subject who continued treatment in the blinded expanded phase; Listing 16.2.1), and withdrawal by subject (0.8% of subjects).

Study populations are discussed in Section 11.1.

Table 6: Subject Disposition (All Randomized Subjects)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Safety Population [a]	125 (100%)	124 (100%)	249 (100%)
ITT Population [b]	125 (100%)	124 (100%)	249 (100%)
PP Population [c]	125 (100%)	124 (100%)	249 (100%)
Primary Reason for Discontinuing ADI-PEG 20 or Placebo			
Adverse Event	19 (15.2%)	14 (11.3%)	33 (13.3%)
Death	5 (4.0%)	10 (8.1%)	15 (6.0%)
Lack of Efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Compliance	0 (0.0%)	0 (0.0%)	0 (0.0%)
Physician Decision	2 (1.6%)	3 (2.4%)	5 (2.0%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Progressive Disease	85 (68.0%)	84 (67.7%)	169 (67.9%)
Protocol Violation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sponsor Request	0 (0.0%)	0 (0.0%)	0 (0.0%)
Start Other Anti-Cancer Treatment	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Terminated	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by Subject	8 (6.4%)	12 (9.7%)	20 (8.0%)
Other [d]	6 (4.8%)	0 (0.0%)	6 (2.4%)
Missing	0 (0.0%)	1 (0.8%)	1 (0.4%)
Primary Reason for Study Termination			
Withdrawal by Subject	2 (1.6%)	0 (0.0%)	2 (0.8%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Terminated	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death [e]	105 (84.0%)	116 (93.5%)	221 (88.8%)
Other [f]	18 (14.4%)	8 (6.5%)	26 (10.4%)

[a] Safety Population includes all randomized subjects who received at least one dose of the study medication. Treatment group assignment is based on the treatment actually received.

[b] ITT Population includes all randomized subjects. Treatment group assignment is based on the randomized treatment assignment.

[c] PP Population includes all ITT subjects who had no major protocol violations that may potentially affect the primary and secondary efficacy measures. Treatment group assignment is based on the randomized treatment assignment.

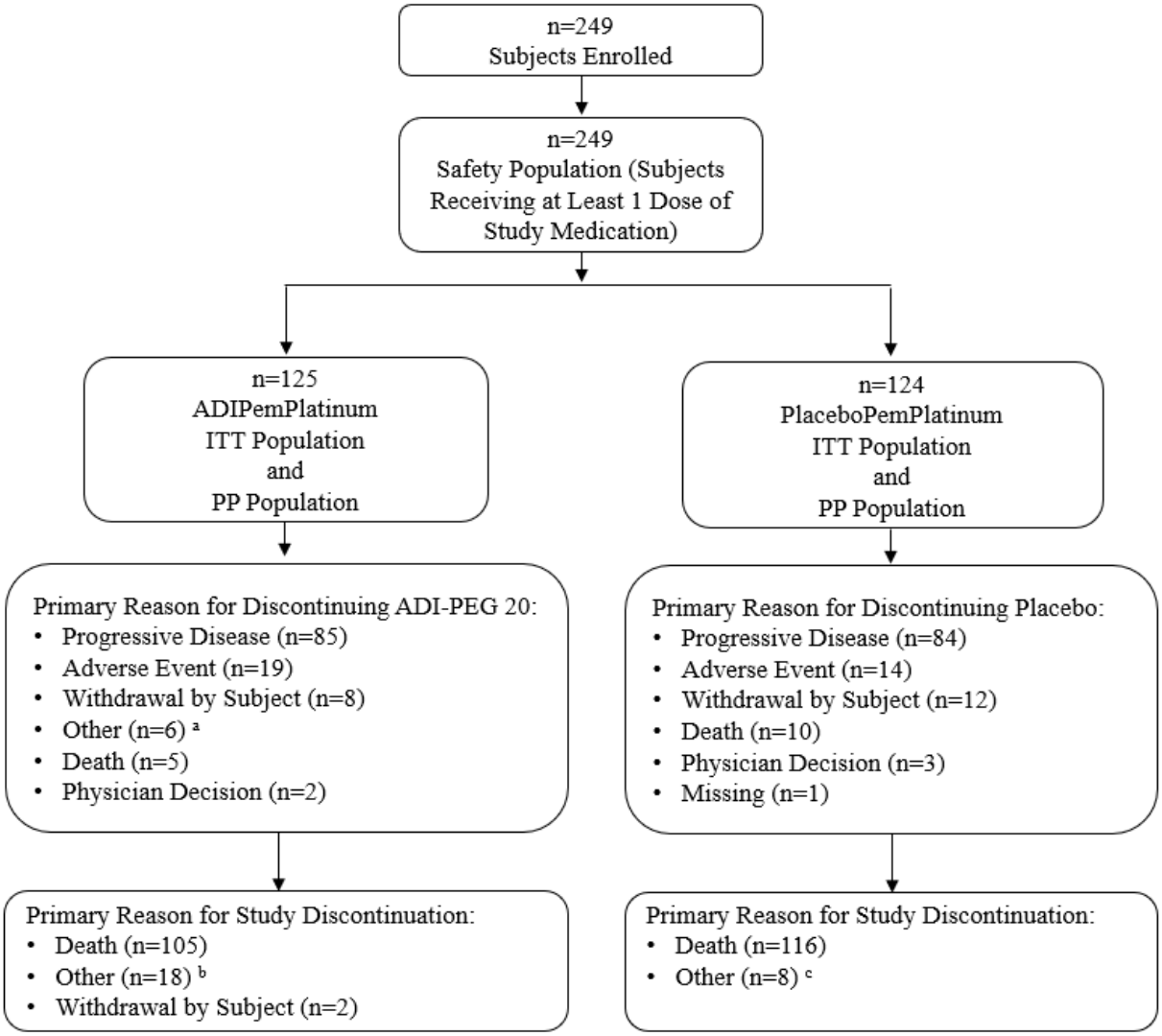
[d] Included subjects who completed treatment; see Listing 16.2.1 for details.

[e] Three additional subjects (Subjects 0107-0003, 0112-0002, and 0107-0007) stopped the study and a date of death was obtained and entered into EDC (reasons for study termination of subject decision to withdraw consent for Subjects 0107-0003 and 0112-0002 and "other: moved to Oregon" for Subject 0107-0007; Listing 16.2.1).

[f] Includes subjects who were still alive and in follow-up at the end of the study; see Listing 16.2.1 for details.

Source: Table 14.1.1.1.

Figure 1: Disposition of Subjects (All Randomized Subjects)



[a] "Other" referred to stable disease, trial completion/stable disease, and subject continuing in the expanded phase. See Listing 16.2.1 for details.
[b] "Other" referred to study completion for the majority of subjects with a reason of "other", 1 subject with study termination, 2 subjects moving away, 1 subject with an unknown reason, and 1 subject who continued treatment in the blinded expanded phase. See Listing 16.2.1 for details.
[c] "Other" referred to study completion. See Listing 16.2.1 for details.
Source: Table 14.1.1.1, Listing 16.2.1

Subject disposition by study center is provided in Table 14.1.1.2.

10.2. Protocol Deviations

A summary of the major protocol deviations is presented in Table 7. Results were similar between groups, with 22 subjects (8.8%) overall with a major protocol deviation (12 subjects [9.6%] and 10 subjects [8.1%] for the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively).

Overall, the most common major protocol deviations were procedures/assessments and study procedures (5 subjects [2.0%], each), SAE criteria (4 subjects [1.6%]), and inclusion/exclusion (3 subjects [1.2%]).

Major protocol deviations are listed by subject in Listing 16.2.2.1. Informed consent and eligibility criteria are listed by subject in Listing 16.2.2.2.

No subjects were excluded from the efficacy analysis (Listing 16.2.3).

Table 7: Major Protocol Deviations (ITT Population)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Any Major Protocol Deviations	12 (9.6%)	10 (8.1%)	22 (8.8%)
ICF	1 (0.8%)	0 (0.0%)	1 (0.4%)
Inclusion/Exclusion	1 (0.8%)	2 (1.6%)	3 (1.2%)
IP Administration	0 (0.0%)	1 (0.8%)	1 (0.4%)
Procedures-Assessments	2 (1.6%)	3 (2.4%)	5 (2.0%)
SAE Criteria	3 (2.4%)	1 (0.8%)	4 (1.6%)
Serious Breach of GCP	1 (0.8%)	0 (0.0%)	1 (0.4%)
Stratification Error	1 (0.8%)	1 (0.8%)	2 (0.8%)
Study Procedures [a]	3 (2.4%)	2 (1.6%)	5 (2.0%)

[a] Subjects all started on carboplatin instead of cisplatin. The protocol was subsequently amended to allow subjects to start on carboplatin without first starting on cisplatin; see Appendix 16.1.1.

Note: Subjects reporting more than one deviation in a category were counted only once and subjects may have been included in more than one category.

Source: Table 14.1.2

11. EFFICACY EVALUATION

11.1. Data Sets Analyzed

Definitions of the analysis populations are provided in Section 9.7.1.2. A summary of study populations is presented in Table 6. All subjects (100%) enrolled in the study were included in the Safety, ITT, and PP Populations.

11.2. Demographic and Other Baseline Characteristics

11.2.1. Subject Demographics

A summary of subject demographics for the Safety Population is presented in Table 8. Subject demographics were similar between groups.

Overall, the mean age of subjects was 69.4 years of age, and a majority of subjects were male (82.7%), white (93.2%), and not Hispanic or Latino (94.8%).

A by-subject listing of subject demographics is provided in Listing 16.2.4.1.

Table 8: Subject Demographics (Safety Population)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Age (years) [a]			
n	125	124	249
Mean (SD)	69.5 (7.98)	69.4 (7.91)	69.4 (7.93)
Median	71.0	70.0	71.0
Min, Max	28, 84	34, 86	28, 86
Sex			
Male	102 (81.6%)	104 (83.9%)	206 (82.7%)
Female	23 (18.4%)	20 (16.1%)	43 (17.3%)
Ethnicity			
Hispanic or Latino	2 (1.6%)	2 (1.6%)	4 (1.6%)
Not Hispanic or Latino	119 (95.2%)	117 (94.4%)	236 (94.8%)
Unknown	4 (3.2%)	5 (4.0%)	9 (3.6%)
Race			
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	5 (4.0%)	5 (4.0%)	10 (4.0%)
Black or African American	3 (2.4%)	0 (0.0%)	3 (1.2%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	116 (92.8%)	116 (93.5%)	232 (93.2%)
Other	1 (0.8%)	3 (2.4%)	4 (1.6%)

[a] Age was calculated relative to the date of informed consent.
Source: Table 14.1.3.1

11.2.2. Subject Baseline Characteristics

A summary of subject baseline characteristics is presented in Table 9. Subject baseline characteristics were similar between groups. Overall, mean height was 171.05 cm, mean weight

was 77.15 kg, mean BSA was 1.889 m^2, and the majority of subjects (73.9%) had an ECOG performance status of 1.

A by-subject listing of ECOG performance status is provided in Listing 16.2.9.5.

Table 9: Subject Baseline Characteristics (Safety Population)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Height (cm)			
n	123	121	244
Mean (SD)	171.45 (7.856)	170.64 (8.258)	171.05 (8.052)
Median	172.00	171.00	171.95
Min, Max	150.5, 188.2	144.8, 190.0	144.8, 190.0
Weight (kg)			
n	125	124	249
Mean (SD)	77.92 (15.265)	76.37 (13.794)	77.15 (14.542)
Median	78.00	74.90	75.80
Min, Max	43.0, 142.0	40.3, 131.0	40.3, 142.0
BSA (m^2)			
n	125	124	249
Mean (SD)	1.897 (0.1894)	1.881 (0.1844)	1.889 (0.1867)
Median	1.900	1.880	1.890
Min, Max	1.42, 2.31	1.27, 2.41	1.27, 2.41
ECOG Performance Status			
0	38 (30.4%)	27 (21.8%)	65 (26.1%)
1	87 (69.6%)	97 (78.2%)	184 (73.9%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Baseline was defined as the last available measurement taken prior to the first dose of study drug.
Source: Table 14.1.4.1

A summary of subject disease history is presented in Table 10. Subject disease history was similar between groups.

Overall, the largest percentages of subjects had Stage III (28.5%; including IIIA, IIIB, and IIIC) or Stage IV (22.9%) MPM. Approximately half of subjects (48.2%) had biphasic MPM and half of subjects (51.8%) had sarcomatoid MPM. A majority of subjects did not have previous radiation treatment (94.8%) or surgeries (85.1%) related to actual cancer.

By-subject listings of prior radiation treatments and prior surgeries to treat cancer are provided in Listing 16.2.4.3 and Listing 16.2.4.4, respectively.

Table 10: Subject Disease History (Safety Population)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Stage of Malignant Pleural Mesothelioma			
0	0 (0.0%)	0 (0.0%)	0 (0.0%)
I	0 (0.0%)	2 (1.6%)	2 (0.8%)
IA	8 (6.4%)	5 (4.0%)	13 (5.2%)
IB	16 (12.8%)	12 (9.7%)	28 (11.2%)
II	12 (9.6%)	16 (12.9%)	28 (11.2%)
IIIA	18 (14.4%)	18 (14.5%)	36 (14.5%)
IIIB	13 (10.4%)	21 (16.9%)	34 (13.7%)
IIIC	0 (0.0%)	1 (0.8%)	1 (0.4%)
IV	28 (22.4%)	29 (23.4%)	57 (22.9%)
Unknown	30 (24.0%)	20 (16.1%)	50 (20.1%)
Type of Histology			
Biphasic	60 (48.0%)	60 (48.4%)	120 (48.2%)
Sarcomatoid	65 (52.0%)	64 (51.6%)	129 (51.8%)
Previous Radiation Treatments Related to Actual Cancer			
Yes	4 (3.2%)	9 (7.3%)	13 (5.2%)
No	121 (96.8%)	115 (92.7%)	236 (94.8%)
Previous Surgeries Related to Actual Cancer			
Yes	18 (14.4%)	19 (15.3%)	37 (14.9%)
No	107 (85.6%)	105 (84.7%)	212 (85.1%)

Source: Table 14.1.5.1

11.3. Measurements of Treatment Compliance

As described in Section 9.4.8, ADI-PEG 20 or placebo was administered by study staff via IM injection to subjects once weekly, and the Investigator or appropriate designee maintained a record of all study medications received and dispensed. Therefore, no additional measures of treatment compliance were performed for this study.

Extent of exposure summary data are presented and discussed in Section 12.1.

11.4. Efficacy Results and Tabulations of Individual Subject Data

11.4.1. Analysis of Efficacy

A by-subject listing of derived efficacy data is provided in Listing 16.2.6.1.

11.4.1.1. Primary Efficacy Endpoint

11.4.1.1.1. Phase 2 Portion - Response Rate

A summary of objective RR for the ITT Population for the phase 2 portion is presented in Table 11. A numerically greater percentage of subjects had a best tumor response of stable disease in the ADIPemPlatinum group compared with the PlaceboPemPlatinum group (71.3% and 62.9%, respectively), with similar percentages of subjects with PR (13.8% and 12.4%, respectively) or CR (0% and 1.1%, respectively) in both groups. The objective RR was similar between groups (13.8% and 13.5% for the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively; p = 0.9489; relative risk ratio [95% CI] = 1.02 [0.50, 2.11]).

By-subject listings of response assessment (RECIST criteria), target lesions, non-target lesions, and new lesions are provided in Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4, and Listing 16.2.6.5, respectively.

Table 11: Objective Response Rate – Phase 2 Subjects (ITT Population)

Best Tumor Response [a]	ADIPemPlatinum (N = 87)	PlaceboPemPlatinum (N = 89)	P-value [c]	Relative Risk Ratio (95% CI) [d]
CR	0 (0.0%)	1 (1.1%)	-	-
PR	12 (13.8%)	11 (12.4%)	-	-
SD	62 (71.3%)	56 (62.9%)	-	-
PD	6 (6.9%)	10 (11.2%)	-	-
Missing or Not Evaluable	7 (8.0%)	11 (12.4%)	-	-
Objective Response Rate (CR or PR) [b]	12 (13.8%)	12 (13.5%)	0.9489	1.02 (0.50, 2.11)

[a] The best tumor response was the best response recorded from the start of the treatment until EOT taking into account any requirement for confirmation.
[b] Objective RR was calculated as the proportion of subjects whose best tumor response from all post-baseline tumor assessments was CR or PR.
[c] P-value comparing ADIPemPlatinum to PlaceboPemPlatinum was based on the CMH test stratified by tumor histology (biphasic vs sarcomatoid).
[d] Relative Risk Ratio (ADIPemPlatinum/PlaceboPemPlatinum) was the common relative risk of having a response (CR or PR) based on the Mantel-Haenszel estimator controlling for tumor histology. A relative risk ratio greater than 1 was favorable to ADIPemPlatinum.
Source: Table 14.2.1.1

11.4.1.1.2. Phase 3 Portion – Overall Survival

A summary of OS for the ITT Population for the phase 3 portion (the phase 3 primary endpoint) is presented in Table 12. The number (%) of subjects who died during the study was smaller for the ADIPemPlatinum group (108 subjects [86.4%]) compared with the PlaceboPemPlatinum group (116 subjects [93.5%]). In addition, the median OS was statistically significantly longer for the ADIPemPlatinum group (9.30 months) when compared with the PlaceboPemPlatinum group (7.66 months; hazard ratio of 0.71; p = 0.0234).

A Kaplan-Meier plot of OS is presented in Figure 2. The probability of survival was higher for the ADIPemPlatinum group throughout the study compared with the PlaceboPemPlatinum group.

A summary of OS by tumor histology for the ITT Population for the phase 3 portion is presented in Table 13. Lower numbers (%) of subjects had events for the ADIPemPlatinum groups for both tumor histology types, compared with the PlaceboPemPlatinum group (biphasic: 51 subjects [85.0%] vs 54 subjects [90.0%], respectively; sarcomatoid: 57 subjects [87.7%] vs 62 subjects [96.9%], respectively). In addition, the median OS was longer for the ADIPemPlatinum group when compared with the PlaceboPemPlatinum group for both tumor histology types (biphasic: 12.16 months vs 10.38 months, respectively; sarcomatoid: 7.00 months vs 5.96 months, respectively). When data were stratified by tumor histology type, the hazard ratios (95% CIs) for both biphasic MPM and sarcomatoid MPM favored ADIPemPlatinum over PlaceboPemPlatinum (0.68 [0.48, 0.98] and 0.80 [0.55, 1.18], respectively), with statistical significance being reached for the sarcomatoid, but not the biphasic, tumor type (p-values of 0.0393 and 0.2614, respectively). These comparisons for OS by tumor type were added for informative purposes as

post-hoc analyses and were not predefined analyses in the SAP and were not statistically powered.

A by-subject listing of long-term follow-up is provided in Listing 16.2.6.6.

Table 12: Overall Survival – Phase 3 Subjects (ITT Population)

Survival Estimates (Months)	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Number (%) of Subjects with Event	108 (86.4%)	116 (93.5%)
Number (%) of Subjects Censored	17 (13.6%)	8 (6.5%)
Quartiles (95% CI) [a]		
25th Percentile	5.13 (3.75, 5.85)	3.79 (2.79, 4.90)
Median [b]	9.30 (7.85, 11.79)	7.66 (6.14, 9.53)
75th Percentile	18.30 (13.93, 21.98)	13.27 (10.94, 17.02)
Range (Subjects with Event)	0.23, 36.99	0.69, 40.44
Range (All Subjects)	0.23, 55.69	0.69, 49.22
Hazard Ratio (95% CI) [c]	0.71 (0.55, 0.93)	
P-value [d]	0.0234	

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

[a] Kaplan-Meier product-limit estimates.

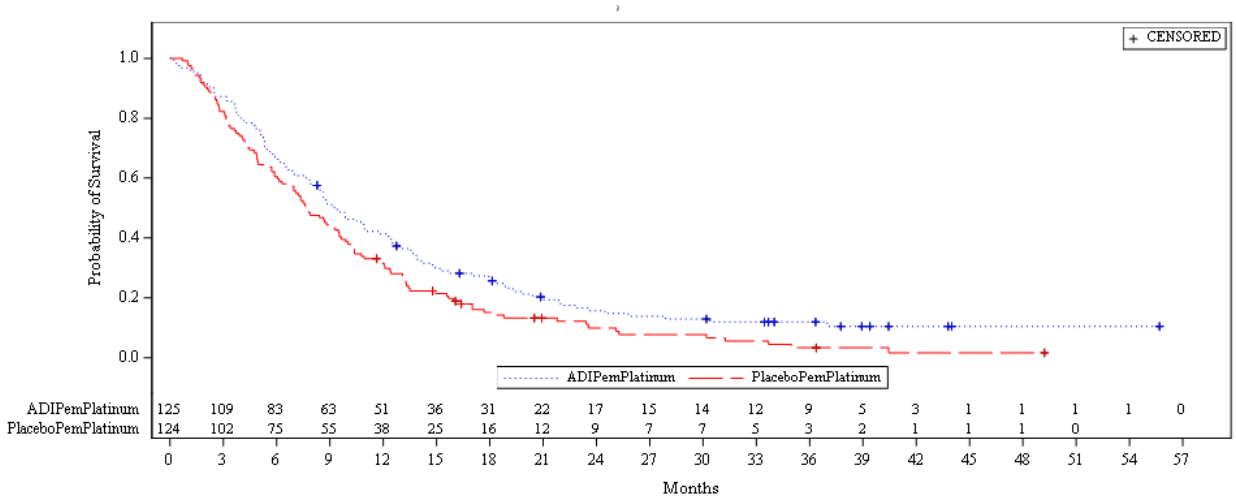
[b] Median was defined to be the smallest observed survival time for which the value of the estimated survival function was less than or equal to 0.5.

[c] Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI were obtained from a Cox proportional hazards model adjusting for tumor histology (biphasic vs sarcomatoid). A hazard ratio less than 1 was favorable to ADIPemPlatinum.

[d] P-value comparing the treatment groups was based on the log-rank test stratified by tumor histology (biphasic vs sarcomatoid).

Source: Table 14.2.3.1

Figure 2: Kaplan-Meier Plot of OS – Phase 3 Subjects (ITT Population)



Notes:

- Analysis population was the ITT Population: Included all randomized subjects.
- Overall Survival was calculated as the time from randomization until death. In the event that no death was documented prior to study termination or analysis cutoff, OS was censored at the last known date the subject was known to be alive (using last contact day or last dose day).
- Total number of subjects from the analysis population was 249, including 25 censored subjects (17 from ADIPemPlatinum, 8 from PlaceboPemPlatinum) and 224 subjects with OS events (108 from ADIPemPlatinum, 116 from PlaceboPemPlatinum).

Source: Figure 14.4.1.1

Table 13: Overall Survival by Tumor Histology– Phase 3 Subjects (ITT Population)

Survival Estimates (Months)	Biphasic		Sarcomatoid	
	ADIPemPlatinum (N = 60)	PlaceboPemPlatinum (N = 60)	ADIPemPlatinum (N = 65)	PlaceboPemPlatinum (N = 64)
Number (%) of Subjects with Event	51 (85.0%)	54 (90.0%)	57 (87.7%)	62 (96.9%)
Number (%) of Subjects Censored	9 (15.0%)	6 (10.0%)	8 (12.3%)	2 (3.1%)
Quartiles (95% CI) [a]				
25th Percentile	6.77 (5.26, 8.64)	4.91 (3.71, 7.82)	3.68 (2.46, 5.06)	3.07 (1.87, 4.04)
Median [b]	12.16 (8.64, 13.93)	10.38 (7.82, 13.44)	7.00 (5.13, 10.51)	5.96 (4.27, 7.36)
75th Percentile	21.98 (14.92, 30.39)	17.02 (13.44, 25.26)	14.78 (10.94, 21.03)	10.09 (7.36, 12.39)
Range (Subjects with Event)	1.12, 36.99	1.02, 40.44	0.23, 24.48	0.69, 30.19
Range (All Subjects)	1.12, 55.69	1.02, 49.22	0.23, 43.99	0.69, 36.37
Hazard Ratio (95% CI) [c]	0.80 (0.55, 1.18)	-	0.68 (0.48, 0.98)	-
P-value [d]	0.2614	-	0.0393	-

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

[a] Kaplan-Meier product-limit estimates

[b] Median was defined as the smallest observed survival time for which the value of the estimated survival function was less than or equal to 0.5.

[c] Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI were obtained from a Cox proportional hazards model. A hazard ratio less than 1 was favorable to ADIPemPlatinum.

[d] P-value comparing the treatment groups was based on the log-rank test.

Source: Table 14.2.3.3

11.4.1.2. Secondary Efficacy Endpoints

11.4.1.2.1. Phase 2 Portion – Duration of Response

A summary of DOR for the ITT Population for the phase 2 portion is presented in Table 14.

The number (%) of subjects who were censored (ie, did not have tumor progression or death at the EOT) was greater for the ADIPemPlatinum group (8 subjects [66.7%]) compared with the PlaceboPemPlatinum (3 subjects [25.0%]). Due to the large percentage of subjects who were censored in the ADIPemPlatinum group, it was not possible to calculate a DOR for this group. The hazard ratio (95% CI) of 0.34 (0.10, 1.14) favored ADIPemPlatinum over PlaceboPemPlatinum, indicating a longer, but not statistically significantly different, DOR, with a p-value of 0.0918.

Table 14: Duration of Response – Phase 2 Subjects (ITT Population)

Survival Estimates (Months)	ADIPemPlatinum (N = 87)	PlaceboPemPlatinum (N = 89)
Number of Subjects with Best Overall Response of CR or PR	12	12
Number (%) of Subjects with Event	4 (33.3%)	9 (75.0%)
Number (%) of Subjects Censored	8 (66.7%)	3 (25.0%)
Quartiles (95% CI) [a]		
25th Percentile	4.63 (3.71, NA)	3.65 (2.79, 4.63)
Median [b]	NA (NA, NA)	4.63 (3.65, 11.76)
75th Percentile	NA (NA, NA)	11.76 (4.63, NA)
Range (Subjects with Event)	3.71, 6.11	2.79, 11.99
Range (All Subjects)	2.56, 22.34	2.79, 11.99
Hazard Ratio (95% CI) [c]	0.34 (0.10, 1.14)	
P-value [d]	0.0918	

Note: DOR was defined 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 EOT were censored using the date of the last tumor assessment demonstrating no tumor progression.

[a] Kaplan-Meier product-limit estimates.

[b] Median was defined to be the smallest observed survival time for which the value of the estimated survival function was less than or equal to 0.5.

[c] Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI were obtained from a Cox proportional hazards model adjusting for tumor histology (biphasic vs sarcomatoid). A hazard ratio less than 1 was favorable to ADIPemPlatinum.

[d] P-value comparing the treatment groups was based on the log-rank test stratified by tumor histology (biphasic vs sarcomatoid).

Source: Table 14.2.2.1

11.4.1.2.2. Phase 3 Portion – Progression-Free Survival

A summary of PFS for the ITT Population for the phase 3 portion (the phase 3 secondary endpoint) is presented in Table 15. The number (%) of subjects with a PFS event (tumor progression or death) during the study was smaller for the ADIPemPlatinum group (71 subjects [56.8%]) compared with the PlaceboPemPlatinum group (74 subjects [59.7%]). In addition, the median PFS was statistically significantly longer for the ADIPemPlatinum group (6.24 months) when compared with the PlaceboPemPlatinum group (5.65 months; hazard ratio of 0.65; p = 0.0193).

A Kaplan-Meier plot of PFS is presented in Figure 3. The probability of PFS was higher for the ADIPemPlatinum group throughout the study compared with the PlaceboPemPlatinum group.

A summary of PFS by tumor histology for the ITT Population for the phase 3 portion is presented in Table 16. For the biphasic tumor histology type, the number (%) of subjects with a PFS event (tumor progression or death) was smaller for the ADIPemPlatinum group compared with the PlaceboPemPlatinum group (36 subjects [60.0%] vs 41 subjects [68.3%], respectively). For the sarcomatoid tumor histology type, similar numbers (%) of subjects had events (35 subjects [53.8%] vs 33 subjects [51.6%], respectively). The median PFS was longer for the ADIPemPlatinum group when compared with the PlaceboPemPlatinum group for both tumor histology types (biphasic: 6.90 months vs 5.78 months, respectively; sarcomatoid: 6.11 months

vs 4.14 months, respectively). When data were stratified by tumor histology type, the hazard ratios (95% CIs) for both biphasic MPM and sarcomatoid MPM favored ADIPemPlatinum over PlaceboPemPlatinum (0.74 [0.47, 1.16] and 0.60 [0.37, 0.99], respectively), with statistical significance being reached for the sarcomatoid, but not the biphasic, tumor type (p-values of 0.0411 and 0.1886, respectively). These comparisons for PFS by tumor type were added for informative purposes as post-hoc analyses and were not predefined analyses in the SAP and were not statistically powered.

Table 15: Progression-Free Survival – Phase 3 Subjects (ITT Population)

Survival Estimates (Months)	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Number (%) of Subjects with Event	71 (56.8%)	74 (59.7%)
Number (%) of Subjects Censored	54 (43.2%)	50 (40.3%)
Quartiles (95% CI) [a]		
25th Percentile	3.98 (2.89, 4.24)	2.60 (2.14, 3.19)
Median [b]	6.24 (5.78, 7.43)	5.65 (4.14, 5.91)
75th Percentile	9.53 (7.62, 12.91)	7.62 (6.05, 9.53)
Range (Subjects with Event)	0.23, 19.61	0.69, 15.93
Range (All Subjects)	0.03, 24.15	0.03, 15.93
Hazard Ratio (95% CI) [c]	0.65 (0.46, 0.90)	
P-value [d]	0.0193	

Note: Progression-free survival was defined as the time from randomization until date of tumor progression or death. In the event that no tumor progression or death was documented prior to EOT, analysis cutoff, or the start of confounding anticancer therapy, PFS was censored at the date of the last tumor assessment demonstrating no tumor progression.

[a] Kaplan-Meier product-limit estimates.

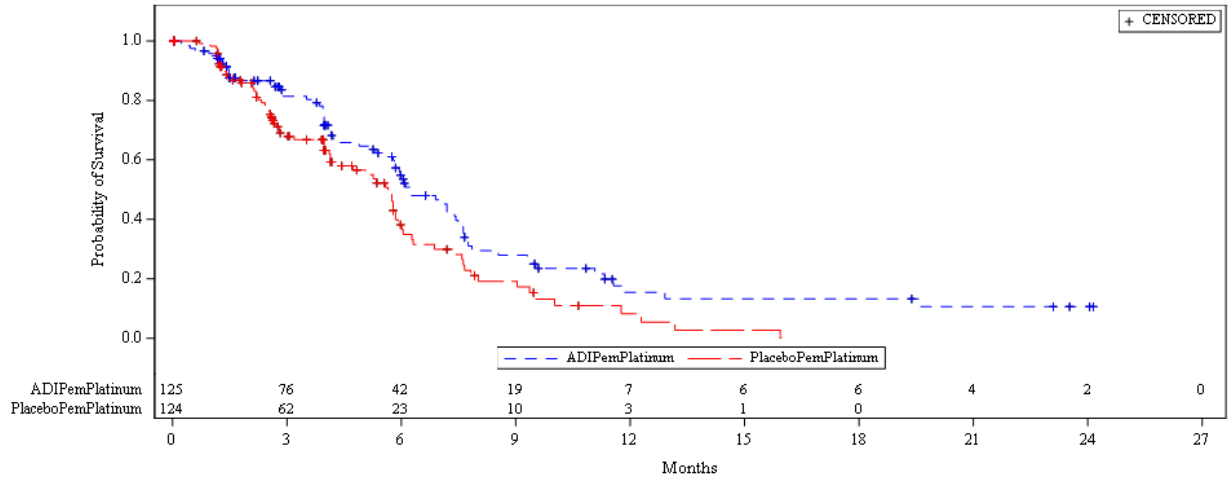
[b] Median was defined to be the smallest observed survival time for which the value of the estimated survival function was less than or equal to 0.5.

[c] Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI were obtained from a Cox proportional hazards model adjusting for tumor histology (biphasic vs sarcomatoid). A hazard ratio less than 1 was favorable to ADIPemPlatinum.

[d] P-value comparing the treatment groups was based on the log-rank test stratified by tumor histology (biphasic vs sarcomatoid).

Source: Table 14.2.4.1

Figure 3: Kaplan-Meier Plot of PFS – Phase 3 Subjects (ITT Population)



Notes:
- Analysis population was the ITT Population: Included all randomized subjects.
- Progression-free survival was calculated as the time from randomization until date of tumor progression or death. In the event that no tumor progression or death was documented prior to EOT, analysis cutoff, or the start of confounding anticancer therapy, PFS was censored at the date of the last tumor assessment demonstrating no tumor progression.
- Total number of subjects from the analysis population was 249, including 104 censored subjects (54 from ADIPemPlatinum, 50 from PlaceboPemPlatinum) and 145 subjects with PFS events (71 from ADIPemPlatinum, 74 from PlaceboPemPlatinum).

Source: Figure 14.4.2.1

Table 16: Progression-Free Survival by Tumor Histology– Phase 3 Subjects (ITT Population)

Survival Estimates (Months)	Biphasic		Sarcomatoid	
	ADIPemPlatinum (N = 60)	PlaceboPemPlatinum (N = 60)	ADIPemPlatinum (N = 65)	PlaceboPemPlatinum (N = 64)
Number (%) of Subjects with Event	36 (60.0%)	41 (68.3%)	35 (53.8%)	33 (51.6%)
Number (%) of Subjects Censored	24 (40.0%)	19 (31.7%)	30 (46.2%)	31 (48.4%)
Quartiles (95% CI) [a]				
25th Percentile	4.24 (2.83, 5.95)	2.79 (2.14, 5.06)	3.52 (1.48, 4.14)	2.43 (1.22, 2.92)
Median [b]	6.90 (5.85, 7.49)	5.78 (5.06, 7.43)	6.11 (3.98, 7.66)	4.14 (2.92, 5.85)
75th Percentile	9.30 (7.43, 19.61)	8.02 (6.87, 10.02)	9.53 (7.62, NA)	6.05 (5.78, NA)
Range (Subjects with Event)	0.95, 19.61	1.15, 15.93	0.23, 12.91	0.69, 12.29
Range (All Subjects)	0.03, 24.05	0.03, 15.93	0.03, 24.15	0.03, 12.29
Hazard Ratio (95% CI) [c]	0.74 (0.47, 1.16)	-	0.60 (0.37, 0.99)	-
P-value [d]	0.1886	-	0.0411	-

Note: Progression-free survival was defined as the time from randomization until date of tumor progression or death. In the event that no tumor progression or death was documented prior to EOT, analysis cutoff, or the start of confounding anticancer therapy, PFS was censored at the date of the last tumor assessment demonstrating no tumor progression.

[a] Kaplan-Meier product-limit estimates

[b] Median was defined as the smallest observed survival time for which the value of the estimated survival function was less than or equal to 0.5.

[c] Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI were obtained from a Cox proportional hazards model. A hazard ratio less than 1 was favorable to ADIPemPlatinum.

[d] P-value comparing the treatment groups was based on the log-rank test.

Source: Table 14.2.4.3

11.4.1.3. Pharmacodynamic Results

A summary of pharmacodynamic parameter values by visit for the ITT Population is presented for the ADIPemPlatinum group in Table 14.2.5.1. Pharmacodynamic blood sampling is listed by subject in Listing 16.2.5.5.

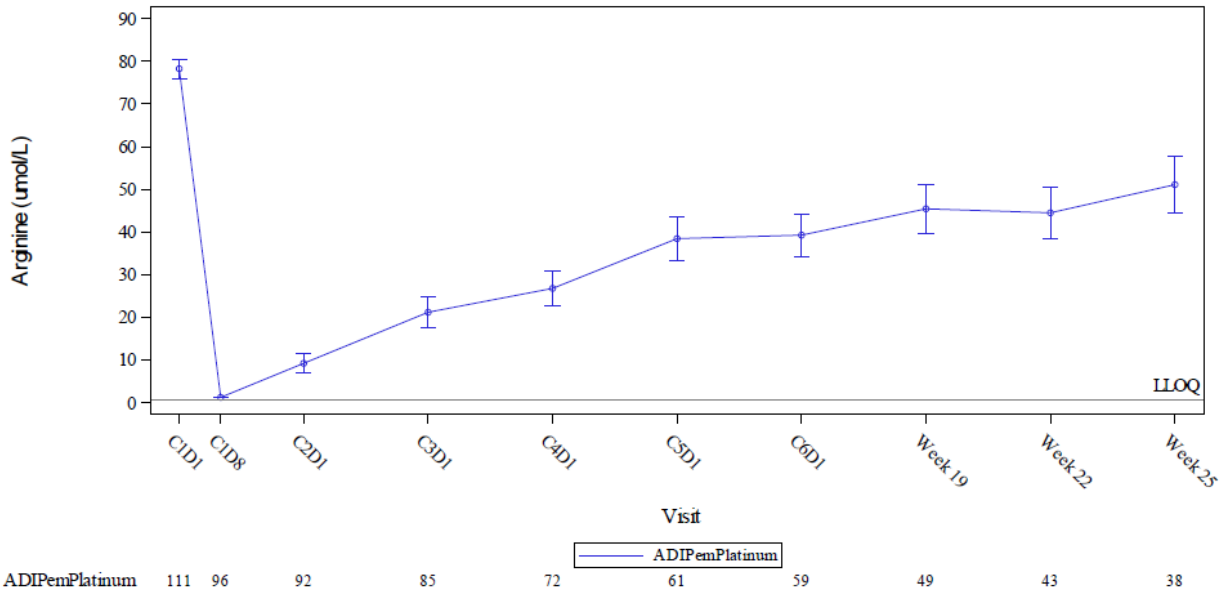
It should be noted that the plasma samples used for these analyses were obtained from subjects weekly on the day of next dosing, on the 7th day after the prior dose. This sampling schedule provided information on the plasma arginine and citrulline levels at the end of a week after each dosing. Thus, if there was depletion or partial reduction of plasma arginine levels during Days 1 through 7 after each dosing, the current sampling schedule would not have been able to detect it.

Mean arginine and citrulline blood levels over time are presented in Figure 4 and Figure 5, respectively. At baseline, the mean arginine blood level value was 78.27 µmol/L for the ADIPemPlatinum group (Table 14.2.5.1). At C1D8, the mean value rapidly decreased to BQL (1.21 µmol/L; change from baseline of - 77.98 µmol/L), and while mean values increased over the study span after C1D8, a decrease from baseline was sustained through the last sampling time point at Week 25 (mean value of 51.09 µmol/L, with a change from baseline of - 39.13 µmol/L).

At baseline, the mean citrulline blood level value was 31.01 µmol/L for the ADIPemPlatinum group (Table 14.2.5.1). At C1D8, the mean value rapidly increased to 397.90 µmol/L (change from baseline of + 374.80 µmol/L), and while mean values then decreased to ~150 µmol/L at C6D1, they remained above that level through the last sampling time point at Week 25 (mean value of 170.31 µmol/L, with a change from baseline of + 142.77 µmol/L).

The pharmacodynamic data demonstrated that repetitive dosing of ADI-PEG 20 resulted in sustained decreases in peripheral blood arginine, with a concomitant rise in citrulline.

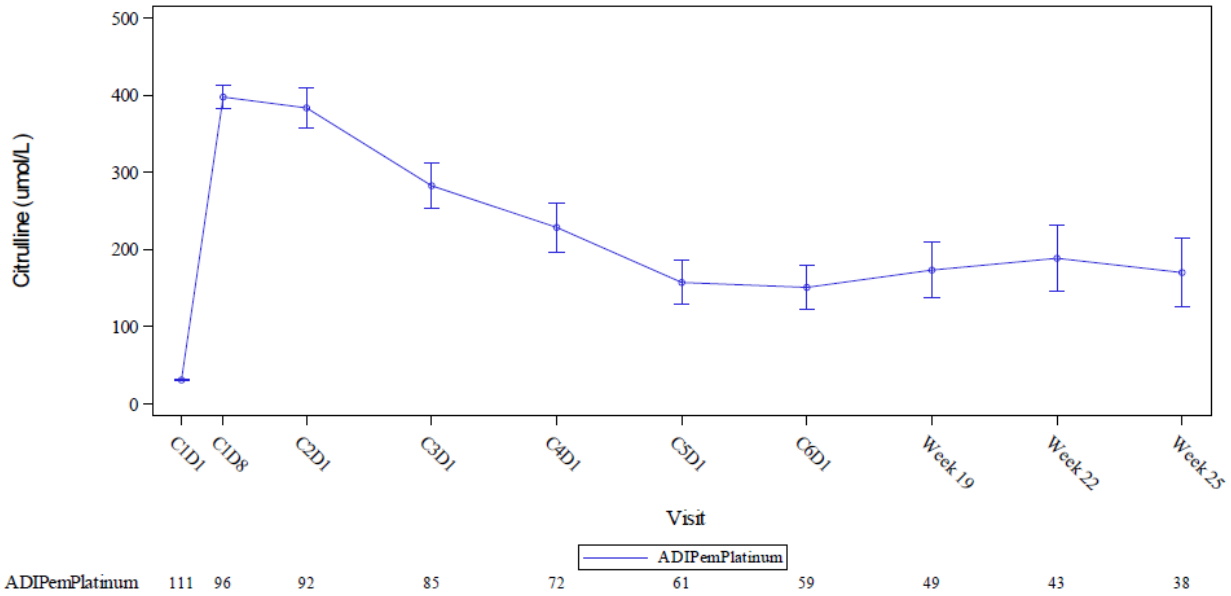
Figure 4: Mean Arginine Blood Levels Over Time (ITT Population)



Notes:
- Baseline was the value at Cycle 1, Day 1.
- The figure presents the mean (± standard error) at each scheduled visit. Values below the figure represent the number of subjects with non-missing values at each visit.
- Results marked as BQL were assigned values of LLOQ/2 for summary purposes. For Arginine, LLOQ = 0.75 and ULOQ = 750.

Source: Figure 14.4.4.1

Figure 5: Mean Citrulline Blood Levels Over Time (ITT Population)



Notes:
- Baseline was the value at Cycle 1, Day 1.
- The figure presents the mean (± standard error) at each scheduled visit. Values below the figure represent the number of subjects with non-missing values at each visit.
- Results marked as BQL were assigned values of LLOQ/2 for summary purposes. For Citrulline, LLOQ = 1.5 and ULOQ = 1500.

Source: Figure 14.4.4.2

11.4.1.4. Immunogenicity Results

A summary of immunogenicity parameters (ADI-PEG 20 ADA and anti-PEG antibody) by visit for the ITT Population is presented for the ADIPemPlatinum group in Table 14.2.5.2. Immunogenicity blood sampling is listed by subject in Listing 16.2.5.5.

As described in Section 11.4.1.3 for pharmacodynamic data, it should be noted that the plasma samples used for immunogenicity analyses were obtained from subjects weekly on the day of next dosing, on the 7th day after the prior dose.

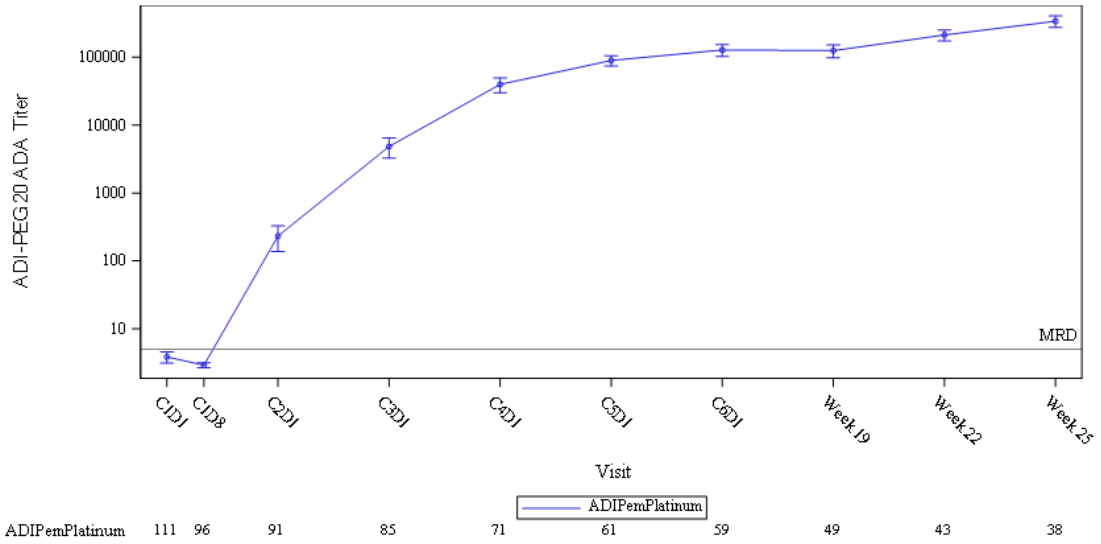
Mean anti-ADI-PEG 20 antibody blood levels over time are presented in Figure 6. At baseline, the mean ADI-PEG 20 ADA titer was 3.8 for the ADIPemPlatinum group (Table 14.2.5.2). At C1D8, the mean titer was 2.9 (change from baseline of -0.5), and at C2D1, the mean titer increased to 232.2 (change from baseline of + 212.0). Mean titers increased over the study after C1D8, with a mean titer of 340724.4 at the last sampling time point at Week 25 (change from baseline of + 348982.8).

Immunogenicity data showed an increase in mean ADI-PEG 20 ADA titers over time and suggested that there was a correlation between decreased levels of circulating arginine following C1D8 (shown in Figure 4) and an increase in antibody titers.

At baseline, 4.5% of subjects had detectible anti-PEG antibodies with low titers (< 1070) before treatment with ADI-PEG 20 (Table 14.2.5.2). Subjects with detectable anti-PEG antibodies did not exceed 8.3% of subjects at any time point through the last sampling time point at Week 25,

and individual titers did not exceed 3740. Detection of anti-PEG antibodies appeared to be sporadic, of short duration, low level, and did not correlate with the presence or absence of anti-ADI-PEG 20 antibodies or length of treatment with ADI-PEG 20.

Figure 6: Mean Anti-ADI-PEG 20 Antibody Titers Over Time (ITT Population)



Notes:
- Baseline was the value at Cycle 1, Day 1.
- The figure presents the mean (± standard error) at each scheduled visit. Values below the figure represent the number of subjects with non-missing values at each visit.
- Negative results and results marked as below MRD were assigned values of MRD/2 for summary purposes. For ADI-PEG 20 ADA Titer, MRD = 5.

Source: Figure 14.4.4.3

11.4.2. Statistical/Analytical Issues

11.4.2.1. Adjustments for Covariates

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

11.4.2.2. Handling of Dropouts or Missing Data

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

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

No other imputations of missing data were made.

11.4.2.3. Interim Analyses and Data Monitoring

This study included two separate interim analyses:

- The first interim analysis was conducted at the end of the phase 2 portion, after adequate response assessment of the first 176 subjects enrolled. This interim analysis

evaluated the treatment effect on RR in the ITT Population. The results of the first interim analysis were that the difference in RR between the two treatment groups was not statistically significant. The decision was made to not submit for accelerated approval and the study continued as planned.

- The second interim analysis was performed once 50% of the planned OS events for phase 3 had occurred (ie, 169 of the 338 planned OS events). This interim analysis evaluated OS in the ITT Population in an unblinded manner. The results of the second interim analysis were that Option 1 below was selected with the original planned target number of OS events. However, based on the positive results from this second interim analysis, and due to slow study enrollment related to an evolving treatment landscape for MPM and the COVID-19 pandemic, the DSMB recommended that Polaris contact regulatory authorities to consider ending enrollment within the next 3 months and continue follow up so that all subjects had at least one year of follow up. This strategy was discussed with the FDA and enrollment was stopped in August 2021.

The RR data were analyzed at the end of the phase 2 portion to support accelerated approval. The OS data at the second interim analysis were 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 was applied at the second interim analysis to support a decision to possibly terminate the study due to futility. The treatment's futility was evaluated based on the comparison of the median OS times in the ADIPemPlatinum and PlaceboPemPlatinum groups. The study was to be allowed to be terminated if the median OS in the ADIPemPlatinum group was less than that in the PlaceboPemPlatinum group. This futility stopping rule was to be non-binding and could be overridden by the DSMB and/or Polaris.

A sample size re-estimation rule was applied at the second interim analysis to support a decision to possibly increase the target number of OS events. The target number of OS events could have been modified based on the CP for the OS evaluation in the ITT Population.

The following sample size re-estimation rule was applied:

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

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

Details regarding the DSMB instituted for this study are included in Section 9.1.6.

11.4.2.4. Multicenter Studies

This was a global, multicenter study. Efficacy data collected from all study centers were pooled for data analysis.

11.4.2.5. Multiple Comparison/Multiplicity

The efficacy endpoint (RR) was evaluated at the end of the phase 2 portion at $\alpha = 0.05$ (two-sided) for the purpose of determining if the data supported accelerated approval.

Since comparison of RR was only 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 was maintained at $\alpha = 0.05$.

The primary endpoint (OS) was 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 was performed for the purposes of testing for futility and possible re-estimation of sample size as described in Section 11.4.2.3. Analysis at the interim and final analysis was 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 $\alpha = 0.00001$ was paid for the second interim analysis, and the allocated $\alpha = 0.04999$ was used for the final analysis.

The secondary endpoint of PFS (of the phase 3 portion) was tested because the primary analysis of OS was statistically significant, thus maintaining the type 1 error at $\alpha = 0.05$.

11.4.2.6. Use of an "Efficacy Subset" of Subjects

The primary efficacy analysis was performed on the ITT Population; the PP Population was to be utilized as a sensitivity analysis. The PP Population excluded subjects who had major protocol violations that may have potentially affected the primary and secondary efficacy measures. However, all subjects enrolled in the study were included in the ITT and PP Populations; therefore, duplicative data summaries were not produced.

11.4.2.7. Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8. Examination of Subgroups

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

11.4.3. Tabulation of Individual Response Data

Not applicable.

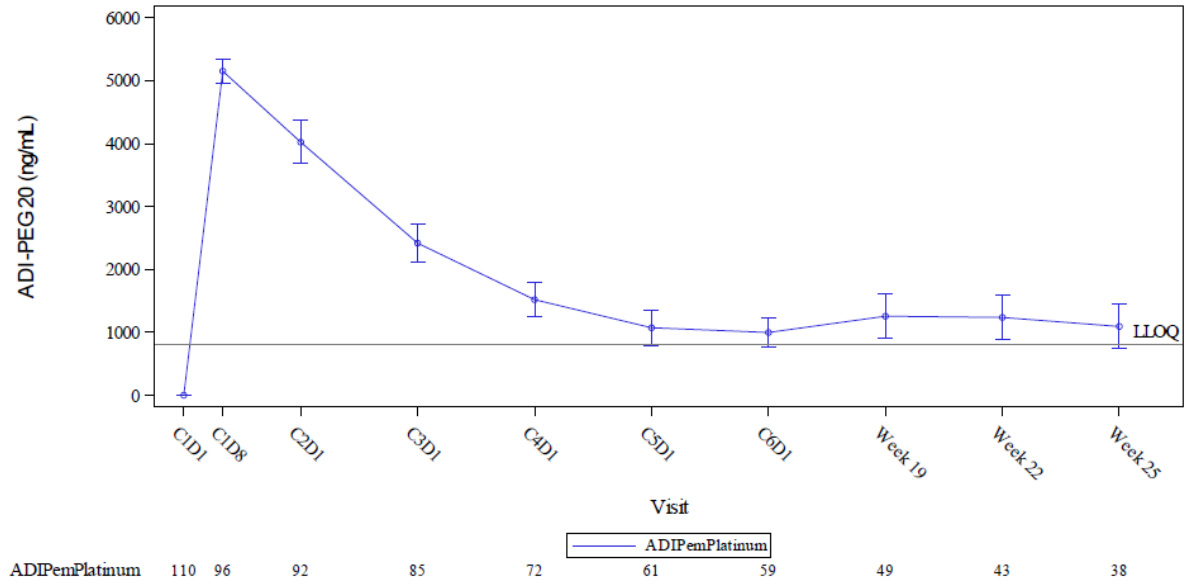
11.4.4. Drug Dose, Drug Concentration, and Relationships to Response

A summary of PK concentrations for the ITT Population is presented in Table 14.2.5.3. ADI-PEG 20 concentration data is listed by subject in Listing 16.2.5.6.

As described in Section 11.4.1.3 for pharmacodynamic data, it should be noted that the plasma samples used for PK analyses were obtained from subjects weekly on the day of next dosing, on the 7th day after the prior dose.

Mean ADI-PEG 20 concentration levels over time are presented in Figure 7. At baseline, as expected, the mean ADI-PEG 20 concentration was 0 ng/mL for the ADIPemPlatinum group (Table 14.2.5.3). At C1D8, the mean concentration increased from 0 to 5152.0 ng/mL. After C1D8, the mean concentration began to decline until it reached just above the LLOQ (800 ng/mL), and it remained there until the last sampling time point at Week 25 (mean concentration of 1093.3 ng/mL).

Figure 7: Mean ADI-PEG 20 Concentration Levels Over Time (ITT Population)



Notes:
- Baseline was the value at Cycle 1, Day 1.
- The figure presents the mean (± standard error) at each scheduled visit. Values below the figure represent the number of subjects with non-missing values at each visit.
- Results marked as BQL are assigned values of LLOQ/2 for summary purposes. For ADI-PEG 20, LLOQ = 800 and ULOQ = 10000.

Source: Figure 14.4.4.5

11.4.5. Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.6. By-Subject Displays

Complete listings of individual response data are provided in Appendix 16.2.6.

11.4.7. Efficacy Conclusions

The efficacy conclusions from the phase 2 portion of the study were as follows:

- A numerically greater percentage of subjects had a best tumor response of stable disease in the ADIPemPlatinum group compared with the PlaceboPemPlatinum group (71.3% and 62.9%, respectively), with similar percentages of subjects with PR (13.8% and 12.4%, respectively) or CR (0% and 1.1%, respectively) in both groups. The objective RR (the phase 2 primary endpoint) was similar between groups (13.8% and 13.5% for the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively; p = 0.9489); relative risk ratio [95% CI] = 1.02 [0.50, 2.11]).
- For DOR (the phase 2 secondary endpoint), the hazard ratio (95% CI) of 0.34 (0.10, 1.14) favored ADIPemPlatinum over PlaceboPemPlatinum, indicating a longer, but not statistically significantly different, DOR, with a p-value of 0.0918.

The efficacy conclusions from the phase 3 portion of the study were as follows:

- The probability of survival was higher for the ADIPemPlatinum group throughout the study compared with the PlaceboPemPlatinum group. The number (%) of subjects who died during the study was smaller for the ADIPemPlatinum group (108 subjects [86.4%]) compared with the PlaceboPemPlatinum group (116 subjects [93.5%]). In addition, the median OS (the phase 3 primary endpoint) was statistically significantly longer for the ADIPemPlatinum group (9.30 months) when compared with the PlaceboPemPlatinum group (7.66 months; hazard ratio of 0.71; p = 0.0234).
- When OS data were stratified by tumor histology type, the hazard ratios (95% CIs) for both biphasic MPM and sarcomatoid MPM favored ADIPemPlatinum over PlaceboPemPlatinum (0.68 [0.48, 0.98] and 0.80 [0.55, 1.18], respectively), with statistical significance being reached for the sarcomatoid, but not the biphasic, tumor type (p values of 0.0393 and 0.2614, respectively). These comparisons for OS by tumor type were added for informative purposes as post-hoc analyses and were not predefined analyses in the SAP and were not statistically powered.
- The probability of PFS was higher for the ADIPemPlatinum group throughout the study compared with the PlaceboPemPlatinum group. The median PFS (the phase 3 secondary endpoint) was statistically significantly longer for the ADIPemPlatinum group (6.24 months) when compared with the PlaceboPemPlatinum group (5.65 months; hazard ratio of 0.65; p = 0.0193).
- The median PFS was longer for the ADIPemPlatinum group when compared with the PlaceboPemPlatinum group for both tumor histology types (biphasic: 6.90 months vs 5.78 months, respectively; sarcomatoid: 6.11 months vs 4.14 months, respectively). When data were stratified by tumor histology type, the hazard ratios (95% CIs) for both biphasic MPM and sarcomatoid MPM favored ADIPemPlatinum over PlaceboPemPlatinum (0.74 [0.47, 1.16] and 0.60 [0.37, 0.99], respectively), with statistical significance being reached for the sarcomatoid, but not the biphasic, tumor type (p-values of 0.0411 and 0.1886, respectively). These comparisons for PFS by tumor type were added for informative purposes as post-hoc analyses and were not predefined analyses in the SAP and were not statistically powered.

The pharmacodynamic conclusions were as follows:

- The pharmacodynamic data demonstrated that repetitive dosing of ADI-PEG 20 resulted in sustained decreases in peripheral blood arginine, with a concomitant rise in citrulline.

The immunogenicity conclusions were as follows:

- Immunogenicity data showed an increase in mean ADI-PEG 20 ADA titers over time and suggested that there was a correlation between decreased levels of circulating arginine following C1D8 and an increase in antibody titers. Despite the development of anti-ADI-PEG 20 antibodies over the course of 25 weeks, PK/pharmacodynamic measurements indicated that at 7 days post-dose at each time point collected, the mean arginine levels remained below baseline, mean citrulline levels remained above baseline, and mean ADI-PEG 20 concentration remained above the LLOQ throughout the course of treatment.

The PK conclusions were as follows:

- At baseline, as expected, the mean ADI-PEG 20 concentration was 0 ng/mL for the ADIPemPlatinum group. At C1D8, the mean concentration increased from 0 to 5152.0 ng/mL. After C1D8, the mean concentration began to decline until it reached just above the LLOQ (800 ng/mL), and it remained there until the last sampling time point at Week 25 (mean concentration of 1093.3 ng/mL).

12. SAFETY EVALUATION

12.1. Extent of Exposure

A summary of the extent of exposure for the Safety Population is provided in Table 17.

The mean number of doses of ADI-PEG 20 was greater than that for placebo (22.0 vs 17.0 doses, respectively). The mean total dose of ADI-PEG 20 was 1475.0 mg. For both groups, for doses withheld, the main reason was AE (40.0% and 31.5% of subjects for the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively).

Exposure to pemetrexed, cisplatin, and carboplatin was similar between the ADIPemPlatinum and PlaceboPemPlatinum groups, including reasons for doses withheld or reduced.

By-subject listings of ADI-PEG 20/placebo, pemetrexed, cisplatin, and carboplatin administration are provided in Listing 16.2.5.1, Listing 16.2.5.2, Listing 16.2.5.3, and Listing 16.2.5.4, respectively.

Table 17: Extent of Exposure (Safety Population)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Number of Doses of ADI-PEG 20/Placebo		
n	125	124
Mean (SD)	22.0 (20.52)	17.0 (13.39)
Median	18.0	14.0
Min, Max	1, 104	1, 69
Total Dose of ADI-PEG 20 Received (mg)		
n	125	NA
Mean (SD)	1475.0 (1393.72)	NA
Median	1151.0	NA
Min, Max	54.7, 7416.0	NA
Subjects With at Least One Dose Withheld of ADI-PEG 20/ Placebo	73 (58.4%)	59 (47.6%)
Dose Withheld Due to [a]:		
Adverse Event	50 (40.0%)	39 (31.5%)
Other Reason	36 (28.8%)	32 (25.8%)
Number of Doses of Pemetrexed		
n	122	124
Mean (SD)	4.3 (1.77)	4.1 (1.73)
Median	4.5	4.0
Min, Max	1, 6	1, 6
Total Dose of Pemetrexed (mg)		
n	122	124
Mean (SD)	3702.5 (1566.31)	3597.8 (1605.93)
Median	3825.0	3600.0
Min, Max	700, 6600	690, 6600
Subjects With at Least One Dose Withheld of Pemetrexed	122 (97.6%)	116 (93.5%)
Dose Withheld Due to [a]:		
Adverse Event	47 (37.6%)	33 (26.6%)
Non-compliance	0 (0.0%)	2 (1.6%)
Not Applicable/ Not Scheduled	120 (96.0%)	116 (93.5%)
Other Reason	23 (18.4%)	10 (8.1%)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects With at Least One Dose Reduced of Pemetrexed	41 (32.8%)	35 (28.2%)
Dose Reduced Due to [a]:		
Adverse Event	31 (24.8%)	30 (24.2%)
Other Reason	12 (9.6%)	9 (7.3%)
Number of Doses of Cisplatin		
n	92	100
Mean (SD)	3.8 (1.93)	3.4 (1.79)
Median	4.0	3.5
Min, Max	1, 6	1, 6
Total Dose of Cisplatin (mg)		
n	92	99
Mean (SD)	489.5 (258.52)	445.6 (239.08)
Median	452.9	435.0
Min, Max	85, 1145	104, 984
Subjects With at Least One Dose Withheld of Cisplatin	123 (98.4%)	116 (93.5%)
Dose Withheld Due to [a]:		
Adverse Event	37 (29.6%)	34 (27.4%)
Non-compliance	0 (0.0%)	3 (2.4%)
Not Applicable/ Not Scheduled	119 (95.2%)	114 (91.9%)
Other Reason	26 (20.8%)	22 (17.7%)
Subjects With at Least One Dose Reduced of Cisplatin	42 (33.6%)	36 (29.0%)
Dose Reduced Due to [a]:		
Adverse Event	30 (24.0%)	28 (22.6%)
Other Reason	17 (13.6%)	11 (8.9%)
Number of Subjects who Received Any Dose of Carboplatin	46 (36.8%)	42 (33.9%)
Number of Doses of Carboplatin		
n	46	42
Mean (SD)	3.7 (1.86)	3.6 (1.75)
Median	4.0	4.0
Min, Max	1, 6	1, 6
Total Dose of Carboplatin (mg)		
n	46	42
Mean (SD)	1675.9 (835.32)	1604.9 (835.08)
Median	1540.8	1575.0
Min, Max	500, 3618	324, 3500

[a] Subjects were included in all categories that applied.
Source: Table 14.3.5.1

12.2. Adverse Events

12.2.1. Brief Summary of Adverse Events

An overall summary of TEAEs for the Safety Population is provided in Table 18, and results were generally similar between groups.

Overall, 2973 TEAEs and 217 TESAEs were reported during the study. Similar numbers of TEAEs (1570 and 1403 events) and TESAEs (106 and 111 events) were reported between the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively.

Overall, a majority of subjects reported at least one TEAE (98.8%), and the largest percentages of these subjects had TEAEs that were moderate in intensity, severe in intensity, or life-threatening (24.1%, 47.0%, and 13.7%, respectively).

A small percentage of subjects (4.8%) had TEAEs leading to premature withdrawal from the study.

The majority of subjects had TEAEs that were considered related to ADI-PEG 20 or placebo (66.3% overall; 68.8% and 63.7%, respectively).

Approximately half of subjects had TESAEs (49.4%), with the largest percentage of subjects with TESAEs that were severe in intensity (27.7%). A small percentage of subjects (9.2%) had TESAEs considered related to ADI-PEG 20 or placebo.

A small percentage of subjects had a TEAE leading to discontinuation of ADI-PEG 20 or placebo (16.9%), and approximately half of subjects had a TEAE leading to dose interruption of ADI-PEG 20 or placebo (45.4%).

The majority of subjects had TEAEs that were related to pemetrexed (91.1%), cisplatin (94.3%), or carboplatin (89.8%), with similar percentages between groups. Smaller percentages of subjects had TEAEs leading to discontinuation, interruption, or reduction of pemetrexed (13.8%, 35.8%, and 20.7%, respectively), cisplatin (23.4%, 32.8%, and 28.1%, respectively), or carboplatin (10.2%, 35.2%, and 25.0%, respectively). Similar results were observed between groups for the percentages of subjects who had TEAEs leading to discontinuation, interruption, or reduction of these medications, with the exception of a greater percentage in the ADIPemPlatinum group for TEAE requiring dose interruption of pemetrexed (41.0%) compared with the PlaceboPemPlatinum group (30.6%) and a greater percentage in the ADIPemPlatinum group for TEAE requiring discontinuation of carboplatin (19.6%) compared with the PlaceboPemPlatinum group (0%).

Small percentages of subjects had TESAEs considered related to pemetrexed (21.5%), cisplatin (25.5%), or carboplatin (12.5%).

Table 18: Overall Summary of TEAEs (Safety Population)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Total Number of TEAEs	1570	1403	2973
Total Number of TESAEs	106	111	217
Number (%) of Subjects Reporting at Least One:			
TEAE	123 (98.4%)	123 (99.2%)	246 (98.8%)
TEAE by Severity [a]			
Grade 1: Mild	6 (4.8%)	10 (8.1%)	16 (6.4%)
Grade 2: Moderate	25 (20.0%)	35 (28.2%)	60 (24.1%)
Grade 3: Severe	62 (49.6%)	55 (44.4%)	117 (47.0%)
Grade 4: Life-threatening	23 (18.4%)	11 (8.9%)	34 (13.7%)
Grade 5: Death	7 (5.6%)	12 (9.7%)	19 (7.6%)
TESAE	62 (49.6%)	61 (49.2%)	123 (49.4%)
TESAE by Severity [a]			
Grade 1: Mild	4 (3.2%)	3 (2.4%)	7 (2.8%)
Grade 2: Moderate	7 (5.6%)	7 (5.6%)	14 (5.6%)
Grade 3: Severe	35 (28.0%)	34 (27.4%)	69 (27.7%)
Grade 4: Life-threatening	9 (7.2%)	6 (4.8%)	15 (6.0%)
Grade 5: Death	7 (5.6%)	11 (8.9%)	18 (7.2%)

TEAE Leading to Premature Withdrawal from the Study	5 (4.0%)	7 (5.6%)	12 (4.8%)
TEAE Related to ADI-PEG 20/Placebo [b]	86 (68.8%)	79 (63.7%)	165 (66.3%)
TESAE Related to ADI-PEG 20/Placebo [b]	11 (8.8%)	12 (9.7%)	23 (9.2%)
TEAE Leading to Discontinuation of ADI-PEG 20/Placebo	25 (20.0%)	17 (13.7%)	42 (16.9%)
TEAE Requiring Dose Interruption of ADI-PEG 20 /Placebo	59 (47.2%)	54 (43.5%)	113 (45.4%)
Number of subjects who received any dose of Pemetrexed	122	124	246
TEAE Related to Pemetrexed [b]	114 (93.4%)	110 (88.7%)	224 (91.1%)
TESAE Related to Pemetrexed [b]	23 (18.9%)	30 (24.2%)	53 (21.5%)
TEAE Leading to Discontinuation of Pemetrexed	17 (13.9%)	17 (13.7%)	34 (13.8%)
TEAE Requiring Dose Interruption of Pemetrexed	50 (41.0%)	38 (30.6%)	88 (35.8%)
TEAE Requiring Dose Reduction of Pemetrexed	28 (23.0%)	23 (18.5%)	51 (20.7%)
Number of subjects who received any dose of Cisplatin	92	100	192
TEAE Related to Cisplatin [b]	87 (94.6%)	94 (94.0%)	181 (94.3%)
TESAE Related to Cisplatin [b]	22 (23.9%)	27 (27.0%)	49 (25.5%)
TEAE Leading to Discontinuation of Cisplatin	18 (19.6%)	27 (27.0%)	45 (23.4%)
TEAE Requiring Dose Interruption of Cisplatin	34 (37.0%)	29 (29.0%)	63 (32.8%)
TEAE Requiring Dose Reduction of Cisplatin	29 (31.5%)	25 (25.0%)	54 (28.1%)
Number of subjects who received any dose of Carboplatin	46	42	88
TEAE Related to Carboplatin [b]	42 (91.3%)	37 (88.1%)	79 (89.8%)
TESAE Related to Carboplatin [b]	6 (13.0%)	5 (11.9%)	11 (12.5%)
TEAE Leading to Discontinuation of Carboplatin	9 (19.6%)	0 (0.0%)	9 (10.2%)
TEAE Requiring Dose Interruption of Carboplatin	17 (37.0%)	14 (33.3%)	31 (35.2%)
TEAE Requiring Dose Reduction of Carboplatin	12 (26.1%)	10 (23.8%)	22 (25.0%)

[a] Subjects reporting more than one AE were counted only once using the highest severity.
[b] Related events included those reported as “Possibly,” “Probably,” or “Definitely” related to study drug.
Source: Table 14.3.1.1

12.2.2. Display of Adverse Events

12.2.2.1. Most Frequently Occurring Treatment-Emergent Adverse Events

A summary of the most frequently occurring (reported for ≥ 10% in either group) TEAEs is presented in Table 19. The most common TEAEs in the ADIPemPlatinum group were nausea, fatigue, and constipation, and the most common TEAEs in the PlaceboPemPlatinum group were nausea, fatigue, and decreased appetite. Results were similar between groups, with the exception of constipation, neutropenia, and neutrophil count deceased, with greater percentages of subjects reporting these events in the ADIPemPlatinum group, and decreased appetite, with a greater percentage of subject reporting this event in the PlaceboPemPlatinum group.

In regard to the percentages of subjects with neutropenia and neutrophil count decreased, the rates of related complications such as neutropenic sepsis (ADIPemPlatinum: 4 subjects [3.2%],

PlaceboPemPlatinum: 2 subjects [1.6%]), febrile neutropenia (ADIPemPlatinum: 2 subjects [1.6%], PlaceboPemPlatinum: 0 subjects [0.0%]), and pneumonia (ADIPemPlatinum: 5 subjects [4.0%], PlaceboPemPlatinum: 8 subjects [6.5%]) were low (Table 14.3.1.2).

Table 19: Most Frequently Occurring (≥ 10% in Either Group) TEAEs by Preferred Term (Safety Population)

Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Nausea	65 (52.0%)	67 (54.0%)
Fatigue	66 (52.8%)	62 (50.0%)
Constipation	54 (43.2%)	41 (33.1%)
Anaemia	34 (27.2%)	38 (30.6%)
Decreased appetite	26 (20.8%)	44 (35.5%)
Dyspnoea	35 (28.0%)	30 (24.2%)
Vomiting	23 (18.4%)	32 (25.8%)
Diarrhoea	20 (16.0%)	24 (19.4%)
Non-cardiac chest pain	26 (20.8%)	17 (13.7%)
Rash	24 (19.2%)	18 (14.5%)
Cough	19 (15.2%)	20 (16.1%)
Neutropenia	28 (22.4%)	10 (8.1%)
Neutrophil count decreased	24 (19.2%)	10 (8.1%)
Dysgeusia	14 (11.2%)	18 (14.5%)
Pyrexia	17 (13.6%)	13 (10.5%)
Oral candidiasis	11 (8.8%)	14 (11.3%)

Note: Subjects reporting more than one AE were counted only once. Summary included all events reported by ≥ 10% of subjects in the Safety Population.
[a] AEs were coded to preferred term using MedDRA, version 19.1.
Source: Table 14.3.1.3

All TEAEs by SOC and preferred term are provided in Table 14.3.1.2.

12.2.3. Analysis of Adverse Events

12.2.3.1. Severity of Adverse Events

A summary of the most frequently occurring (reported for ≥ 5% in either group) severe or life-threatening TEAEs is presented in Table 20. Approximately half of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had severe (Grade 3) TEAEs (49.6% and 44.4%, respectively). A total of 18.4% and 8.9% of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively, had life-threatening (Grade 4) TEAEs during the study. The most common severe TEAEs were anemia, neutropenia, and neutrophil count decreased for the ADIPemPlatinum group and anemia, fatigue, and neutrophil count decreased for the PlaceboPemPlatinum group. The most common life-threatening TEAEs were neutropenia and neutrophil count decreased for both groups. Results were generally similar between groups by preferred term for severe and life-threatening TEAEs. The larger percentage of subjects with life-threatening TEAEs in the ADIPemPlatinum group compared with the PlaceboPemPlatinum group was largely driven by greater percentages of subjects with neutropenia and neutrophil count decreased in the ADIPemPlatinum group.

There were 7 (5.6%) subjects with fatal TEAEs in the ADIPemPlatinum group and 12 (9.7%) subjects with fatal TEAEs in the PlaceboPemPlatinum group (Table 14.3.1.4). For the

ADIPemPlatinum group, these fatal TEAEs by preferred term were sudden death (2 subjects), cardiac arrest (2 subjects), pneumonia (1 subject), neutropenic sepsis (1 subject), and myocardial infarction (1 subject; however, this subject's death occurred > 30 days past the last dose of ADI-PEG 20). For the PlaceboPemPlatinum group, these fatal TEAEs by preferred term were pneumonia (4 subjects), cerebrovascular accident (2 subjects), sepsis (2 subjects), coronavirus infection (2 subjects), septic shock (2 subjects), non-cardiac chest pain (1 subject), dyspnea (1 subject), and acute respiratory failure (1 subject). Full narratives for subjects in the ADIPemPlatinum group who died due to TEAEs are provided in Section 14.3.3, with the exception of the subject who died due to myocardial infarction.

Table 20: Most Frequently Occurring (≥ 5% in Either Group) Severe or Life-Threatening TEAEs by Preferred Term (Safety Population)

Preferred Term [a]	ADIPemPlatinum (N = 125)		PlaceboPemPlatinum (N = 124)	
	Grade 3	Grade 4	Grade 3	Grade 4
Subjects Reporting at Least One Severe/ Life-Threatening TEAE	62 (49.6%)	23 (18.4%)	55 (44.4%)	11 (8.9%)
Anaemia	12 (9.6%)	0 (0.0%)	13 (10.5%)	0 (0.0%)
Neutropenia	10 (8.0%)	9 (7.2%)	3 (2.4%)	2 (1.6%)
Neutrophil count decreased	9 (7.2%)	6 (4.8%)	5 (4.0%)	4 (3.2%)
Non-cardiac chest pain	8 (6.4%)	0 (0.0%)	4 (3.2%)	0 (0.0%)
Dyspnoea	7 (5.6%)	1 (0.8%)	3 (2.4%)	0 (0.0%)
Hyponatraemia	7 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatigue	6 (4.8%)	0 (0.0%)	7 (5.6%)	0 (0.0%)

Note: At each level of summarization (any event and preferred term), subjects reporting more than one AE were counted only once using the highest CTCAE grade.

[a] AEs were coded to preferred term using MedDRA, version 19.1.

Source: Table 14.3.1.4

12.2.3.2. Relationship of Adverse Events to Study Drug

12.2.3.2.1. Relationship of Adverse Events to ADI-PEG 20/Placebo

A summary of the most frequently occurring TEAEs considered related to ADI-PEG 20/placebo (reported for ≥ 5% in either group) is presented in Table 21, and the results were generally similar between groups. The majority of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had TEAEs considered related to ADI-PEG 20 or placebo, respectively (68.8% and 63.7%, respectively). The most common of these were nausea, fatigue, and rash for the ADIPemPlatinum group and nausea, fatigue, and decreased appetite for the PlaceboPemPlatinum group.

A summary of TEAEs ≥ Grade 3 considered related to ADI-PEG 20/placebo, for preferred terms reported for > 1 subject in either group, is presented in Table 22. A greater percentage of subjects reported at least one ≥ Grade 3 TEAE considered related to ADI-PEG 20 in the ADIPemPlatinum group (28.8%) compared with those considered related to placebo in the PlaceboPemPlatinum group (16.9%). However, the percentage of subjects reporting each preferred term was small and similar between groups.

Of note, 3 (2.4%) subjects in the ADIPemPlatinum group had a ≥ Grade 3 anaphylactic reaction TEAE considered related to ADI-PEG 20, whereas no subjects in the PlaceboPemPlatinum

group had a ≥ Grade 3 anaphylactic reaction TEAE considered related to placebo. Additional information was later obtained for one of the subjects in the ADIPemPlatinum group who had a Grade 3 anaphylactic reaction TEAE considered related to ADI-PEG 20 that changed Polaris' initial comments and led Polaris to disagree with the diagnosis. Specifically, Subject 0209-0004 reported a related non-serious Grade 3 anaphylactic reaction, but there was no documented change in vital signs to indicate distress, no hypotension, no mention of labored breathing to indicate bronchospasm, nor was there documentation of rash, urticaria, hives or swollen lips as would be anticipated with a Grade 3 anaphylactic event.

Table 21: Most Frequently Occurring (≥ 5% in Either Group) TEAEs Considered Related to ADI-PEG 20/Placebo by Preferred Term (Safety Population)

Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects Reporting at Least One Related TEAE [b]	86 (68.8%)	79 (63.7%)
Nausea	35 (28.0%)	30 (24.2%)
Fatigue	24 (19.2%)	27 (21.8%)
Rash	18 (14.4%)	9 (7.3%)
Constipation	14 (11.2%)	8 (6.5%)
Vomiting	12 (9.6%)	12 (9.7%)
Anaemia	11 (8.8%)	11 (8.9%)
Decreased appetite	9 (7.2%)	15 (12.1%)
Neutropenia	9 (7.2%)	7 (5.6%)
Neutrophil count decreased	8 (6.4%)	3 (2.4%)
Platelet count decreased	8 (6.4%)	5 (4.0%)
Diarrhoea	7 (5.6%)	9 (7.3%)

Note: At each level of summarization (any event and preferred term), subjects reporting more than one AE were counted only once using the closest relationship to ADI-PEG 20/Placebo.

[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

[b] Included all events reported as "Possibly," "Probably," or "Definitely" related to ADI-PEG 20/Placebo.

Source: Table 14.3.1.5

Table 22: TEAEs ≥ Grade 3 Related to ADI-PEG 20/Placebo (Preferred Terms Reported for > 1 Subject in Either Group) (Safety Population)

System Organ Class / Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects Reporting at Least One Related TEAE ≥ Grade 3	36 (28.8%)	21 (16.9%)
Blood and lymphatic system disorders	12 (9.6%)	5 (4.0%)
Anaemia	6 (4.8%)	3 (2.4%)
Neutropenia	6 (4.8%)	2 (1.6%)
Investigations	12 (9.6%)	5 (4.0%)
Neutrophil count decreased	7 (5.6%)	2 (1.6%)
Platelet count decreased	4 (3.2%)	2 (1.6%)
White blood cell count decreased	3 (2.4%)	0 (0.0%)
Gastrointestinal disorders	4 (3.2%)	2 (1.6%)
Nausea	2 (1.6%)	1 (0.8%)
General disorders and administration site conditions	3 (2.4%)	3 (2.4%)
Fatigue	2 (1.6%)	2 (1.6%)
Infections and infestations	3 (2.4%)	2 (1.6%)
Neutropenic sepsis	2 (1.6%)	1 (0.8%)
Metabolism and nutrition disorders	2 (1.6%)	3 (2.4%)
Hyponatraemia	2 (1.6%)	0 (0.0%)
Immune system disorders	4 (3.2%)	0 (0.0%)
Anaphylactic reaction [b]	3 (2.4%)	0 (0.0%)

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one related and ≥ Grade 3 AE were counted only once. Related AEs were those reported as "Possibly," "Probably," or "Definitely" related to ADI-PEG 20/Placebo.

[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

[b] For one of the subjects (Subject 0209-0004) in the ADIPemPlatinum group who had a Grade 3 anaphylactic reaction TEAE considered related to ADI-PEG 20, additional information was obtained that led Polaris to disagree with the diagnosis (see Section 12.2.3.2.1).

Source: Table 14.3.1.8

12.2.3.2.2. Relationship of Adverse Events to Pemetrexed

A summary of the most frequently occurring TEAEs considered related to pemetrexed (reported for ≥ 5% in either group) is presented in Table 23. The majority of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had TEAEs considered related to pemetrexed (91.2% and 88.7%, respectively). The most common of these were nausea, fatigue, and anemia. Results were similar between groups, with the exception of neutropenia and neutrophil count deceased, with greater percentages of subjects reporting these events in the ADIPemPlatinum group (20.8% and 18.4%, respectively) compared with the PlaceboPemPlatinum group (7.3%, each).

A summary of TEAEs ≥ Grade 3 considered related to pemetrexed, for preferred terms reported for > 1 subject in either group, is presented in Table 24. A greater percentage of subjects reported at least one ≥ Grade 3 TEAE considered related to pemetrexed in the ADIPemPlatinum group (51.2%) compared with the PlaceboPemPlatinum group (38.7%). However, the percentages of subjects reporting most preferred terms were small and similar between groups, with the exception of neutropenia, which was reported for a greater percentage of subjects in the ADIPemPlatinum group (13.6%) compared with the PlaceboPemPlatinum group (3.2%).

Table 23: Most Frequently Occurring (≥ 5% in Either Group) TEAEs Considered Related to Pemetrexed by Preferred Term (Safety Population)

Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects Reporting at Least One Related TEAE [b]	114 (91.2%)	110 (88.7%)
Nausea	55 (44.0%)	50 (40.3%)
Fatigue	55 (44.0%)	49 (39.5%)
Anaemia	30 (24.0%)	34 (27.4%)
Constipation	27 (21.6%)	18 (14.5%)
Neutropenia	26 (20.8%)	9 (7.3%)
Neutrophil count decreased	23 (18.4%)	9 (7.3%)
Decreased appetite	22 (17.6%)	33 (26.6%)
Vomiting	17 (13.6%)	24 (19.4%)
Diarrhoea	13 (10.4%)	16 (12.9%)
Dysgeusia	12 (9.6%)	14 (11.3%)
Platelet count decreased	12 (9.6%)	7 (5.6%)
White blood cell count decreased	11 (8.8%)	5 (4.0%)
Pyrexia	10 (8.0%)	1 (0.8%)
Mucosal inflammation	10 (8.0%)	11 (8.9%)
Lethargy	10 (8.0%)	7 (5.6%)
Blood creatinine increased	9 (7.2%)	6 (4.8%)
Rash	9 (7.2%)	11 (8.9%)
Dyspnoea	8 (6.4%)	6 (4.8%)
Stomatitis	7 (5.6%)	10 (8.1%)
Lacrimation increased	6 (4.8%)	10 (8.1%)
Asthenia	3 (2.4%)	7 (5.6%)
Weight decreased	3 (2.4%)	8 (6.5%)
Lower respiratory tract infection	3 (2.4%)	7 (5.6%)

Note: At each level of summarization (any event and preferred term), subjects reporting more than one AE were counted only once using the closest relationship to Pemetrexed.

[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

[b] Included all events reported as "Possibly," "Probably," or "Definitely" related to Pemetrexed.

Source: Table 14.3.1.6

Table 24: TEAEs ≥ Grade 3 Related to Pemetrexed (Preferred Terms Reported for > 1 Subject in Either Group) (Safety Population)

System Organ Class / Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects Reporting at Least One Related TEAE ≥ Grade 3	64 (51.2%)	48 (38.7%)
Blood and lymphatic system disorders	28 (22.4%)	17 (13.7%)
Anaemia	11 (8.8%)	11 (8.9%)
Neutropenia	17 (13.6%)	4 (3.2%)
Thrombocytopenia	1 (0.8%)	2 (1.6%)
Investigations	20 (16.0%)	11 (8.9%)
Neutrophil count decreased	15 (12.0%)	7 (5.6%)
White blood cell count decreased	6 (4.8%)	2 (1.6%)
Platelet count decreased	5 (4.0%)	2 (1.6%)
Lymphocyte count decreased	1 (0.8%)	2 (1.6%)
Infections and infestations	8 (6.4%)	11 (8.9%)
Neutropenic sepsis	4 (3.2%)	2 (1.6%)
Lower respiratory tract infection	1 (0.8%)	2 (1.6%)
Pneumonia	0 (0.0%)	3 (2.4%)
Sepsis	1 (0.8%)	2 (1.6%)
Gastrointestinal disorders	7 (5.6%)	8 (6.5%)
Nausea	2 (1.6%)	4 (3.2%)
Diarrhoea	2 (1.6%)	3 (2.4%)
Vomiting	0 (0.0%)	4 (3.2%)
Stomatitis	2 (1.6%)	0 (0.0%)
General disorders and administration site conditions	7 (5.6%)	8 (6.5%)
Fatigue	5 (4.0%)	6 (4.8%)
Mucosal inflammation	0 (0.0%)	2 (1.6%)
Respiratory, thoracic and mediastinal disorders	2 (1.6%)	6 (4.8%)
Pulmonary embolism	0 (0.0%)	5 (4.0%)
Dyspnoea	2 (1.6%)	1 (0.8%)
Metabolism and nutrition disorders	2 (1.6%)	5 (4.0%)
Dehydration	0 (0.0%)	2 (1.6%)
Nervous system disorders	5 (4.0%)	1 (0.8%)
Lethargy	4 (3.2%)	0 (0.0%)

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one related and ≥ Grade 3 AE were counted only once. Related AEs were those reported as "Possibly," "Probably," or "Definitely" related to Pemetrexed.

[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

Source: Table 14.3.1.9

12.2.3.2.3. Relationship of Adverse Events to the Platinum Agent

A summary of the most frequently occurring TEAEs considered related to the platinum agent (reported for ≥ 5% in any group) is presented in Table 25. The majority of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had TEAEs considered related to the platinum agent (91.8% and 93.5%, respectively). The most common of these were nausea, fatigue, and anemia. Results were similar between groups, with the exception of neutropenia and neutrophil count deceased, with greater percentages of subjects reporting these events in the ADIPemPlatinum group (20.5% and 18.9%, respectively) compared with the PlaceboPemPlatinum group (7.3% and 8.1%, respectively).

In the ADIPemPlatinum group, a greater percentage of subjects had TEAEs of nausea (48.9%), neutrophil count decreased (20.7%), blood creatinine increased (12.0%), and dysgeusia (13.0%)

in the cisplatin group compared with the carboplatin group (32.6%, 8.7%, 2.2%, and 0%, respectively). In addition, a greater percentage of subjects reported anemia in the carboplatin group compared with the cisplatin group (32.6% vs 19.6%, respectively). In the PlaceboPemPlatinum group, a greater percentage of subjects had nausea (52.0%) in the cisplatin group compared with the carboplatin group (23.8%), and a greater percentage of subjects had anemia and thrombocytopenia (38.1% and 11.9%, respectively) in the carboplatin group compared with the cisplatin group (21.0% and 0%, respectively).

A summary of TEAEs ≥ Grade 3 considered related to the platinum agent, for preferred terms reported for > 1 subject in either group, is presented in Table 26. A greater percentage of subjects reported at least one ≥ Grade 3 TEAE considered related to the platinum agent in the ADIPemPlatinum group (54.4%) compared with the PlaceboPemPlatinum group (40.3%). However, the percentages of subjects reporting most preferred terms were small and similar between groups, with the exception of neutropenia, which was reported for a greater percentage of subjects in the ADIPemPlatinum group (14.4%) compared with the PlaceboPemPlatinum group (3.2%).

Table 25: Most Frequently Occurring (≥ 5% in Any Group) TEAEs Considered Related to the Platinum Agent by Preferred Term (Safety Population)

	ADIPemPlatinum (N = 125)			PlaceboPemPlatinum (N = 124)		
Preferred Term [a]	**Related to Cisplatin**	**Related to Carboplatin**	**Related to the Platinum Agent**	**Related to Cisplatin**	**Related to Carboplatin**	**Related to the Platinum Agent**
Received Any Dose of Corresponding Platinum Agent Drug	92	46	122	100	42	124
Subjects Reporting at Least One Related TEAE [b]	87 (94.6%)	42 (91.3%)	112 (91.8%)	94 (94.0%)	37 (88.1%)	116 (93.5%)
Nausea	45 (48.9%)	15 (32.6%)	58 (47.5%)	52 (52.0%)	10 (23.8%)	59 (47.6%)
Fatigue	43 (46.7%)	20 (43.5%)	57 (46.7%)	39 (39.0%)	14 (33.3%)	50 (40.3%)
Anaemia	18 (19.6%)	15 (32.6%)	30 (24.6%)	21 (21.0%)	16 (38.1%)	35 (28.2%)
Constipation	22 (23.9%)	7 (15.2%)	28 (23.0%)	15 (15.0%)	6 (14.3%)	19 (15.3%)
Neutropenia	20 (21.7%)	8 (17.4%)	25 (20.5%)	4 (4.0%)	5 (11.9%)	9 (7.3%)
Neutrophil count decreased	19 (20.7%)	4 (8.7%)	23 (18.9%)	9 (9.0%)	2 (4.8%)	10 (8.1%)
Decreased appetite	17 (18.5%)	6 (13.0%)	22 (18.0%)	23 (23.0%)	11 (26.2%)	33 (26.6%)
Vomiting	12 (13.0%)	4 (8.7%)	16 (13.1%)	22 (22.0%)	7 (16.7%)	28 (22.6%)
Diarrhoea	9 (9.8%)	3 (6.5%)	12 (9.8%)	11 (11.0%)	5 (11.9%)	16 (12.9%)
Blood creatinine increased	11 (12.0%)	1 (2.2%)	12 (9.8%)	5 (5.0%)	3 (7.1%)	7 (5.6%)
Platelet count decreased	9 (9.8%)	6 (13.0%)	12 (9.8%)	4 (4.0%)	3 (7.1%)	7 (5.6%)
Dysgeusia	12 (13.0%)	0 (0.0%)	12 (9.8%)	10 (10.0%)	6 (14.3%)	15 (12.1%)
White blood cell count decreased	9 (9.8%)	3 (6.5%)	11 (9.0%)	5 (5.0%)	0 (0.0%)	5 (4.0%)
Mucosal inflammation	5 (5.4%)	5 (10.9%)	10 (8.2%)	7 (7.0%)	4 (9.5%)	11 (8.9%)
Pyrexia	4 (4.3%)	6 (13.0%)	10 (8.2%)	1 (1.0%)	0 (0.0%)	1 (0.8%)
Neuropathy peripheral	8 (8.7%)	2 (4.3%)	10 (8.2%)	8 (8.0%)	1 (2.4%)	9 (7.3%)
Lethargy	9 (9.8%)	1 (2.2%)	10 (8.2%)	7 (7.0%)	1 (2.4%)	8 (6.5%)
Dyspnoea	6 (6.5%)	2 (4.3%)	8 (6.6%)	3 (3.0%)	2 (4.8%)	5 (4.0%)
Tinnitus	8 (8.7%)	0 (0.0%)	8 (6.6%)	4 (4.0%)	0 (0.0%)	4 (3.2%)
Hypomagnesaemia	7 (7.6%)	2 (4.3%)	7 (5.7%)	2 (2.0%)	1 (2.4%)	3 (2.4%)
Rash	5 (5.4%)	2 (4.3%)	7 (5.7%)	7 (7.0%)	3 (7.1%)	9 (7.3%)
Acute kidney injury	6 (6.5%)	1 (2.2%)	7 (5.7%)	5 (5.0%)	1 (2.4%)	6 (4.8%)
Oral candidiasis	5 (5.4%)	1 (2.2%)	6 (4.9%)	6 (6.0%)	1 (2.4%)	7 (5.6%)
Stomatitis	5 (5.4%)	1 (2.2%)	5 (4.1%)	6 (6.0%)	4 (9.5%)	9 (7.3%)
Thrombocytopenia	2 (2.2%)	2 (4.3%)	4 (3.3%)	0 (0.0%)	5 (11.9%)	5 (4.0%)
Oropharyngeal pain	1 (1.1%)	3 (6.5%)	4 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspepsia	2 (2.2%)	1 (2.2%)	3 (2.5%)	6 (6.0%)	1 (2.4%)	7 (5.6%)
Asthenia	3 (3.3%)	1 (2.2%)	3 (2.5%)	3 (3.0%)	4 (9.5%)	7 (5.6%)

Preferred Term [a]	ADIPemPlatinum (N = 125)			PlaceboPemPlatinum (N = 124)		
	Related to Cisplatin	Related to Carboplatin	Related to the Platinum Agent	Related to Cisplatin	Related to Carboplatin	Related to the Platinum Agent
Weight decreased	2 (2.2%)	1 (2.2%)	3 (2.5%)	5 (5.0%)	1 (2.4%)	6 (4.8%)
Lower respiratory tract infection	3 (3.3%)	0 (0.0%)	3 (2.5%)	5 (5.0%)	1 (2.4%)	6 (4.8%)
Lacrimation increased	3 (3.3%)	0 (0.0%)	3 (2.5%)	6 (6.0%)	2 (4.8%)	6 (4.8%)
Leukopenia	1 (1.1%)	0 (0.0%)	1 (0.8%)	2 (2.0%)	3 (7.1%)	5 (4.0%)
Epistaxis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.1%)	3 (2.4%)

Notes:
• "Platinum Agent" included both cisplatin and carboplatin.
• At each level of summarization (any event and preferred term), subjects reporting more than one AE were counted only once using the closest relationship to the platinum agent.
• Denominators were the number of subjects who received any dose of the corresponding platinum agent.
[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.
[b] Included all events reported as "Possibly," "Probably," or "Definitely" related to the platinum agent.
Source: Table 14.3.1.7

Table 26: TEAEs ≥ Grade 3 Related to the Platinum Agent (Preferred Terms Reported for > 1 Subject in Either Group) (Safety Population)

System Organ Class / Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects Reporting at Least One Related TEAE ≥ Grade 3	68 (54.4%)	50 (40.3%)
Blood and lymphatic system disorders	29 (23.2%)	16 (12.9%)
Anaemia	11 (8.8%)	11 (8.9%)
Neutropenia	18 (14.4%)	4 (3.2%)
Thrombocytopenia	1 (0.8%)	2 (1.6%)
Investigations	19 (15.2%)	13 (10.5%)
Neutrophil count decreased	15 (12.0%)	9 (7.3%)
White blood cell count decreased	5 (4.0%)	2 (1.6%)
Platelet count decreased	4 (3.2%)	2 (1.6%)
Lymphocyte count decreased	1 (0.8%)	2 (1.6%)
Infections and infestations	8 (6.4%)	10 (8.1%)
Neutropenic sepsis	4 (3.2%)	2 (1.6%)
Lower respiratory tract infection	1 (0.8%)	2 (1.6%)
Pneumonia	0 (0.0%)	3 (2.4%)
Gastrointestinal disorders	6 (4.8%)	10 (8.1%)
Nausea	2 (1.6%)	5 (4.0%)
Diarrhoea	2 (1.6%)	3 (2.4%)
Vomiting	0 (0.0%)	5 (4.0%)
General disorders and administration site conditions	7 (5.6%)	8 (6.5%)
Fatigue	5 (4.0%)	6 (4.8%)
Mucosal inflammation	0 (0.0%)	2 (1.6%)
Metabolism and nutrition disorders	5 (4.0%)	5 (4.0%)
Hyponatraemia	3 (2.4%)	0 (0.0%)
Dehydration	0 (0.0%)	2 (1.6%)
Respiratory, thoracic and mediastinal disorders	3 (2.4%)	5 (4.0%)
Pulmonary embolism	0 (0.0%)	4 (3.2%)
Dyspnoea	2 (1.6%)	1 (0.8%)
Nervous system disorders	6 (4.8%)	1 (0.8%)
Lethargy	4 (3.2%)	0 (0.0%)
Renal and urinary disorders	2 (1.6%)	2 (1.6%)
Acute kidney injury	2 (1.6%)	2 (1.6%)

Notes:
- "Platinum agent" includes both cisplatin and carboplatin
- At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one related and ≥ Grade 3 AE were counted only once. Related AEs were those reported as "Possibly," "Probably," or "Definitely" related to the platinum agent.

[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

Source: Table 14.3.1.10

12.2.4. Listing of Adverse Events by Subject

All AEs are provided by subject in Listing 16.2.7. Additional AE listings are provided in Appendix 16.2.7.

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1. Deaths

A total of 224 subjects died during the study, with a cause of death of malignant disease for the majority of subjects (Table 14.3.2.1). As noted in Table 6, 3 of the 224 subjects (Subjects 0107-0003, 0112-0002, and 0107-0007) stopped the study and a date of death was obtained and entered into EDC (reasons for study termination of subject decision to withdraw consent for Subjects 0107-0003 and 0112-0002 and "other: moved to Oregon" for Subject 0107-0007; Listing 16.2.1).

A by-subject listing of all deaths during the study is provided in Table 14.3.2.1.

Full narratives for subjects in the ADIPemPlatinum group who died within 30 days of last dose of study treatment, excluding deaths where reason for death was malignant disease, are provided in Section 14.3.3.

12.3.1.2. Other Serious Adverse Events

A summary of TESAEs, for preferred terms reported for > 1 subject in either group, is presented in Table 27, and results were generally similar between groups. Approximately half of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had TESAEs (49.6% and 49.2%, respectively). The most common TESAEs for the ADIPemPlatinum group were noncardiac chest pain, dyspnea, and acute kidney injury, with no TESAEs reported for > 5% of subjects in this group. The most common TESAEs for the PlaceboPemPlatinum group were pyrexia and nausea, with no other TESAEs reported for > 5% of subjects in this group. Of note, 2 (1.6%) subjects in the ADIPemPlatinum group had a TESAE of anaphylactic reaction, whereas no subjects in the PlaceboPemPlatinum group had a TESAE of anaphylactic reaction.

A by-subject listing of all SAEs during the study is provided in Table 14.3.2.2.

Table 27: TESAEs (Preferred Terms Reported for > 1 Subject in Either Group) (Safety Population)

System Organ Class / Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects Reporting at Least One TESAE	62 (49.6%)	61 (49.2%)
Infections and infestations	19 (15.2%)	20 (16.1%)
Pneumonia	5 (4.0%)	6 (4.8%)
Sepsis	1 (0.8%)	6 (4.8%)
Lower respiratory tract infection	2 (1.6%)	3 (2.4%)
Neutropenic sepsis	3 (2.4%)	2 (1.6%)
Corona virus infection	1 (0.8%)	2 (1.6%)
Septic shock	1 (0.8%)	2 (1.6%)
Urinary tract infection	3 (2.4%)	0 (0.0%)
Lung infection	2 (1.6%)	0 (0.0%)
General disorders and administration site conditions	15 (12.0%)	11 (8.9%)
Pyrexia	5 (4.0%)	8 (6.5%)
Non-cardiac chest pain	6 (4.8%)	3 (2.4%)
Fatigue	1 (0.8%)	2 (1.6%)
Sudden death	2 (1.6%)	0 (0.0%)
Gastrointestinal disorders	9 (7.2%)	16 (12.9%)
Nausea	1 (0.8%)	7 (5.6%)
Vomiting	2 (1.6%)	5 (4.0%)
Constipation	2 (1.6%)	3 (2.4%)
Diarrhoea	2 (1.6%)	2 (1.6%)
Abdominal pain	1 (0.8%)	2 (1.6%)
Respiratory, thoracic and mediastinal disorders	10 (8.0%)	7 (5.6%)
Dyspnoea	6 (4.8%)	2 (1.6%)
Pulmonary embolism	2 (1.6%)	2 (1.6%)
Pleural effusion	2 (1.6%)	1 (0.8%)
Cardiac disorders	9 (7.2%)	2 (1.6%)
Atrial fibrillation	4 (3.2%)	0 (0.0%)
Cardiac arrest	2 (1.6%)	0 (0.0%)
Renal and urinary disorders	6 (4.8%)	4 (3.2%)
Acute kidney injury	6 (4.8%)	4 (3.2%)
Blood and lymphatic system disorders	3 (2.4%)	6 (4.8%)
Anaemia	0 (0.0%)	5 (4.0%)
Febrile neutropenia	2 (1.6%)	0 (0.0%)
Metabolism and nutrition disorders	4 (3.2%)	5 (4.0%)
Dehydration	0 (0.0%)	3 (2.4%)
Hyponatraemia	3 (2.4%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	2 (1.6%)	7 (5.6%)
Musculoskeletal chest pain	1 (0.8%)	3 (2.4%)
Nervous system disorders	3 (2.4%)	6 (4.8%)
Cerebrovascular accident	1 (0.8%)	3 (2.4%)
Lethargy	2 (1.6%)	0 (0.0%)
Injury, poisoning and procedural complications	5 (4.0%)	2 (1.6%)
Fall	2 (1.6%)	1 (0.8%)
Investigations	2 (1.6%)	4 (3.2%)
Alanine aminotransferase increased	0 (0.0%)	2 (1.6%)
Immune system disorders	4 (3.2%)	0 (0.0%)
Anaphylactic reaction	2 (1.6%)	0 (0.0%)

System Organ Class / Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Psychiatric disorders	1 (0.8%)	2 (1.6%)
Confusional state	1 (0.8%)	2 (1.6%)

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one TESAE were counted only once.
[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.
Source: Table 14.3.1.14

12.3.1.3. Other Significant Adverse Events

12.3.1.3.1. Adverse Events Leading to Treatment Discontinuation

12.3.1.3.1.1. Adverse Events Leading to ADI-PEG 20/Placebo Discontinuation

A summary of TEAEs leading to ADI-PEG 20/placebo discontinuation, for preferred terms reported for > 1 subject in either group, is presented in Table 28.

A larger percentage of subjects in the ADIPemPlatinum group (20.0%) discontinued from ADI-PEG 20 than discontinued placebo in the PlaceboPemPlatinum group (13.7%).

A by-subject listing of all AEs leading to ADI-PEG 20/placebo discontinuation or interruption during the study is provided in Table 14.3.2.3.

The most common TEAEs leading to ADI-PEG 20 discontinuation were anaphylactic reaction (3 subjects [2.4%]) and fatigue, pyrexia, and cardiac arrest (2 subjects [1.6%] each). No other TEAEs leading to discontinuation of ADI-PEG 20 were reported for more than 1 subject. Additional information was later obtained for one of the subjects in the ADIPemPlatinum group who had a Grade 3 anaphylactic reaction TEAE that led to discontinuation of ADI-PEG 20 that changed Polaris' initial comments and led Polaris to disagree with the diagnosis (see Section 12.2.3.2.1).

In the PlaceboPemPlatinum group, only dyspnea (2 subjects [1.6%]) was reported for more than 1 subject as a TEAE leading to discontinuation of placebo.

Table 28: TEAEs Leading to ADI-PEG 20/Placebo Discontinuation (Preferred Terms Reported for > 1 Subject in Either Group) (Safety Population)

System Organ Class / Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subject Reporting at Least One TEAE Leading to Discontinuation of ADI-PEG 20/Placebo	25 (20.0%)	17 (13.7%)
General disorders and administration site conditions	5 (4.0%)	2 (1.6%)
Fatigue	2 (1.6%)	1 (0.8%)
Pyrexia	2 (1.6%)	0 (0.0%)
Cardiac disorders	3 (2.4%)	1 (0.8%)
Cardiac arrest	2 (1.6%)	0 (0.0%)
Immune system disorders	4 (3.2%)	0 (0.0%)
Anaphylactic reaction [b]	3 (2.4%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	3 (2.4%)
Dyspnoea	1 (0.8%)	2 (1.6%)

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one AE leading to discontinuation of ADI-PEG 20/placebo were counted only once.

[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

[b] For one of the subjects (Subject 0209-0004) in the ADIPemPlatinum group who had a Grade 3 anaphylactic reaction TEAE the led to discontinuation of ADI-PEG 20, additional information was obtained that led Polaris to disagree with the diagnosis (see Section 12.2.3.2.1).

Source: Table 14.3.1.11

12.3.1.3.1.2. Adverse Events Leading to Pemetrexed Discontinuation

A summary of TEAEs leading to pemetrexed discontinuation, for preferred terms reported for > 1 subject in either group, is presented in Table 29.

A similar percentage of subjects in the ADIPemPlatinum group (13.6%) discontinued from pemetrexed as that in the PlaceboPemPlatinum group (13.7%).

The most common TEAEs leading to pemetrexed discontinuation in the ADIPemPlatinum group were diarrhea (3 subjects [2.4%]) and dyspnea (2 subjects [1.6%]). No other TEAEs leading to discontinuation of pemetrexed in the ADIPemPlatinum group were reported for more than 1 subject.

In the PlaceboPemPlatinum group, only anemia (3 subjects [2.4%]) and fatigue and dyspnea (2 subjects [1.6%] each) were reported for more than 1 subject as a TEAE leading to discontinuation of pemetrexed.

A by-subject listing of all AEs leading to pemetrexed discontinuation, reduction, or interruption during the study is provided in Table 14.3.2.4.

Table 29: TEAEs Leading to Pemetrexed Discontinuation (Preferred Terms Reported for > 1 Subject in Either Group) (Safety Population)

System Organ Class / Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subject Reporting at Least One TEAE Leading to Discontinuation of Pemetrexed	17 (13.6%)	17 (13.7%)
Gastrointestinal disorders	6 (4.8%)	1 (0.8%)
Diarrhoea	3 (2.4%)	0 (0.0%)
General disorders and administration site conditions	3 (2.4%)	3 (2.4%)
Fatigue	1 (0.8%)	2 (1.6%)
Blood and lymphatic system disorders	1 (0.8%)	4 (3.2%)
Anaemia	1 (0.8%)	3 (2.4%)
Respiratory, thoracic and mediastinal disorders	2 (1.6%)	3 (2.4%)
Dyspnoea	2 (1.6%)	2 (1.6%)

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one AE leading to discontinuation of pemetrexed were counted only once.
[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.
Source: Table 14.3.1.12

12.3.1.3.1.3. Adverse Events Leading to Platinum Agent Discontinuation

A summary of TEAEs leading to platinum agent (cisplatin and/or carboplatin) discontinuation, for preferred terms reported for > 1 subject in either group, is presented in Table 30.

A similar percentage of subjects in the ADIPemPlatinum group (19.2%) discontinued from the platinum agent as that in the PlaceboPemPlatinum group (21.8%).

The most common TEAEs leading to platinum agent discontinuation in the ADIPemPlatinum group were diarrhea, fatigue, pyrexia (3 subjects [2.4%] each), and blood creatinine increased and dyspnea (2 subjects [1.6%] each). No other TEAEs leading to discontinuation of the platinum agent in the ADIPemPlatinum group were reported for more than 1 subject.

In the PlaceboPemPlatinum group, the most common TEAEs leading to platinum agent discontinuation were vomiting (4 subjects [3.2%]), fatigue and anemia (3 subjects [2.4%] each), and nausea, neuropathy peripheral, neutrophil count decreased, acute kidney injury, and deafness (2 subjects [1.6%] each). No other TEAEs leading to discontinuation of the platinum agent in the PlaceboPemPlatinum group were reported for more than 1 subject.

By-subject listings of all AEs leading to cisplatin or carboplatin discontinuation, reduction, or interruption during the study are provided in Table 14.3.2.5 and Table 14.3.2.6, respectively.

Table 30: TEAEs Leading to Platinum Agent Discontinuation (Preferred Terms Reported for > 1 Subject in Either Group) (Safety Population)

System Organ Class / Preferred Term [a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subject Reporting at Least One TEAE Leading to Discontinuation of the Platinum Agent	24 (19.2%)	27 (21.8%)
Gastrointestinal disorders	6 (4.8%)	5 (4.0%)
Vomiting	1 (0.8%)	4 (3.2%)
Diarrhoea	3 (2.4%)	0 (0.0%)
Nausea	1 (0.8%)	2 (1.6%)
General disorders and administration site conditions	6 (4.8%)	4 (3.2%)
Fatigue	3 (2.4%)	3 (2.4%)
Pyrexia	3 (2.4%)	0 (0.0%)
Nervous system disorders	2 (1.6%)	5 (4.0%)
Neuropathy peripheral	0 (0.0%)	2 (1.6%)
Blood and lymphatic system disorders	1 (0.8%)	4 (3.2%)
Anaemia	0 (0.0%)	3 (2.4%)
Investigations	3 (2.4%)	2 (1.6%)
Neutrophil count decreased	1 (0.8%)	2 (1.6%)
Blood creatinine increased	2 (1.6%)	0 (0.0%)
Renal and urinary disorders	1 (0.8%)	3 (2.4%)
Acute kidney injury	1 (0.8%)	2 (1.6%)
Ear and labyrinth disorders	1 (0.8%)	2 (1.6%)
Deafness	0 (0.0%)	2 (1.6%)
Respiratory, thoracic and mediastinal disorders	2 (1.6%)	1 (0.8%)
Dyspnoea	2 (1.6%)	1 (0.8%)

Notes:
- "Platinum agent" included both cisplatin and carboplatin
- At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one AE leading to discontinuation of the platinum agent were counted only once.

[a] AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

Source: Table 14.3.1.13

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives for subjects in the ADIPemPlatinum group with TESAEs considered related to ADI-PEG 20, subjects with AEs considered related to ADI-PEG 20 leading to ADI-PEG 20 discontinuation, and subjects who died within 30 days of last dose of study treatment, excluding deaths where reason for death was malignant disease, are provided in Section 14.3.3.

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

A total of 224 subjects died during the study, with a cause of death of malignant disease for the majority of subjects.

Approximately half of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had TESAEs (49.6% and 49.2%, respectively). The most common TESAEs for the ADIPemPlatinum group were noncardiac chest pain, dyspnea, and acute kidney injury, with no TESAEs reported for > 5% of subjects in this group. The most common TESAEs for the PlaceboPemPlatinum

group were pyrexia and nausea, with no other TESAEs reported for > 5% of subjects in this group.

A larger percentage of subjects in the ADIPemPlatinum group (20.0%) discontinued from ADI-PEG 20 than the percentage of subjects who discontinued placebo in the PlaceboPemPlatinum group (13.7%). The most common TEAEs leading to ADI-PEG 20 discontinuation were anaphylactic reaction (3 subjects [2.4%]) and fatigue, pyrexia, and cardiac arrest (2 subjects [1.6%] each). No other TEAEs leading to discontinuation of ADI-PEG 20 were reported for more than 1 subject. For one of the subjects in the ADIPemPlatinum group who had a Grade 3 anaphylactic reaction TEAE that led to discontinuation from ADI-PEG 20, additional information was obtained that led Polaris to disagree with the diagnosis (see Section 12.2.3.2.1). In the PlaceboPemPlatinum group, only dyspnea (2 subjects [1.6%]) was reported for more than 1 subject as a TEAE leading to discontinuation of placebo.

A similar percentage of subjects in the ADIPemPlatinum group (13.6%) discontinued from pemetrexed as that in the PlaceboPemPlatinum group (13.7%). The most common TEAEs leading to pemetrexed discontinuation in the ADIPemPlatinum group were diarrhea (3 subjects [2.4%]) and dyspnea (2 subjects [1.6%]). No other TEAEs leading to discontinuation of pemetrexed in the ADIPemPlatinum group were reported for more than 1 subject. In the PlaceboPemPlatinum group, only anemia (3 subjects [2.4%]) and fatigue and dyspnea (2 subjects [1.6%] each) were reported for more than 1 subject as a TEAE leading to discontinuation of pemetrexed.

A similar percentage of subjects in the ADIPemPlatinum group (19.2%) discontinued from the platinum agent as that in the PlaceboPemPlatinum group (21.8%). The most common TEAEs leading to platinum agent discontinuation in the ADIPemPlatinum group were diarrhea, fatigue, pyrexia (3 subjects [2.4%] each), and blood creatinine increased and dyspnea (2 subjects [1.6%] each). No other TEAEs leading to discontinuation of the platinum agent in the ADIPemPlatinum group were reported for more than 1 subject. In the PlaceboPemPlatinum group, the most common TEAEs leading to platinum agent discontinuation were vomiting (4 subjects [3.2%]), fatigue and anemia (3 subjects [2.4%] each), and nausea, neuropathy peripheral, neutrophil count decreased, acute kidney injury, and deafness (2 subjects [1.6%] each). No other TEAEs leading to discontinuation of the platinum agent in the PlaceboPemPlatinum group were reported for more than 1 subject.

12.4. Clinical Laboratory Evaluation

12.4.1. Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Individual subject hematology results are included in Listing 16.2.8.1, and those that were abnormal are included by CTCAE grade in Table 14.3.4.1. Individual subject chemistry results are included in Listing 16.2.8.2, and those that were abnormal are included by CTCAE grade in Table 14.3.4.2.

12.4.2. Evaluation of Each Laboratory Parameter

Taking the laboratory results observed by visit (see Section 12.4.2.1) together with shifts from baseline by severity grading (see Section 12.4.2.2), it is important to note that the rate of shifts

from Grade 0 to 3 for neutrophils in the ADIPemPlatinum group was higher (19.8%) than that in the PlaceboPemPlatinum group (8.6%). Additionally, there was a large percentage of subjects with creatinine abnormalities (due to cisplatin administration), with no difference in the percentages of subjects with creatinine abnormalities between the ADIPemPlatinum and PlaceboPemPlatinum groups (Table 14.3.6.5). No other clinically relevant changes from baseline in laboratory parameters were noted.

12.4.2.1. Laboratory Values Over Time

Hematology results observed by visit and change from baseline are included in Table 14.3.6.1. Chemistry results observed by visit and change from baseline are included in Table 14.3.6.3. Out-of-range values were reported for most laboratory parameters (Listing 16.2.8.1 and Listing 16.2.8.2); however, for most laboratory parameters, no clinically relevant changes were observed (see Section 12.4.2).

12.4.2.2. Individual Subject Changes

A shift table for hematology from baseline to worst post-baseline value is included in Table 14.3.6.2 for laboratory parameters that did not have an NCI CTCAE grading, and the results were generally similar between groups. The largest percentages of subjects with a shift in hematology parameters from normal to high were observed for monocytes for the ADIPemPlatinum and PlaceboPemPlatinum groups (26.9% and 17.0% of subjects, respectively) and for eosinophils in the ADIPemPlatinum group (20.2% and 5.4% of subjects in the ADIPemPlatinum group and PlaceboPemPlatinum group, respectively). The largest percentages of subjects with a shift in hematology parameters from normal to low were observed for the following for the ADIPemPlatinum and PlaceboPemPlatinum groups: RBC count (59.7% and 57.4% of subjects, respectively), hematocrit (53.8% and 53.0% of subjects, respectively), and monocytes (42.9% and 50.9% of subjects, respectively).

A shift table for chemistry from baseline to worst post-baseline value is included in Table 14.3.6.4 for laboratory parameters that did not have an NCI CTCAE grading, and the results were generally similar between groups. The largest percentages of subjects with a shift in chemistry parameters from normal to high were observed for the following for the ADIPemPlatinum and PlaceboPemPlatinum groups: BUN (20.2% and 27.0% of subjects, respectively). The largest percentages of subjects with a shift in chemistry parameters from normal to low were observed for the following for the ADIPemPlatinum and PlaceboPemPlatinum groups: total protein (21.9% and 26.1% of subjects, respectively) and chloride (35.1% and 40.0% of subjects, respectively).

Shift from baseline to worst post-baseline NCI CTCAE toxicity grade by laboratory parameter is provided in Table 14.3.6.5, and the results were generally similar between groups. The only shifts from none (Grade 0), mild (Grade 1), or moderate (Grade 2) at baseline to severe (Grade 3) or life-threatening (Grade 4) post-baseline that occurred for ≥ 10% of subjects were the following:

- WBC: Grade 0 to Grade 3 for the ADIPemPlatinum group, 21 subjects (17.6%), and the PlaceboPemPlatinum group, 17 subjects (14.8%)

- Neutrophils: Grade 0 to Grade 3 for the ADIPemPlatinum group, 24 subjects (19.8%) (The shift from Grade 0 to Grade 3 for PlaceboPemPlatinum was 8.6%).
- Lymphocytes: Grade 0 to Grade 3 for the ADIPemPlatinum group, 12 subjects (10.1%), and for the PlaceboPemPlatinum group, 18 subjects (16.1%)
- Glucose: Grade 2 to Grade 3 for the ADIPemPlatinum group, 6 subjects (20.0%), and the PlaceboPemPlatinum group, 5 subjects (15.2%)

12.4.2.3. Individual Clinically Significant Abnormalities

Abnormal hematology results and CTCAE grades per subject are listed in Table 14.3.4.1. Abnormal chemistry results and CTCAE grades per subject are listed in Table 14.3.4.2.

Any clinically significant laboratory abnormalities that were reported as AEs, are provided by system organ class and preferred term in Table 31, and are included by subject in Listing 16.2.7. The most common laboratory-related TEAEs for the ADIPemPlatinum and PlaceboPemPlatinum groups were anemia (27.2% and 30.6%, respectively), neutropenia (22.4% and 8.1%, respectively), and neutrophil count decreased (19.2% and 8.1%, respectively). Results were generally similar between the ADIPemPlatinum and PlaceboPemPlatinum groups for the percentage of subjects with laboratory-related TEAEs, with the exception of neutropenia and neutrophil count decreased, which were both more common in the ADIPemPlatinum group, as indicated above.

Severe laboratory-related TEAEs are discussed in Section 12.2.3.1 and laboratory-related TEAEs considered related to study medication are discussed in Section 12.2.3.2. Laboratory-related TESAEs are discussed in Section 12.3.1.2, and full narratives for subjects in the ADIPemPlatinum group with TESAEs considered related to ADI-PEG 20 are provided in Section 14.3.3. No subjects had fatal laboratory-related AEs.

Table 31: Laboratory-Related TEAEs by Preferred Term (Safety Population)

System Organ Class / Preferred Term[a]	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Blood and lymphatic system disorders	55 (44.0%)	47 (37.9%)	102 (41.0%)
Anaemia	34 (27.2%)	38 (30.6%)	72 (28.9%)
Neutropenia	28 (22.4%)	10 (8.1%)	38 (15.3%)
Thrombocytopenia	4 (3.2%)	7 (5.6%)	11 (4.4%)
Leukopenia	1 (0.8%)	5 (4.0%)	6 (2.4%)
Lymphadenopathy	2 (1.6%)	1 (0.8%)	3 (1.2%)
Pancytopenia	1 (0.8%)	2 (1.6%)	3 (1.2%)
Febrile neutropenia	2 (1.6%)	0 (0.0%)	2 (0.8%)
Leukocytosis	1 (0.8%)	0 (0.0%)	1 (0.4%)
Lymphopenia	0 (0.0%)	1 (0.8%)	1 (0.4%)
Neutrophilia	0 (0.0%)	1 (0.8%)	1 (0.4%)
Normochromic normocytic anaemia	1 (0.8%)	0 (0.0%)	1 (0.4%)
Investigations	54 (43.2%)	48 (38.7%)	102 (41.0%)
Neutrophil count decreased	24 (19.2%)	10 (8.1%)	34 (13.7%)
Blood creatinine increased	13 (10.4%)	8 (6.5%)	21 (8.4%)
Platelet count decreased	13 (10.4%)	8 (6.5%)	21 (8.4%)
White blood cell count decreased	12 (9.6%)	5 (4.0%)	17 (6.8%)
Alanine aminotransferase increased	5 (4.0%)	7 (5.6%)	12 (4.8%)
Blood alkaline phosphatase increased	3 (2.4%)	6 (4.8%)	9 (3.6%)
Haemoglobin decreased	5 (4.0%)	4 (3.2%)	9 (3.6%)
Blood urea increased	2 (1.6%)	5 (4.0%)	7 (2.8%)
Gamma-glutamyltransferase increased	2 (1.6%)	5 (4.0%)	7 (2.8%)
Lymphocyte count decreased	4 (3.2%)	3 (2.4%)	7 (2.8%)
Aspartate aminotransferase increased	1 (0.8%)	3 (2.4%)	4 (1.6%)
Platelet count increased	1 (0.8%)	2 (1.6%)	3 (1.2%)
Blood bilirubin increased	0 (0.0%)	2 (1.6%)	2 (0.8%)
Blood uric acid increased	1 (0.8%)	1 (0.8%)	2 (0.8%)
Blood bilirubin unconjugated increased	0 (0.0%)	1 (0.8%)	1 (0.4%)
Blood creatinine decreased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Blood glucose increased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Blood iron decreased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Blood potassium decreased	0 (0.0%)	1 (0.8%)	1 (0.4%)
Blood thyroid stimulating hormone increased	0 (0.0%)	1 (0.8%)	1 (0.4%)
Creatinine renal clearance increased	0 (0.0%)	1 (0.8%)	1 (0.4%)
Gastric pH decreased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Glomerular filtration rate decreased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Haematocrit decreased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Hepatic enzyme increased	0 (0.0%)	1 (0.8%)	1 (0.4%)
International normalised ratio increased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Liver function test abnormal	0 (0.0%)	1 (0.8%)	1 (0.4%)
Neutrophil count increased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Prothrombin time prolonged	1 (0.8%)	0 (0.0%)	1 (0.4%)
Red blood cell count decreased	1 (0.8%)	0 (0.0%)	1 (0.4%)
Sputum abnormal	0 (0.0%)	1 (0.8%)	1 (0.4%)
Troponin increased	0 (0.0%)	1 (0.8%)	1 (0.4%)

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one AE were counted only once.
[a] AEs were coded to preferred term using MedDRA, version 19.1.
Source: Table 14.3.1.2

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1. Vital Signs

Individual vital sign measurements by subject are included in Listing 16.2.9.1. Any clinically significant vital sign changes were reported as AEs and are included in Table 14.3.1.2 and Listing 16.2.7. There were no apparent treatment-related trends with respect to vital signs.

12.5.2. Physical Examination

Physical examination findings are presented by subject in Listing 16.2.9.2. Any clinically significant changes in these parameters were reported as AEs and are included in Table 14.3.1.2 and Listing 16.2.7. There were no apparent treatment-related trends with respect to physical examinations.

12.5.3. Electrocardiograms

Twelve-lead ECG results are summarized in Table 14.3.7.1, and no clinically relevant changes from baseline were noted.

A shift table for 12-lead ECG results from baseline to worst post-baseline value is included in Table 14.3.7.2. A greater percentage of subjects shifted from normal at baseline to abnormal, not clinically significant, as the worst post-baseline value in the ADIPemPlatinum group (29.2%), compared with the PlaceboPemPlatinum group (17.5%). One subject in each group shifted from normal at baseline to abnormal, clinically significant, as the worst post-baseline value. One subject in each group shifted from abnormal, not clinically significant, to abnormal, clinically significant, in each group.

Few subjects had QT intervals > 450, > 470, or > 500 msec at any time point, few subjects had a change from baseline of > 30 or > 60 msec, and results were similar between groups (Table 14.3.7.3).

Individual 12-lead ECG results are provided in Listing 16.2.9.3.

12.5.4. Concomitant Medications

All subjects in both groups received at least one concomitant medication during the study (Table 14.3.7.4), and percentages of subjects receiving concomitant medications were generally similar between groups by ATC drug class and generic drug name. The most commonly administered concomitant medications for subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups by generic drug name were the following: dexamethasone (76.0% and 79.0%, respectively), folic acid (83.2% and 82.3%, respectively), ondansetron (65.6% and 61.3%, respectively), and paracetamol (49.6% and 50.8%, respectively).

Therapeutic procedures after the EOT are provided in (Table 14.3.7.5), and results were similar between groups, including the rates of subsequent chemotherapy/immunotherapy, which were similar for the ADIPemPlatinum group (57 subjects [45.6%]) and the PlaceboPemPlatinum group (58 subjects [46.8%]). Because of the similar results in the two treatment groups, there was not likely to be a bias regarding an effect of post-treatment procedures.

By-subject listings of concomitant medications, non-medication therapies or treatments/procedures, and therapeutic procedures after the EOT are provided in Listing 16.2.9.6, Listing 16.2.9.7, and Listing 16.2.9.8, respectively.

12.5.5. Medical History

A by-subject listing of subject medical history is provided in Listing 16.2.4.2.

12.5.6. Pregnancy

A by-subject listing of pregnancy test results is provided in Listing 16.2.8.3. There were no pregnancies reported during the study.

12.6. Safety Conclusions

The safety conclusions from the study were as follows:

- The mean number of doses of ADI-PEG 20 was greater than that for placebo (22.0 vs 17.0 doses, respectively). The mean total dose of ADI-PEG 20 was 1475.0 mg. For both groups, for doses withheld, the main reason was AE (40.0% and 31.5% of subjects for the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively). Exposure to pemetrexed, cisplatin, and carboplatin was similar between the ADIPemPlatinum and PlaceboPemPlatinum groups, including reasons for doses withheld or reduced.
- Overall, 2973 TEAEs and 217 TESAEs were reported during the study and TEAE outcomes were similar between groups. Similar numbers of TEAEs (1570 and 1403 events) and TESAEs (106 and 111 events) were reported between the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively.
- Overall, a majority of subjects reported at least one TEAE (98.8%). The most common TEAEs in the ADIPemPlatinum group were nausea, fatigue, and constipation, and the most common TEAEs in the PlaceboPemPlatinum group were nausea, fatigue, and decreased appetite. Results were similar between groups, with the exception of constipation, neutropenia, and neutrophil count deceased, with greater percentages of subjects reporting these events in the ADIPemPlatinum group, and decreased appetite, with a greater percentage of subject reporting this event in the PlaceboPemPlatinum group.
- In regard to the percentages of subjects with neutropenia and neutrophil count decreased, the rates of related complications such as neutropenic sepsis (ADIPemPlatinum: 4 subjects [3.2%], PlaceboPemPlatinum: 2 subjects [1.6%]), febrile neutropenia (ADIPemPlatinum: 2 subjects [1.6%], PlaceboPemPlatinum: 0 subjects [0.0%]), and pneumonia (ADIPemPlatinum: 5 subjects [4.0%], PlaceboPemPlatinum: 8 subjects [6.5%]) were low.
- Approximately half of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had severe (Grade 3) TEAEs (49.6% and 44.4%, respectively). A total of 18.4% and 8.9% of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively, had life-threatening (Grade 4) TEAEs during the study. A small

number of subjects had life-threatening or fatal TEAEs (by preferred term) in each group. The most common severe TEAEs were anemia, neutropenia, and neutrophil count decreased for the ADIPemPlatinum group and anemia, fatigue, and neutrophil count decreased for the PlaceboPemPlatinum group. The most common life-threatening TEAEs were neutropenia and neutrophil count decreased for both groups. Results were generally similar between groups by preferred term for severe and life-threatening TEAEs. The larger percentage of subjects with life-threatening TEAEs in the ADIPemPlatinum group compared with the PlaceboPemPlatinum group was largely driven by greater percentages of subjects with neutropenia and neutrophil count decreased in the ADIPemPlatinum group.

- The majority of subjects had TEAEs that were considered related to ADI-PEG 20 or placebo, respectively (68.8% and 63.7%, respectively). The most common of these were nausea, fatigue, and rash for the ADIPemPlatinum group and nausea, fatigue, and decreased appetite for the PlaceboPemPlatinum group. A greater percentage of subjects reported at least one ≥ Grade 3 TEAE considered related to ADI-PEG 20 in the ADIPemPlatinum group (28.8%) compared with those considered related to placebo in the PlaceboPemPlatinum group (16.9%). However, the percentage of subjects reporting each preferred term was small and similar between groups.
- A total of 224 subjects died during the study, with a cause of death of malignant disease for the majority of subjects. There were 7 (5.6%) subjects with fatal TEAEs in the ADIPemPlatinum group and 12 (9.7%) subjects with fatal TEAEs in the PlaceboPemPlatinum group. For the ADIPemPlatinum group, these fatal TEAEs by preferred term were sudden death (2 subjects), cardiac arrest (2 subjects), pneumonia (1 subject), neutropenic sepsis (1 subject), and myocardial infarction (1 subject however, this subject's death occurred > 30 days past the last dose of ADI-PEG 20). For the PlaceboPemPlatinum group, these fatal TEAEs by preferred term were pneumonia (4 subjects), cerebrovascular accident (2 subjects), sepsis (2 subjects), coronavirus infection (2 subjects), septic shock (2 subjects), non-cardiac chest pain (1 subject), dyspnea (1 subject), and acute respiratory failure (1 subject).
- Approximately half of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had TESAEs (49.6% and 49.2%, respectively), with the largest percentages of subjects with TESAEs that were severe in intensity (28.0% and 27.4%, respectively). The most common TESAEs for the ADIPemPlatinum group were noncardiac chest pain, dyspnea, and acute kidney injury, with no TESAEs reported for > 5% of subjects in this group. The most common TESAEs for the PlaceboPemPlatinum group were pyrexia and nausea, with no other TESAEs reported for > 5% of subjects in this group. Of note, 2 (1.6%) subjects in the ADIPemPlatinum group had a TESAE of anaphylactic reaction, whereas no subjects in the PlaceboPemPlatinum group had a TESAE of anaphylactic reaction. Overall, a small percentage of subjects (9.2%) had TESAEs considered related to ADI-PEG 20 or placebo. Small percentages of subjects had TESAEs considered related to pemetrexed (21.5%), cisplatin (25.5%), or carboplatin (12.5%).
- Overall, a small percentage of subjects had a TEAE leading to discontinuation of ADI-PEG 20 or placebo (16.9%), and approximately half of subjects had a TEAE

leading to dose interruption of ADI-PEG 20 or placebo (45.4%). The most common TEAEs leading to ADI-PEG 20 discontinuation were anaphylactic reaction (3 subjects [2.4%]) and fatigue, pyrexia, and cardiac arrest (2 subjects [1.6%] each). No other TEAEs leading to discontinuation of ADI-PEG 20 were reported for more than 1 subject. For one of the subjects in the ADIPemPlatinum group who had a Grade 3 anaphylactic reaction TEAE that led to discontinuation of ADI-PEG 20, additional information was obtained that led Polaris to disagree with the diagnosis. In the PlaceboPemPlatinum group, only dyspnea (2 subjects [1.6%]) was reported for more than 1 subject as a TEAE leading to discontinuation of placebo.

- The majority of subjects had TEAEs that were related to pemetrexed (91.1%), cisplatin (94.3%), or carboplatin (89.8%), with similar percentages between groups. Smaller percentages of subjects had TEAEs leading to discontinuation, interruption, or reduction of pemetrexed (13.8%, 35.8%, and 20.7%, respectively), cisplatin (23.4%, 32.8%, and 28.1%, respectively), or carboplatin (10.2%, 35.2%, and 25.0%, respectively). Similar results were observed between groups for the percentages of subjects who had TEAEs leading to discontinuation, interruption, or reduction of these medications, with a few exceptions. A greater percentage of subjects reported at least one ≥ Grade 3 TEAE considered related to these medications in the ADIPemPlatinum group compared with those considered related to placebo in the PlaceboPemPlatinum group. However, the percentages of subjects reporting most preferred terms were small and similar between groups.
- Of note, 3 (2.4%) subjects in the ADIPemPlatinum group had a ≥ Grade 3 anaphylactic reaction TEAE considered related to ADI-PEG 20, whereas no subjects in the PlaceboPemPlatinum group had a ≥ Grade 3 anaphylactic reaction TEAE considered related to placebo. For one of the subjects in the ADIPemPlatinum group who had a Grade 3 anaphylactic reaction TEAE considered related to ADI-PEG 20, additional information was obtained that led Polaris to disagree with the diagnosis.
- Overall, a small percentage of subjects (4.8%) had TEAEs leading to premature withdrawal from the study.
- Out-of-range values and shifts in values were reported for most laboratory parameters; however, for most laboratory parameters, no clinically relevant changes were observed. Taking the laboratory results observed by visit together with shifts from baseline by severity grading, it is important to note that the rate of shifts from Grade 0 to 3 for neutrophils in the ADIPemPlatinum group was higher (19.8%) than that in the PlaceboPemPlatinum group (8.6%). Additionally, there was a large percentage of subjects with creatinine abnormalities (due to cisplatin administration), with no difference in the percentages of subjects with creatinine abnormalities between the ADIPemPlatinum and PlaceboPemPlatinum groups. No other clinically relevant changes from baseline in laboratory parameters were noted.
- There were no apparent treatment-related trends with respect to vital signs, ECGs, or physical examinations.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1. Discussion

This report presents the result from a randomized, double-blind, multi-center, phase 2/3 trial of ADI-PEG 20 in combination with pemetrexed and a platinum agent in subjects with unresectable MPM of sarcomatoid or biphasic histologies.

Overall, ADI-PEG 20 administration in combination with pemetrexed and a platinum agent in subjects with unresectable MPM of sarcomatoid or biphasic histologies led to statistically significantly longer median OS (the phase 3 primary endpoint) for the ADIPemPlatinum group (9.30 months) when compared with the PlaceboPemPlatinum group (7.66 months). In addition, the median PFS (the phase 3 secondary endpoint) was statistically significantly longer for the ADIPemPlatinum group (6.24 months) when compared with the PlaceboPemPlatinum group (5.65 months).

A numerically greater percentage of subjects had a best tumor response of stable disease in the ADIPemPlatinum group compared with the PlaceboPemPlatinum group (71.3% and 62.9%, respectively). The objective RR (the phase 2 primary endpoint) was similar between groups (13.8% and 13.5% for the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively).

For DOR (the phase 2 secondary endpoint), the hazard ratio (95% CI) of 0.34 (0.10, 1.14) favored ADIPemPlatinum over PlaceboPemPlatinum, indicating a longer, but not statistically significantly different, DOR (p-value = 0.0918).

The pharmacodynamic data demonstrated that repetitive dosing of ADI-PEG 20 resulted in sustained decreases in peripheral blood arginine, with a concomitant rise in citrulline. Immunogenicity data showed an increase in mean ADI-PEG 20 ADA titers over time and suggested that there was a correlation between decreased levels of circulating arginine following C1D8 and an increase in antibody titers. Despite the development of anti-ADI-PEG 20 antibodies over the course of 25 weeks, PK/pharmacodynamic measurements indicated that at 7 days post-dose at each time point collected, the mean arginine levels remained below baseline, mean citrulline levels remained above baseline, and mean ADI-PEG 20 concentration remained above the LLOQ throughout the course of treatment.

Safety analyses showed that adding ADI-PEG 20 to chemotherapy resulted in an increase in neutropenia, but not an increase in the more serious consequences related to neutropenia, such as sepsis and fever. In addition, a small but important incidence of anaphylaxis and other allergic reactions was observed in the ADIPemPlatinum group, which was generally absent in the PlaceboPemPlatinum group.

Overall, 2973 TEAEs and 217 TESAEs were reported during the study and TEAE outcomes were similar between groups. Similar numbers of TEAEs (1570 and 1403 events) and TESAEs (106 and 111 events) were reported between the ADIPemPlatinum and PlaceboPemPlatinum groups, respectively.

Overall, a majority of subjects reported at least one TEAE (98.8%). As would be expected following the types of therapy administered in this study, the most common TEAEs in the ADIPemPlatinum group were nausea, fatigue, and constipation, and the most common TEAEs in the PlaceboPemPlatinum group were nausea, fatigue, and decreased appetite. Results were

similar between groups, with the exception of constipation, neutropenia, and neutrophil count deceased, with greater percentages of subjects reporting these events in the ADIPemPlatinum group, and decreased appetite, with a greater percentage of subject reporting this event in the PlaceboPemPlatinum group. In regard to the percentages of subjects with neutropenia and neutrophil count decreased, the rates of related complications such as neutropenic sepsis (ADIPemPlatinum: 4 subjects [3.2%], PlaceboPemPlatinum: 2 subjects [1.6%]), febrile neutropenia (ADIPemPlatinum: 2 subjects [1.6%], PlaceboPemPlatinum: 0 subjects [0.0%]), and pneumonia (ADIPemPlatinum: 5 subjects [4.0%], PlaceboPemPlatinum: 8 subjects [6.5%]) were low.

A small number of subjects had life-threatening or fatal TEAEs (by preferred term) in each group.

A total of 224 subjects died during the study, with a cause of death of malignant disease for the majority of subjects. There were 7 (5.6%) subjects with fatal TEAEs in the ADIPemPlatinum group and 12 (9.7%) subjects with fatal TEAEs in the PlaceboPemPlatinum group.

Approximately half of subjects in the ADIPemPlatinum and PlaceboPemPlatinum groups had TESAEs (49.6% and 49.2%, respectively), with the largest percentages of subjects with TESAEs that were severe in intensity (28.0% and 27.4%, respectively). The most common TESAEs for the ADIPemPlatinum group were noncardiac chest pain, dyspnea, and acute kidney injury, with no TESAEs reported for > 5% of subjects in this group.

Out-of-range values and shifts in values were reported for most laboratory parameters; however, for most laboratory parameters, no clinically relevant changes were observed. Taking the laboratory results observed by visit together with shifts from baseline by severity grading, it is important to note that the rate of shifts from Grade 0 to 3 for neutrophils in the ADIPemPlatinum group was higher (19.8%) than that in the PlaceboPemPlatinum group (8.6%). Additionally, there was a large percentage of subjects with creatinine abnormalities (due to cisplatin administration), with no difference in the percentages of subjects with creatinine abnormalities between the ADIPemPlatinum and PlaceboPemPlatinum groups. No other clinically relevant changes from baseline in laboratory parameters were noted. Also, there were no apparent treatment-related trends with respect to vital signs, ECGs, or physical examinations.

13.2. Conclusions

Overall, ADI-PEG 20 administration in combination with pemetrexed and a platinum agent in subjects with unresectable MPM of sarcomatoid or biphasic histologies led to statistically significantly longer median OS (the phase 3 primary endpoint). In addition, the median PFS (the phase 3 secondary endpoint) was statistically significantly longer for the ADIPemPlatinum group when compared with the PlaceboPemPlatinum group. The objective RR (the phase 2 primary endpoint) was similar between groups, and for DOR (the phase 2 secondary endpoint), ADIPemPlatinum had a longer, but not statistically significantly different, DOR over PlaceboPemPlatinum. The safety profile of subjects who were administered ADI-PEG 20 was generally similar to that of subjects who were administered placebo, indicating that the efficacy observed was of clinical value without an increased risk to the subject.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1. Demographic Data Summary Figures and Tables

Number	Title	Population
Table 14.1.1.1	Subject Disposition	All Randomized Subjects
Table 14.1.1.2	Subject Disposition by Study Center	All Randomized Subjects
Table 14.1.2	Major Protocol Deviations	ITT Population
Table 14.1.3.1	Demographic Characteristics	Safety Population
Table 14.1.4.1	Baseline Characteristics	Safety Population
Table 14.1.5.1	Disease History	Safety Population

14.2. Efficacy Data Summary Figures and Tables

Number	Title	Population
Table 14.2.1.1	Objective Response Rate - Phase 2 Subjects	ITT Population
Table 14.2.2.1	Duration of Response - Phase 2 Subjects	ITT Population
Table 14.2.3.1	Overall Survival	ITT Population
Table 14.2.3.3	Overall Survival by Tumor Histology	ITT Population
Table 14.2.4.1	Progression Free Survival	ITT Population
Table 14.2.4.3	Progression Free Survival by Tumor Histology	ITT Population
Table 14.2.5.1	Pharmacodynamic Parameters	ITT Population
Table 14.2.5.2	Immunogenicity Parameters	ITT Population
Table 14.2.5.3	Pharmacokinetic Concentrations	ITT Population

14.3. Safety Data Summary Figures and Tables

14.3.1. Displays of Adverse Events

Number	Title	Population
Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety Population
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.3	Most Frequently-Occurring (≥ 10% Overall) Treatment-Emergent Adverse Events by Preferred Term	Safety Population
Table 14.3.1.4	Treatment-Emergent Adverse Events by CTCAE Grade, System Organ Class, and Preferred Term	Safety Population
Table 14.3.1.5	Treatment-Emergent Adverse Events by Relationship to ADI-PEG 20/Placebo, System Organ Class, and Preferred Term	Safety Population
Table 14.3.1.6	Treatment-Emergent Adverse Events by Relationship to Pemetrexed, System Organ Class, and Preferred Term	Safety Population
Table 14.3.1.7	Treatment-Emergent Adverse Events by Relationship to the Platinum Agent by System Organ Class, and Preferred Term	Safety Population
Table 14.3.1.8	Treatment-Emergent Grade ≥ 3 Adverse Events Related to ADI-PEG 20/Placebo by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.9	Treatment-Emergent Grade ≥ 3 Adverse Events Related to Pemetrexed by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.10	Treatment-Emergent Grade ≥ 3 Adverse Events Related to the Platinum Agent by System Organ Class and Preferred Term	Safety Population

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

Number	Title	Population
Table 14.3.1.11	Treatment-Emergent Adverse Events Leading to Discontinuation of ADI-PEG 20 ⁄ Placebo by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.12	Treatment-Emergent Adverse Events Leading to Discontinuation of Pemetrexed by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.13	Treatment-Emergent Adverse Events Leading to Discontinuation of the Platinum Agent by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.14	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.1	Listing of Deaths	Safety Population
Table 14.3.2.2	Listing of Serious Adverse Events	Safety Population
Table 14.3.2.3	Listing of Adverse Events Leading to ADI-PEG 20/Placebo Discontinuation or Interruption	Safety Population
Table 14.3.2.4	Listing of Adverse Events Leading to Pemetrexed Discontinuation, Reduction or Interruption	Safety Population
Table 14.3.2.5	Listing of Adverse Events Leading to Cisplatin Discontinuation, Reduction or Interruption	Safety Population
Table 14.3.2.6	Listing of Adverse Events Leading to Carboplatin Discontinuation, Reduction or Interruption	Safety Population

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Subject ID	Reason for Narrative			
	TESAE	Discontinued	Death	AESI
0101-0008	X	X		X
0101-0011	X			
0103-0001	X		X	
0103-0003	X			
0201-0015	X	X		X
0201-0049	X	X		
0204-0005	X			X
0207-0001	X	X	X	
0208-0003	X	X	X	
0209-0004		X		X
0212-0002	X	X	X	
0218-0002	X		X	
0218-0005	X			
0303-0001	X			
0304-0002	X	X	X	
0305-0004	X	X		X

14.3.4. Abnormal Laboratory Value Listing

Number	Title	Population
Table 14.3.4.1	Listing of Abnormal Hematology Values	Safety Population
Table 14.3.4.2	Listing of Abnormal Chemistry Values	Safety Population

14.3.5. Extent of Exposure

Number	Title	Population
Table 14.3.5.1	Extent of Exposure	Safety Population

14.3.6. Laboratory Summary Tables

Number	Title	Population
Table 14.3.6.1	Hematology – Univariate Summary by Parameter and Visit	Safety Population
Table 14.3.6.2	Hematology – Shift from Baseline to Worst Post-Baseline Value by Parameter	Safety Population
Table 14.3.6.3	Chemistry – Univariate Summary by Parameter and Visit	Safety Population
Table 14.3.6.4	Chemistry – Shift from Baseline to Worst Post-Baseline Value by Parameter	Safety Population
Table 14.3.6.5	Shift from Baseline to Worst Post-Baseline NCI CTCAE Toxicity Grade by Laboratory Parameter	Safety Population

14.3.7. Other Safety Summary Tables

Number	Title	Population
Table 14.3.7.1	12-Lead Electrocardiogram – Univariate Summary by Parameter and Visit	Safety Population
Table 14.3.7.2	12-Lead Electrocardiogram Interpretation – Shift from Baseline to Worst Post-Baseline Value	Safety Population
Table 14.3.7.3	12-Lead Electrocardiogram - Abnormal QT Interval Categories	Safety Population

14.4. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Summary Figures and Tables

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16. APPENDICES

16.1. Study Information

Appendix 16.1.1 Protocol and Protocol Amendments

Appendix 16.1.2 Sample Case Report Form

Appendix 16.1.3 List of IECs and IRBs and Representative Written Information for Subjects

Appendix 16.1.4 List and Description of Investigators and Other Important Participants in the Study

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Appendix 16.1.8 Audit Certificates

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Listing 16.2.2.1 Major Protocol Deviations

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