OncoMed Pharmaceuticals, Inc

M18-006

A 3-Arm Phase 2 Double-Blind Randomized Study of Gemcitabine, Abraxane® Plus Placebo versus Gemcitabine, Abraxane® plus 1 or 2 Truncated Courses of Demcizumab in Subjects with 1st-Line Metastatic Pancreatic Ductal Adenocarcinoma

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Statistical Analysis Plan

Version *2.4*

Prepared by:

PPD

[redacted]

Confidential

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Signature Page for Statistical Analysis Plan (SAP)

Approval of SAP – Version 2.4

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
aPTT	Activated Partial Thromboplastin Time
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BNP	B-type Natriuretic Peptide
BOR	Best Overall Response
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography (Scan)
CTCAE	Common Toxicity Criteria for Adverse Events (National Cancer Institute)
DOR	Duration of Response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
INR	International Normalized Ratio
IRF	Independent Review Facility
ITT	Intent-To-Treat (Population)
IV	Intravenous
IWRS/IVRS	Interactive Web Randomization System/Interactive Voice Randomization System
kg	Kilogram(S)
LDH	Lactic Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not Evaluable
OS	Overall Survival

Abbreviation or Term	Definition/Explanation
PD	Progressive Disease Or Pharmacodynamic
PFS	Progression-free Survival
PK	Pharmacokinetic
PP	Per Protocol (population)
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease or Standard Deviation
SLD	Sum of the Longest Diameters
SOC	System Organ Class
ULN	Upper Limit of Normal

1. Introduction

This is a 3-arm phase 2 double-blind randomized study of Gemcitabine, Abraxane Plus Placebo versus Gemcitabine, Abraxane plus 1 or 2 Truncated Courses of Demcizumab in Subjects with 1st-Line Metastatic Pancreatic Ductal Adenocarcinoma. The current study is being conducted under the sponsorship of OncoMed Pharmaceuticals, Inc. This document describes the planned statistical analyses, which is based on Protocol M18-006 amendment 4 (Effective Date: 31 March 2016).

2. Treatments

There are three arms in this study, and they are defined as following:

Arm 1 (Placebo/Placebo): Abraxane and gemcitabine plus placebo (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles) and then Abraxaneand gemcitabine until disease progression.

Arm 2 (Demcizumab/Placebo): Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles) and then Abraxane and gemcitabine until disease progression.

Arm 3: (Demcizumab/Decizumab): Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus demcizumab (3 cycles) and then Abraxane and gemcitabine until disease progression.

3. Objectives

Primary Objective:

1. To compare the efficacy of Arm 1 to the pooled decizumab arms (i.e., Arm 1 to Arms 2 and 3) in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma

Secondary Objectives:

2. To compare the efficacy of Arm 1 to Arm 2, and Arm 1 to Arm 3 in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma

3. To compare the safety of Arm 1 to Arm 2, Arm 1 to 3, and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

4. To determine the rate of immunogenicity against demcizumab when combined with Abraxane® and gemcitabine in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

5. To determine population pharmacokinetics of demcizumab in subjects receiving demcizumab and Abraxane® and gemcitabine in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

   Exploratory Objectives:

6. To compare the safety and efficacy of Arm 2 to Arm 3 in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

7. To compare the exploratory biomarkers of Arm 1 to Arm 2, Arm 1 to 3, and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

4. Investigational Plan

4.1. Overall Study Design and Plan

This is a randomized, double blind, 3 arm (1:1:1) study in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma. Prior to randomization, subjects will undergo screening to determine study eligibility. Two hundred and one evaluable subjects will be randomized via an Interactive web randomization system/Interactive voice randomization system (IWRS/IVRS) system.

Demcizumab 3.5 mg/kg or placebo will be administered by intravenous (IV) infusion (prior to the administration of Abraxane and Gemcitabine) once every 2 weeks for either one (1st course through Study Day 70) or two (2nd course begun on Study Day 168 and continued through Study Day 238) 70 day courses.

Abraxane must be administered after the demcizumab, but before gemcitabine administration on days when three drugs are given. Abraxane should be administered by IV infusion at a starting dose of 125 mg/m^2 over 30 minutes on Days 1, 8 and 15 of every 28-day cycle. The dose of Abraxane may be reduced over time if necessary to reduce toxicity.

Gemcitabine must be administered after the administration of demcizumab and Abraxane. Gemcitabine should be administered by IV infusion at a starting dose of 1000 mg/m^2 over 30 minutes once weekly for 3 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest every 28 days. The dose of gemcitabine may be reduced over time if necessary to reduce toxicity.

4.2. Study Endpoints

Primary Endpoint

- To compare the hazard of progression using the Investigator assessed progression-free survival time between subjects in Arm 1 and the pooled demcizumab arms (i.e., Arms 2 + 3) in 1st-line metastatic pancreatic ductal adenocarcinoma.

Secondary Endpoints

- To compare the hazard of progression using the Investigator assessed progression-free survival time between subjects in Arm 1 and Arm 2, and Arm 1 and Arm 3 in 1st-line metastatic pancreatic ductal adenocarcinoma.
- To compare the Investigator-assessed RECIST response rate (the rate of complete response + partial response) in Arm 1 to Arm 2 , Arm 1 to 3, and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic cancer.
- To compare the Investigator-assessed RECIST clinical benefit rate (i.e., the rate of complete response + partial response + stable disease) in Arm 1 to Arm 2, Arm 1 to 3, and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To compare the Investigator-assessed progression-free survival at 6 months in Arm 1 to Arm 2, Arm 1 to 3, and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To determine the half-life, volume of distribution and clearance of demcizumab when combined with Abraxane® and gemcitabine in with subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To compare the safety profile through adverse event monitoring (including attribution of adverse events and serious adverse events [SAEs]), physical examination, vital signs, and clinical laboratory testing as outlined in the Schedule of Assessments (see Appendix B of Protocol) between Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma. To compare the incidence of anti-demcizumab antibody development and neutralizing antibody development in subjects with 1st-line locally advanced or metastatic pancreatic ductal adenocarcinoma being treated with Abraxane® and gemcitabine plus demcizumab in Arm 1 to Arm 2, Arm 1 to 3, and Arms 1 to Arms 2 and 3 pooled.
- To compare the median survival in Arm 1 to Arm 2, Arm 1 to 3, and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

- The compare the Kaplan Meier estimates of survival at 6, 12, 18 and 24 months in Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

Exploratory Endpoints

- To compare the pharmacodynamic and predictive biomarkers for demcizumab and determine their correlation with response in Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled (see Section 11 of Protocol).

- To compare the CA-19-9 response rate (i.e., at least a 50% decline from baseline) between Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-metastatic pancreatic ductal adenocarcinoma

4.3. Treatment Modifications

Any subject who has two consecutive BNP values >100 pg/mL or one value >200 pg/mL will be unblinded by the Investigator through the IWRS/IVRS system. If the subject is receiving demcizumab they will start on a cardioprotective agent such as an ACE inhibitor or carvedilol, unless the BNP elevation occurred more than 100 days after the discontinuation of demcizumab or there is a contraindication to the use of these agents and if appropriate referred to a cardiologist. If they are not on demcizumab they should be cared for according to standard medical practice. The selection and dose of the ACE inhibitor to be administered or the dose of carvedilol to be administered should be based on the recommendations in standard guidelines for treating heart failure (Ref 1). If there is a contraindication to administering both of these agents, the patient's treatment should be discussed with the OncoMed Medical Monitor.

In addition, subjects must have their dose of demcizumab or placebo held for any of the following findings:

BNP of ≥300 pg/mL

LVEF decline ≥10% from baseline and a LVEF value that is <50%

Clinically significant pulmonary hypertension (i.e., the subject has a peak tricuspid velocity >3.4 m/s on Doppler echocardiogram, has been seen by a cardiologist and was diagnosed with clinically significant pulmonary hypertension)

Signs and symptoms of heart failure

Administration of the subject's chemotherapy should be continued while demcizumab or placebo is being held.

Dosing of demcizumab or placebo must continue to be held until the subjects has:

BNP <300 pg/mL

LVEF value that is >50%

No clinically significant pulmonary hypertension, and

No signs or symptoms of heart failure

Any subject who has a BNP of ≥300 pg/mL that is considered to be related to demcizumab, ≥10% decline in left ventricular ejection fraction and a LVEF value that is <50%, signs and symptoms of heart failure or clinically significant pulmonary hypertension (i.e., the subject has a peak tricuspid velocity >3.4 m/s on doppler echocardiogram and has been seen by a cardiologist and diagnosed with clinical significant pulmonary hypertension) that persists beyond Day 70 or occurs beyond Day 70 must have their demcizumab permanently discontinued.

Demcizumab/placebo must also be discontinued for any of the following:

BNP of ≥400 pg/mL

≥Grade 2 pulmonary hypertension

Evidence of Grade ≥2 bleeding (except for readily manageable local bleeding, such as hemorrhoidal bleeding)

Hypertensive crisis

Hypertensive encephalopathy

Blood pressure of ≥ 200/120 mmHg

Need for therapeutic anti-coagulation

If therapeutic anti-coagulation is no longer required, the subject may receive any remaining demcizumab/placebo administrations

If the demcizumab/placebo needs to be held or discontinued, the administration of the chemotherapy should continue until disease progression, unless contraindicated.

5. General Statistical Considerations

5.1. Sample Size

Type 1 error is controlled at the 0.10 one sided level. Two hundred and one subjects followed until 125 PFS events have been observed will provide 80 percent power to detect a hazard ratio of 0.67 which corresponds to an increase in median PFS from 5.5 months to 8.2 months.

5.2. Randomization, Stratification, and Blinding

Eligible subjects will be randomly assigned to treatment in a 1:1:1 allocation ratio to receive arm1 (Placebo/Placebo), arm 2 (Demcizumab/Placebo), and arm 3 (Demcizumab/ Demcizumab) using double-blind method. Subjects will be stratified by Eastern Cooperative Oncology Group

(ECOG) performance status (0 or 1), region (United States/ Canada or Europe/Australia) and CA19-9 (0 – ULN, >ULN – 59ULN, >59ULN). At least two-hundred and one subjects will be randomized via an IWRS/IVRS system to one of the three arms.

For the final overall survival analysis, unblinding will be done at the study level as well as the individual patient level. For earlier interim analyses of overall survival as well as other data, unblinding will be done at the overall study results level, but unblinding will not be done at the individual patient level (i.e., OncoMed will received unblinded tables and figures, but the patient listings will be blinded).

5.3. Subject Populations for Analysis

There will be 201 subjects randomized in the trial.

The Intent-to-Treat (ITT) Population comprises all subjects who receive at least one partial or complete dose of demcizumab or placebo. All baseline characteristics and demographic, efficacy, immunogenicity, and biomarker data will be analyzed using the ITT Population.

The Per Protocol Population (PP) is comprised of all randomized subjects who received at least one dose of demcizumab or placebo and had at least one post baseline tumor assessment. All efficacy data will be analyzed using the PP population as well as the ITT Population.

The Safety Population comprises all subjects who receive at least one partial or complete dose of demcizumab or placebo and who have at least one post-dosing safety evaluation. All safety endpoints will be summarized using the Safety Population.

The Pharmacokinetic (PK) Population comprises all subjects who receive at least one partial or complete dose of demcizumab or placebo and who provide adequate PK samples, as defined by the PK specialist, to calculate the PK parameters. Subjects with protocol violations will be assessed on a subject-by-subject basis for inclusion in the PK Population. PK analysis will be conducted using the Pharmacokinetic Population.

The Response Evaluable Population comprises all subjects who receive at least one dose of study drug and who have at least one post-baseline disease response (CR or PR). Duration of response will be analyzed using Response Evaluable Population.

6. Subject Disposition

6.1. Disposition

Subject disposition will be summarized for the ITT Population. A disposition of subjects includes the number and percentage of subjects for the following categories: subjects who were

randomized, subjects who are in study, subjects who discontinued from the study, and subjects who ended of follow up. All percentages will be based on the number of patients randomized.

The reasons for discontinuation of study and end of follow-up will also be summarized in this table. Analysis population will be summarized for all subjects.

Subject disposition data will be also presented in a listing.

6.2. Protocol Deviations

The following protocol deviations will be recorded and summarized for the Intent-to-Treat population in the final report: 1) randomization violations, 2) dosing violations, 3) concomitant therapy violations, and 4) continuation of therapy when treatment should have been discontinued. A list of patients with protocol deviation will be also presented.

7. Demographics and Medical History

Demographic and medical history will be analyzed using the ITT Population.

Quantitative and/or categorical summaries will be presented for demographics, medical history, metastasis information, and other baseline characteristics. For continuous variables, data will be summarized by count of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, data will be summarized as frequency counts and percentages.

7.1. Demographics and Baseline Characteristics

Age will be calculated as the integer part of (Informed Consent Date – Birth Date +1)/365.25. The demographic characteristics consist of age, sex, ethnicity, and race. The baseline characteristics also consist of baseline height (cm), baseline weight (kg), metastatic sites, number of metastatic sites, hepatic metastasis, and NLR (neutrophil to lymphocyte ratio). Demographic and baseline characteristics will be summarized as frequency counts and percentages.

Metastasis diagnosis dates, sites, and hepatic metastasis status will be listed.

7.2. Medical History

7.2.1. General Medical History

The number and percentage of patients with any medical history will be summarized overall and for each body system and preferred term.

Subject medical history data including specific details will be presented in a listing.

7.2.2. Cancer Diagnosis History

Cancer diagnosis history including Stage at initial diagnosis, whether or not the subject has measureable disease per RECIST 1.1 will be tabulated. Stratification factors will be also summarized and listed.

A listing of cancer diagnosis history will be presented.

7.2.3. Prior and during Follow-up Period Cancer Treatments and Therapies

The number and percentage of subjects who have received prior cancer treatments including prior systemic treatment, prior surgery to treat their cancer, and prior radiotherapy will be summarized by treatment arm, which will also include frequency counts and percentages of drugs of prior systemic treatment, procedures of prior surgery.

Prior cancer treatments including prior systemic treatment, prior surgical treatment, and prior radiotherapy treatment will be presented as data listings.

Systemic therapy for pancreatic cancer during follow up period will be tabulated and listed. Surgery and radiotherapy will also be listed.

7.3. Inclusion and Exclusion Criteria

See Section 6.1 and 6.2 in study protocol, for details on inclusion and exclusion criteria. Inclusion and exclusion criteria will be presented in a listing for all subjects.

8. Treatments and Medications

8.1. Prior and Concomitant Medications

Prior and concomitant medications will be presented by ITT Population.

Prior medications are defined as medications with a stop date occurring before randomization date. Concomitant medications are defined as medications with a stop date occurring on or after randomization date. Medications for which the start and end dates are missing will be classified as prior and concomitant. Medications will be coded using World Health Organization (WHO) Drug version 01 Sep 2014. Concomitant procedures will not be coded. The number and percentage of patients taking concomitant medications, anti-hypertensive concomitant medications, and ACE inhibitor or carvedilol for BNP increase will be tabulated by WHO drug generic term.

Missing date of prior and concomitant medication will be imputed as in Appendix B.

Prior and concomitant medications and procedures will be also presented in by-patient listings.

Anti-hypertensive concomitant medication and ACE inhibitor or carvedilol for BNP increase will be also summarized separately as at screening and on study in tables and listed.

8.2. Study Treatments

Study treatment will be analyzed by Safety Population.

8.2.1. Extent of Exposure

Treatment exposure will be summarized as duration on treatment and extent of exposure to demcizumab/placebo, abraxane, and gemcitabine in Arms 1, 2 and 3. Duration of exposure, which is defined as last dose date – date of first dose +1, will be summarized quantitatively in days using count of non-missing data, mean, standard deviation, median, minimum, and maximum. Total number of dose taken, cumulative dose, dose intensity, and infusion interrupted will be also summarized.

Dose intensity is defined as cumulative dose/total planned dose. The total planned dose is the sum of the planned doses taken throughout the study. For demcizumab planned dose per cycle= 3.5 mg/kg *baseline weight. For abraxane and gemcitabine, planned dose per visit= administered dose mg/m^2 *0.007184 *(baseline weight^0.425) *(baseline height^0.725). Baseline weight and height are the Day 0 weight and height throughout the study.

Demcizumab 3.5 mg/kg or placebo will be administered by IV infusion (prior to the administration of Abraxane® and gemcitabine) once every 2 weeks for either one (1st course through Study Day 70) or two (2nd course begun on Study Day 168 and continued through Study Day 238) 70 day courses. Subjects will only receive their second 70 day course of placebo or demcizumab if the subject's Day 168:

BNP is ≤100 pg/mL,

peak tricuspid velocity is ≤3.0 m/s

LVEF is ≥50%

The subject did not develop pulmonary hypertension or heart failure while on study.

Treatment exposure including the date of infusion, actual dose amount, reason of interruption will be presented in a listing.

9. Efficacy Analysis

Efficacy endpoints include Progression-Free Survival (PFS), best overall response, duration of response, and overall survival (OS). Duration of response will be analyzed using the Response Evaluable Population and other efficacy endpoints will be analyzed using the ITT Population and PP Population. Pooled demcizumab arms are pooled Arm 2 and Arm 3.

9.1. Primary Efficacy Endpoint

PFS is the primary efficacy endpoint. It is defined as the number of days from randomization until death or disease progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Survival time in days (d) will be converted to months (m) using m= d/30.4375.

A subject is considered to have progressed if they have a RECIST response of progression on or prior to their last on study tumor assessment or if they have died within 56 + 7 days (Tumor assessments are 8 weeks apart) of their last on study tumor assessment. Here, the last on study tumor assessment is the last tumor assessment with a non-missing RECIST response without a gap of 119 days (2*8*7+7 tumor assessments occur every 8 weeks) or more between the current and/or previous tumor assessments. When a subject has progressed (censor=0) their time to progression is the date of progression (date of RECIST response assessment or date of death) minus start date+1. When a subject has not progressed (censor=1) their time to progression is the last on study RECIST tumor assessment date-start date+1. Here the start date is the randomization date.

If a subject received non protocol therapy (NPT) prior to disease progression or received NPT and is not progressed, then the subject will be censored on the last adequate assessment prior to NPT. Non protocol therapy will be determined from a clinical review of the relevant listings. Radiotherapy and surgery directed at a disease site will be considered non-protocol therapy. Bisphosphonates and hormones will not be considered non-protocol therapy.

For subjects who do not experience disease progression and do not have any adequate post-baseline tumor assessments, PFS will be right censored at Day 0. PFS (in months) = (Date of event/censoring - date of first dose + 1)/30.4375. The censoring rules for PFS are included in Table 1 below.

Table 1: Censoring Conventions for PFS

Situation	Date of Progression or Censoring	Outcome
No baseline and/or post baseline tumor assessment and no post baseline event	Randomization date	Censored
Progression documented at or between scheduled visits	Date of scan or clinical assessment of progression	Event
No Progression	Date of last adequate on study assessment	Censored
Death due to any cause before first scheduled post baseline assessment	Date of Death	Event
Death less than 56 +7days from the last tumor assessment without prior progression	Date of Death	Event
Death greater than 56+7 days from the last tumor assessment without prior progression	Date of last adequate tumor assessment	Censored
Received NPT prior to disease progression	Date of last adequate assessment prior to NPT	Censored

The Kaplan-Meier method will be used to estimate the proportion of subjects without progression or death over time and the median progression-free survival time in the pooled demcizumab arms as well as each individual arm of the trial. The 95% confidence intervals for median progression-free survival time will also be calculated for the pooled demcizumab arms as well as each treatment arm. The Kaplan-Meier estimates and the 95% CI will be provided at 6 and 12 months. The p-values for the demcizumab treatment effects (pooled versus control as well as each individual demcizumab arm versus control) will be generated using a stratified log rank test. A stratified Cox proportional hazards regression model will be used to estimate the hazard ratio and its 95% confidence intervals. The stratification factors will be performance status (1 or 0) and region (United States/ Canada or Europe/Australia) and CA19-9 (0 – ULN, >ULN – 59ULN, >59ULN). In addition to the log rank test, the Wilcoxon test will also be used as a sensitivity analysis to evaluate the impact of treatment on PFS.

To evaluate the impact of the second course of demcizumab therapy, a cox regression analysis will be used by pooling Arm 2 and Arm 3 and compared with Arm 1. The model will include a

time dependent covariate to identify who started a second course of Demcizumab. The coefficient for this term will be used to assess the impact of the second course of Demcizumab treatment.

Kaplan-Meier curves of PFS will be plotted for each individual arm (Arm 1, 2, and 3) by stratification factors and overall. For the pooled analysis, Kaplan-Meier curves of PFS for pooled demcizumab arm (pooled Arm 2 and Arm 3) and Arm 1 will be plotted by stratification factors and overall.

9.2. Best Overall Response (BOR)

The best overall response (BOR) is defined as the best response determined by RECIST v1.1 recorded from the start of the treatment until disease progression in the following order of importance: CR, PR, SD, PD, NE, Missing. Response outcomes from a response assessment done anytime less than Study Day 49 will be considered as not evaluable unless the response assessment is PD.

The number and percentage of subjects in each disease response category (CR, PR, SD, PD, NE, and Missing) will be summarized by treatment arm and for the pooled demcizumab arms.

The response rate is the number of subjects per treatment arm who have either a CR or a PR divided by the number of subjects randomized to the respective arms. Clinical benefit rate is the number of subjects per treatment arm who have either a CR or a PR or SD divided by the number of subjects randomized to the respective arms. Both response rate and clinical benefit rate and their 95% confidence intervals by Exact Binomial method will be displayed. The odds ratios and p-value for equality of the response rate between the pooled demcizumab treatment arm and control will be calculated for the two groups using a logistic regression model with performance status, region, and CA19-9 as factors in the model. A similar comparison will be made between each individual demcizumab arm and control.

9.3. Continuous Variable Assessment of Tumor Length

The tumor length will be calculated as the sum of the longest diameters (SLD) for the target lesions (as defined by RECIST v1.1 criteria and determined by the Investigator). The data will be displayed graphically with waterfall plots. Summary statistics including mean, standard deviation, median, minimum, and maximum for tumor length will be presented for baseline, 9 weeks post-baseline, and 18 weeks post-baseline. These summary statistics will also be presented for differences from baseline at 9 and 18 weeks post-baseline. Along with the summary statistics, the 95% confidence intervals of the mean tumor length for each treatment arm and the pooled demcizumab arms at each of the three timepoints will also be presented. An ANCOVA model will be used to test the hypothesis that there is no difference between treatment arms (Arm 1 versus Arm 2, and Arm 1 versus Arm 3) as well as no difference between the pooled demcizumab arms and control with regard to changes from baseline tumor length at

scheduled tumor assessments. Treatment and ECOG PS and region will be factors in the model and baseline tumor length will be used as a covariate. Missing values will not be imputed.

In addition, for target-lesion, the percent rate of change in tumor volume per day for target lesion at progression is 100 × (SLD at progression – SLD at nadir)/ (SLD at nadir × days between Nadir and Progression) as determined by the Investigator will be summarized descriptively by treatment arms. The rate of change in tumor burden at progression has been associated with survival. The rate of change in tumor volume for the target lesion at progression will be summarized for the ITT population and the PP population, respectively.

9.4. Duration of Response

The Investigator-assessed duration of response (DOR) is defined as the time from the first partial or complete response to the time of death or disease progression for subjects. DOR will be using Response Evaluable Population. Subjects who have not experienced death or progression by their last contact will be censored at the time of their last on study radiographic response assessment. DOR (in months) = (Date of event/censoring - date of first response + 1)/30.4375. The censoring rules for DOR are included in Table 2 below.

Table 2: Censoring Conventions for DOR

Situation	Date of Progression or Censoring	Outcome
No assessment after first response	First response date	Censored
Progression documented at or between scheduled visits	Date of scan or clinical assessment of progression	Event
No Progression (or death)	Date of last adequate assessment after first response	Censored
Death due to any cause before first scheduled post baseline assessment	Date of Death	Event
Death less than 56 +7days from the last tumor assessment without prior progression	Date of Death	Event
Death greater than 56+7 days from the last tumor assessment without prior progression	Date of last adequate tumor assessment	Censored
Received NPT prior to disease progression	Date of last adequate assessment prior to NPT	Censored

The Kaplan-Meier method will be used to estimate the duration of response. The 95% confidence intervals for duration of response will also be calculated for the pooled demcizumab arms as well as each treatment arm. The p-value for treatment effect (pooled versus control and each demcizumab arms versus control) will be generated using a stratified log rank test. A stratified Cox proportional hazards regression model will be used to estimate the hazard ratio and its 95% confidence intervals. The stratification factors will be performance status (1 or 0) and region (United States/ Canada or Europe/Australia) and CA19-9 (0 – ULN, >ULN – 59ULN, >59ULN).

9.5. Overall Survival

A comparison of the overall survival (OS) between the pooled demcizumab arms and control as well as each individual demcizumab arm versus control will be performed.

The following algorithm will be applied for the final delivery. The data cutoff date is the date when the 125Th PFS event happens. Overall survival is defined as the number of days from randomization until death occurs if the death date is before the data cutoff date. Subjects who die after the data cutoff date will be censored at cutoff date. When a subject has at least one survival follow-up showing alive after data cutoff date, this subject will be censored on the data cutoff date. Otherwise the subject will be censored at the last available visit/measurement including survival followup which is prior to the cutoff date and shows the subject is alive. No treatment cross-over is permitted in the study. The censoring rules for OS are included in Table 3.

Table 3: Censoring Conventions for OS

Situation	Date of Progression or Censoring	Outcome
Death due to any cause before the data cutoff date	Death Date	Event
Death due to any cause after the data cutoff date	Data cutoff date	Censored
Have at least one survival follow-up showing alive after data cutoff date	Data cutoff date	Censored
None of the above apply	Last date from on study and survival followup periods prior to the data cutoff that shows the subjects is alive	Censored

In the OS follow-up analysis, the censoring rules will be the same except that the data cutoff will be as specified in the protocol.

The Kaplan-Meier method will be used to estimate both the survival curves and the median survival time. The 95% confidence interval for the median survival time will be calculated. A p-value for treatment effect will also be generated using a stratified log rank test. A stratified Cox proportional hazards regression model will be used to estimate the hazard ratio and its 95% confidence intervals. The stratification factors will be performance status (1 or 0), region (United States/ Canada or Europe/Australia), and CA19-9 (0 – ULN, >ULN – 59ULN, >59ULN). The number and percentage of these subjects who are treated as an event and as a censor will be displayed.

The Kaplan Meier estimates of overall survival at 6, 12, 18 and 24 months will be compared between the demcizumab arms (Arm 2, Arm 3) and control (Arm 1) using a simple Z test. Greenwood's formula for the variance of the survival estimate will be used to construct the Z-test.

Kaplan-Meier curves of OS will be plotted for each individual arm (Arm 1, 2, and 3) by stratification factors and overall. For the pooled analysis, Kaplan-Meier curves of OS for pooled demcizumab arm (pooled Arm 2 and Arm 3) and Arm 1 will be plotted by stratification factors and overall.

Phase 2/3 Contingency Plan

This Phase 2 study has been designed with the aim of assisting the go/no go decision of whether to take demcizumab into Phase 3 development. Table 4 presents the statistical plan for this Phase 2 trial. This table differs somewhat from the power table presented in the protocol. The reason for this is that the protocol used the O'Brien Fleming stopping boundary while Table 4 uses the O'Brien Fleming spending function to create the stopping boundary. Using the O'Brien Fleming spending function as below provides flexibility in the timing and in the number of interim analyses that are conducted. Table 4 below supersedes the corresponding table in the protocol.

Table 4: Summary of Power and Type 1 Error for Phase 2 Study

	Interim 1	**Interim 2**	**Final Analysis**
Total Number of Events	87	112	131
Z-Statistic (reject the null)	1.711	1.530	1.431
Z statistic (reject the Alt)	0	0	1.431
Hazard Ratio (reject the null)	0.678	0.736	0.767
Hazard Ratio (reject the alt)	1	1	0.767
Cumulative Power	0.5304	0.7109	0.802
Cumulative Type 1 Error (1-sided)	0.0435	0.0752	0.0995
Cumulative Prob. of Stopping for Futility (Alt)	0.0369	0.043	0.198
Cumulative Prob. of Stopping for Futility (Null)	0.5	0.5783	0.9006

If the results from the above planned analyses of overall survival are promising in that they are either highly statistically significant or the Phase 2 efficacy boundary described above is crossed, Table 5 presents an a priori determined contingency plan which describes how these Phase 2 results will be considered for the purposes of assembling Phase 3 evidence of effectiveness. See Appendix C for details of the calculations.

In this contingency plan, the Phase 2 trial described above is embedded into a Phase 3 trial of approximately 618 subjects. The OS Phase 2 efficacy boundary presented in Table 4 assumes the role of an expansion gate in the Phase 3 trial in that the Phase 2 trial will not be extended to a Phase 3 sized trial unless the OS Phase 2 efficacy boundary in Table 4 is crossed. The OS Phase 2 efficacy boundary appears in Table 5 in the row titled Z Statistic (expand the trial) where the Z statistics at Interims 1, 2 and 3 are the same as the OS Phase 2 efficacy boundary in Table 4. Since the efficacy boundary in Table 4 is assuming the role of an expansion gate in Table 5, the testing associated with the Phase 2 OS efficacy boundary does not contribute to type 1 error for the purpose of assessing the efficacy of demcizumab on overall survival with Phase 3 stringency at the 0.025 one sided level of significance.

If at interim 1 the Z statistic for comparing the hazard of death on demcizumab versus control exceeds 3.938 (hr=0.408) then the result will support the claim that demcizumab prolongs survival. Similarly if the Z statistic exceed 3.746 (hr=0.472) or 3.614 (hr=0.512) respectively at Interim 2 or Interim3 then the result will support the claim that demcizumab prolongs survival. If at Interim 1, 2 or 3 the Z statistic exceeds 1.711, 1.530 or 1.432 respectively but does not exceed 3.938, 3.746 and 3.614 then the trial will be extended to have three more analyses, at 154 and 315 events and the final analysis at 432 events. The first additional analysis beyond what is planned for in the Phase 2 trial at 154 deaths may be accomplished by simply continuing to follow patients who have already been enrolled in the Phase 2 trial. If the hr is less than 0.556 at the fourth analysis of survival then the results will support a claim of OS effectiveness. The remaining analyses will necessarily involve enrolling more patients. If at interim 5 the Z statistic is greater than 2.464(hr=0.745) or the Z statistic at the final analysis is greater than 1.993 (hr=0.816) then the result will also support the claim that demcizumab prolongs survival.

Note that once the Phase 2 efficacy boundary is crossed and enrollment in the trial has restarted the remaining analyses from Interim 1 through Interim 4 may or may not be conducted. The control of type error for the Phase 3 efficacy boundary using the rho family of spending functions with parameter= 4 permits flexibility in the number and timing of interim analyses in this trial.

Under this contingency plan there is 83 percent power to detect a hazard ratio of 0.65. Note that the final analysis of the extended trial would normally be large enough to detect a hazard ratio of 0.75 with 80 percent power and 0.025 type 1 error. The difference is due to the efficacy boundary (expansion boundary) from the Phase 2 trial. Corresponding with the reduced power is a reduction in the type 1 error. The true type 1 error in this contingency design is 0.0127 one sided instead of the nominal 0.025.

Table 5: Summary of Power and Type 1 Error for Phase 2 and Extended Phase 3 Studies

	Currently Planned Phase 2 OS Analyses			Additional OS Analysis to Support Extended Follow-up of Phase 2 Patients	OS Analyses in the Phase 3 Expansion	
	Interim 1[1]	Interim 2[1]	Interim 3[1]	Interim 4[1]	Interim 5[1]	Final Analysis[1]
Total Number of Events	87	112	131	154	315	432
Z-Statistic (reject the null)[2]	3.938	3.746	3.613	3.439	2.464	1.993
Z statistic (expand the trial)[3]	1.711	1.530	1.432			
Z statistic (futility)[4]	0	0	1.432			
Hazard Ratio (reject the null)	0.408	0.472	0.512	0.556	0.745	0.816
Hazard Ratio (expand the trial)	0.678	0.736	0.767			
Hazard Ratio (futility)	1	1	0.767			
Non-Binding Expansion and Futility Boundaries						
Cumulative Power (HR=1.00)	0	1e-04	2e-04	4e-04	0.0071	0.025
Cumulative Power (HR=0.75)	0.0038	0.0115	0.0225	0.0444	0.4789	0.8003
Cumulative Power (HR=0.65)	0.0205	0.0586	0.1071	0.191	0.8739	0.9878
Cumulative Power (HR=0.50)	0.1867	0.3953	0.5643	0.7419	0.9999	1.0000
Cumulative Power (HR=0.40)	0.5362	0.8005	0.9129	0.9742	0.9998	0.9998
Binding Expansion and Futility Boundaries						
Cumulative Power (HR=1.00)	0	1e-04	2e-04	0.0005	0.0053	0.0127
Cumulative Power (HR=0.75)	0.0038	0.0115	0.0225	0.0444	0.3868	0.5341

Table 5: Summary of Power and Type 1 Error for Phase 2 and Extended Phase 3 Studies (Con't)

	Currently Planned Phase 2 OS Analyses			Additional OS Analysis to Support Extended Follow-up of Phase 2 Patients	OS Analyses in the Phase 3 Expansion	
	Interim 1[1]	Interim 2[1]	Interim 3[1]	Interim 4[1]	Interim 5[1]	Final Analysis[1]
Cumulative Power (HR=0.65)	0.0205	0.0586	0.1071	0.1909	0.7762	0.8321
Cumulative Power (HR=0.50)	0.1867	0.3953	0.5643	0.7418	0.9911	0.9914
Cumulative Power (HR=0.40)	0.5362	0.8005	0.9130	0.9742	0.9998	0.9998

1) Interim 1 will occur when the 125th PFS event occurs, interims 2 and 3 will occur based on a data cut-off date of June 1st and November 1st, 2017, respectively. Interims 4 and 5 and the final analysis will occur when 154, 315 and 432 OS events have occurred, respectively.
2) The efficacy boundary that must be crossed to assert that the null hypothesis of no treatment effect has been rejected at the 0.025 one sided level of significance. The boundary is determined from the rho family of spending functions with parameter equal to 4.
3) The efficacy boundary that must be crossed in order for the null hypothesis of no treatment effect to be rejected at the 0.10 one sided level of significance and for the trial to be expanded as represented in interim 4, interim 5 and the final analysis. This boundary was specified in the Phase 2 Yosemite protocol M18-006 based on an O'Brien Fleming group sequential boundary and has been adjusted here to reflect an O'Brien Fleming spending function. The presentation of the Phase 2 efficacy boundary here as based on the O'Brien Fleming spending function supersedes the description of the boundary in the protocol.
4) The boundary which if crossed will result in the trial being stopped for futility.

9.6. Tumor Assessment

Radiographic evaluation for target lesions, non-target lesions, new lesions and not-target lesion treatment data will be presented in listings.

Other than the efficacy tables for PFS, overall survival, and tumor assessment will be also presented in a listing.

9.7. Exploratory Endpoints

Biomarker and pharmacogenomics blood samples will be presented as a listing.

9.8. FFPE Tissue Sample and Tumor Marker CA 19-9

FFPE tissue sample will be tabulated by archival tissue summit status, archival tissue stage of the disease and anatomical location.

Tumor Marker CA 19-9 will be summarized by treatment arm and visit using descriptive statistics of the reported values and change from baseline values. Box plot of Tumor Marker CA 19-9 over time will be also presented.

Both FFPE tissue sample and Tumor Marker CA 19-9 will be presented in listings.

9.9. Sensitivity Analysis

Sensitivity analyses will be performed to assess the impact of NPT for PFS between treatment arms (Arm 1 to Arm 2, and Arm 1 to Arm 3). The censoring rule is the same as the primary endpoint analysis described in Section 9.1 except for the consideration of NPT. In this sensitivity analysis, we do not consider NPT at all. In other words, PDs that happened after NPT will still be counted as events.

10. Safety Analysis

Safety endpoints will be analyzed by treatment arm using the Safety Population.

10.1. Adverse Events

AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) 17.0. Toxicity grade will be defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research,

whether or not considered related to the subject's participation in the research. Any medical condition or clinically significant laboratory abnormality with an onset date before randomization is a pre-existing condition that must be listed on the Medical History Case Report Form (CRF) and should not be considered an AE unless the condition worsens in intensity or frequency after first study drug infusion. A treatment-emergent AE (TEAE) is defined as any event present from the time of randomization through 30 days after the termination visit, which must be documented in the medical record and reported on the AE CRF.

A drug related AE is an event where the investigator indicated that the relationship to study drug was "related" or "Not related". For summaries by relationship, adverse events with missing relationship are counted as "Related". For summaries by CTCAE grade, adverse events with missing CTCAE grade are counted as CTCAE grade 3 – Severe.

All reported AEs will be mapped to standard MedDRA coding terms, grouped by system organ class (SOC) and preferred term (PT) and tabulated by treatment arm. The incidence of AEs in each treatment arm will be tabulated by seriousness, severity, and relationship to study drug.

Overall summary of TEAEs for number of subjects with any TEAEs, serious TEAEs, Demcizumab/Placebo related TEAEs, Abraxane related TEAEs, Gemcitabine related TEAEs, TEAEs leading to study treatment discontinuation, TEAEs leading to death, TEAEs with CTCAE grade 3 or higher, and Demcizumab/Placebo related TEAEs with CTCAE grade 3 or higher will be tabulated by treatment arm. Summary of pulmonary hypertension, heart failure, and bleeding events will be tabulated, including CTCAE grades and relationship to the drugs,

The frequency and percentage of patients with TEAEs will be tabulated by overall incidence:

By SOC and PT.

By SOC and PT for drug related TEAEs.

By SOC and PT with CTCAE grade 3 or higher.

By SOC and PT for drug related TEAEs with CTCAE grade 3 or higher.

By SOC and PT for serious TEAEs.

By SOC and PT for drug related serious TEAEs.

By SOC and PT for TEAEs resulting in study discontinuation.

By SOC and PT for drug related TEAEs resulting in Death.

By descending order of frequency for PT and overall.

By descending order of frequency for PT and overall for related TEAEs.

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented. AEs and SAEs will be also listed.

CTCAE Grade 3 or higher heart failure, pulmonary hypertension or bleeding events AEs will be also listed.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix B.

10.1.1. Death

Total number of deaths and reasons of deaths will be summarized in a table using the safety population. Furthermore, all subject deaths during this study will be presented in a listing. The listing will provide all relevant CRF data pertaining to each subject death.

10.2. Clinical Laboratory Evaluations

All clinical laboratory assessments will be performed using the site's local laboratory with the exception of BNP which will be assessed using the Alere BNP meter. If unit is missing for laboratory assessments, then the assessments will not be summarized in tables.

Hematology:

A complete blood count (CBC) (includes hemoglobin, hematocrit, red blood cell, white blood cell, neutrophils, lymphocytes, eosinophils, monocytes, basophils) with differential and platelet count will be obtained at each protocol-specified visit and an International Normalized Ratio (INR) and Activated partial thrombplastin time (aPTT) will be obtained at baseline.

Serum Chemistry:

Serum chemistries (including albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen [BUN], calcium, chloride, creatinine, glucose, lactic dehydrogenase [LDH], phosphorus, potassium, total protein, aspartate aminotransferase (serum glutamic oxaloacetic transaminase) (AST [SGOT]), alanine aminotransferase (serum glutamic pyruvic transaminase) (ALT [SGPT]), sodium) will be obtained at each protocol-specified visit.

Urinalysis:

Urinalysis (with microscopic analysis) will be obtained during screening and at the time of the termination visit.

BNP Assessment:

BNP will be assessed during Screening and then every 14 days while on treatment and at the time of the termination visit.

Clinical laboratory data (hematology, serum chemistry, and urinalysis) will be summarized by treatment arm using descriptive statistics of the reported values. Change from baseline values for numeric assessments at the point of each subject's minimum post-baseline, maximum post-baseline and the last available measurement in serum chemistry and hematology data will be tabulated. All laboratory tests which have associated CTCAE grades will be summarized as shift tables of the change in NCI CTC from baseline tables to the post-baseline worst CTC grade.

Two-sided CTCAE gradable tests including Calcium, Glucose, Potassium, and Sodium will be summarized in the post-baseline worst high and low CTC grade.

High one-sided CTCAE gradable tests including Alkaline phosphatase, Alanine Aminotransferase, Aspartate Aminotransferase, Bilirubin, Creatinine will be summarized in the post-baseline worst high CTC grade.

Low one-sided CTCAE gradable tests including Albumin, Neutrophils, Phosphorus, Platelets, White Blood Cell, Lymphocytes, and Hemoglobin will be summarized in the post-baseline worst low CTC grade.

BNP Assessment will be summarized by treatment arm and visit. All laboratory tests in chemistry, hematology, urinalysis, coagulation, and BNP assessment will be presented in four data listings respectively. Listing for ACE Inhibitor or Carvedilol for BNP Increase will be also presented.

Box plots for chemistry, hematology and BNP will be presented. Meanwhile, scatter plot of baseline versus worst post-baseline in chemistry and hematology data will be also graphed.

10.3. Vital Signs Measurements

Blood pressure should be measured with the subject in the same position at each study visit. The same cuff method should be used to measure blood pressure (BP) throughout the study.

Vital signs diastolic blood pressure (mmHg) and systolic blood pressure (mmHg) will be summarized by treatment arm using descriptive statistics of the reported values at each visit. Pulse rate (beats/min), respiratory rate (breaths/min), and temperature will be summarized at the point of each subject's minimum post-baseline, maximum post-baseline and the last available measurement in Safety Population.

The vital sign data will be presented in a listing.

10.4. ECOG

ECOG performance status will be listed and summarized for each treatment arm. ECOG performance status scores shift from baseline to worst and shift from baseline to last will be summarized by treatment group at selected scheduled time points.

10.5. Physical Examination

A full physical examination will be done at screening. Subsequently, an abbreviated physical examination will performed at Day 0, every 3 weeks while on treatment and at the termination visit.

A summary of physical examination results at screening and on study will be provided in two separated tables. Individual results will be presented in a listing.

10.6. Electrocardiogram (ECG)

Summaries of descriptive statistics of the reported values and change from baseline values will be calculated for 12-lead ECGs parameters: PR interval, QRS duration, and QTc interval in Safety Population. These summaries will be presented by visit and treatment arm. Transthoracic Doppler echocardiogram values will be summarized by visit and treatment arm. Pulmonary hypertension will be tabulated with frequency and percentage.

The 12-lead ECG results will be presented in a listing. ECG shift table. Transthoracic Doppler echocardiogram and pulmonary hypertension will be also presented in separated listings.

10.7. Colonoscopy and Upper Gastrointestinal Endoscopy

Colonoscopy and Upper Gastrointestinal Endoscopy data from screening tests will be presented in a listing.

10.8. Head CT/MRI Scan

Head computed tomography (CT)/magnetic resonance imaging (MRI) scan data will be presented in a listing.

10.9. Serum Pregnancy Test

Serum pregnancy test results will be presented in a listing.

11. Pharmacokinetics

Plasma sample for PK analysis to be obtained prior to the demcizumab infusion on Days 0, 14, 56, 70, 168, 182, 224 and 238, and at the end of the demcizumab infusion (prior to chemo infusion) on Days 0, 56, 70, 168 and 224 and at termination visit.

Pharmacokinetics will be analyzed using the PK population, which is comprised of all patients who receive at least one partial or complete dose of demcizumab and who have sufficient measurable concentrations, as defined by the PK specialist, to calculate the PK parameters. Patients with protocol violations will be assessed on a patient-by-patient basis for inclusion in the PK Population.

The plasma concentrations will be listed by patient and by Time Point. Plasma concentrations will also be summarized by Time Point (i.e., Day and pre- or post- dose) using nominal time points, with the following descriptive statistics: n, arithmetic mean, SD, coefficient of variation (CV), minimum, median and maximum.

12. Immunogenicity

Immunogenicity endpoints will be analyzed using the ITT population. ADA (anti-drug antibodies or anti-OMP-21M18 antibodies) formation will be reported in screening and confirmatory assays. Samples with confirmed ADA formation will have end point titers (EPT) reported. Samples with confirmed ADA formation will also be assessed for formation of neutralizing antibodies (NAb), in screening, confirmatory and EPT assays.

Definition of variables

- Incidence of ADA: a subject is identified as ADA positive if the subject has any post-dose sample confirmed positive for ADA; the incidence of ADA is the number of ADA positive subjects in a relevant analysis cohort, e.g., dose cohort.
- Incidence of NAb (if applicable): a subject is identified as NAb positive if the subject has any post-dose sample confirmed positive for NAb; the incidence of NAb is the number of NAb positive subjects in a relevant analysis cohort, e.g., dose cohort.

13. Data Safety Monitoring Board Review

Data Safety Monitoring Board (DSMB) Review meetings are conducted on a quarterly basis.

14. Interim Analysis

During the trial, the proportion of subjects developing Grade ≥3 heart failure or pulmonary hypertension will be closely monitored by the DSMB on an ongoing basis. In addition to the ongoing review of safety data by the DSMB, one formal joint interim safety analysis of the Grade >3 heart failure and Grade >3 pulmonary hypertension data from this trial and the ongoing companion trial in 1st line pancreatic cancer will occur after 60 demcizumab-treated subjects between the two studies have completed a minimum of 2 treatment cycles and the last of these 60 demcizumab subjects has been followed for 100 days. Here is the detail:

For the OncoMed M18-006 study patients will be included if they received at least 4 doses of demcizumab/placebo at any time and for the OncoMed M18-007 study patients have received at least 2 doses of demcizumab/placebo at any time

AND

Patients have at least 100 days of AE follow-up from Day 0. This can be accomplished by either being on the corresponding study for at least 100 days or being on study for 70-99 day plus having been out far enough in their 30 post-treatment termination AE follow-up that 100 days for AE data are available.

Following review of these data, the DSMB will inform OncoMed in writing whether the incidence of > Grade 3 heart failure and the incidence of > Grade 3 pulmonary hypertension in the demcizumab-treated subjects is less than or greater than or equal to 15% above the incidence in the control arm.

15. References

1. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Failure 2008;10:933-89

16. Appendices

APPENDIX A: LISTINGS OF TABLES, LISTINGS, AND FIGURES

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Number	Title
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Figure 14.2.1.2	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Each Treatment Arm - ITT Population
Figure 14.2.1.3a	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Arm 1 and Pooled Demcizumab Arms by Stratification Factors - Combination - ITT Population
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Figure 14.2.1.4a	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Each Treatment Arm by Stratification Factors - Combination - ITT Population
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Figure 14.3.1.2	Box Plot of Chemistry Data Over Time - Safety Population
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APPENDIX B: IMPUTATION ALGORITHM FOR PARTIAL OR MISSING DATES

Adverse Event

If onset date is completely missing, then onset date is set to date of first dose.

If (year is present and month and day are missing) or (year and day are present and month is missing):

If year = year of first dose, then set onset month and day to month and day of first dose

If year <year of first dose, then set onset month and day to December 31st.

If year >year of first dose, then set onset month and day to January 1st.

If month and year are present and day is missing:

If year=year of first dose and

If month = month of first dose then set day to day of first dose date

If month <month of first dose then set day to last day of month

If month >month of first dose then set day to 1st day of month

If year <year of first dose then set day to last day of month

If year >year of first dose then set day to 1st day of month

For all other cases, set onset date to date of first dose

Concomitant Medications

If year and month are present and day is missing then set day to first day of month for start date, and set day to last day of month for end date

If year and day are present and month is missing then set month to January for start date, and set month to December for end date

If year is present and month and day are missing then set month and day to January 1 for start date, and set month and day to December 31 for end date

Completely missing date will not be imputed

APPENDIX C: DETAILS OF CALCULATIONS IN TABLE 5

This appendix provides details for the calculations underlying Table 5.

There are three distinct disjoint ways that the study can be extended.

1. The extension boundary is crossed at interim 1 and the Phase 3 boundary is not crossed
2. The extension boundary is not crossed at interim 1 and it is crossed at interim 2 and the Phase 3 boundary is not crossed.
3. The extension boundary is not crossed at interim 1 and interim 2 and it is crossed at interim 3 and the Phase 3 boundary is not crossed.

So to determine the probability of crossing the Phase 3 boundary at interims 4, 5 and 6 we can add the probabilities of crossing the Phase 3 boundary at interims 4,5 and 6 for the three disjoint situations listed above. This is carried out in the calculations below.

Table 1 shows the calculation that determines the Phase 3 efficacy boundary. It is based on the tau family of spending functions with parameter equal to 4. The phase 3 efficacy boundary was created as a design that would provide 80 percent power at a type 1 error of 0.025 one sided with no futility or extension boundary.

Table 1

	Interim 1	Interim 2	Interim 3	Interim 4	Interim 5	Final Analysis
Total Number of Events	87	112	131	154	315	432
Z-Statistic (reject the null)	3.938	3.746	3.613	3.439	2.464	1.993
Z statistic (reject the Alt)	-4	-4	-4	-4	-4	-4
Hazard Ratio (reject the null)	0.408	0.472	0.512	0.556	0.745	0.816
Hazard Ratio (reject the alt)	2.484	2.23	2.099	1.981	1.613	1.504
Nonbinding extension and futility						
Cumulative Power (HR=1.00)	0	1e-04	2e-04	4e-04	0.0071	0.025
Cumulative Power (HR=0.75)	0.0038	0.0115	0.0225	0.0444	0.4789	0.8003
Cumulative Power (HR=0.65)	0.0205	0.0586	0.1071	0.191	0.8739	0.9878
Cumulative Power (HR=0.50)	0.1867	0.3953	0.5643	0.7419	0.9999	1.0000
Cumulative Power (HR=0.40)	0.5362	0.8005	0.9129	0.9742	0.9998	0.9998

Table 2

	Interim 1	**Interim 2**	**Interim 3**	**Interim 4**	**Interim 5**	**Final Analysis**
Total Number of Events	87	112	131	154	315	432
Z-Statistic (reject the null)	3.938	3.746	3.613	3.439	2.464	1.993
Z statistic (reject the Alt)	0	0	1.432	-4	-4	-4
Hazard Ratio (reject the null)	0.408	0.472	0.512	0.556	0.745	0.816
Hazard Ratio (reject the alt)	1	1	0.767			
Cumulative Power (HR=1.00)	0	1e-04	2e-04	4e-04	0.0048	0.0114
Cumulative Power (HR=0.75)	0.0038	0.0115	0.0225	0.0443	0.3719	0.5017
Cumulative Power (HR=0.65)	0.0205	0.0586	0.1071	0.1909	0.7593	0.809
Cumulative Power (HR=0.50)	0.1867	0.3953	0.5643	0.7418	0.989	0.9893
Cumulative Power (HR=0.40)	0.5362	0.8005	0.913	0.9743	0.9997	0.9997

Table 2 presents an approximation of the probabilities associated with this design. The approximation is implemented by using an extension boundary of 0, 0, 1.432. If the expansion boundary is crossed at 1.711 or 1.520 it will most often also cross at 1.432.

Table 3

The expansion boundary is crossed at interim one and the Phase 3 efficacy boundary is not crossed

	Interim 1	**Interim 2**	**Interim 3**	**Interim 4**	**Interim 5**	**Final Analysis**
Total Number of Events	87	112	131	154	315	432
Z-Statistic (reject the null)	3.938	3.746	3.613	3.439	2.464	1.993
Z statistic (reject the Alt)	1.711	-4	-4	-4	-4	-4
Hazard Ratio (reject the null)	0.408	0.472	0.512	0.556	0.745	0.816
Hazard Ratio (reject the alt)	0.678	2.23	2.099	1.981	1.613	1.504
Cumulative Power (HR=1.00)	0	1e-04	2e-04	4e-04	0.0029	0.0062
Cumulative Power (HR=0.75)	0.0038	0.0115	0.0224	0.0425	0.2373	0.3047
Cumulative Power (HR=0.65)	0.0205	0.0586	0.1065	0.1839	0.5454	0.5712
Cumulative Power (HR=0.50)	0.1867	0.3953	0.5626	0.7278	0.9094	0.9095
Cumulative Power (HR=0.40)	0.5362	0.8005	0.912	0.9695	0.9897	0.9897

A1=Columns(4,5,6)-Column(3)

Table 4

The expansion boundary is not crossed at interim 1 and it is crossed at interim3 while the Phase 2 efficacy boundary is not crossed

	Interim 1	**Interim 2**	**Interim 3**	**Interim 4**	**Interim 5**	**Final Analysis**
Total Number of Events	87	112	131	154	315	432
Z-Statistic (reject the null)	1.711	3.746	3.613	3.439	2.464	1.993
Z statistic (reject the Alt)	0	1.53	-4	-4	-4	-4
Hazard Ratio (reject the null)	0.678	0.472	0.512	0.556	0.745	0.816
Hazard Ratio (reject the alt)	1	0.736				
Cumulative Power (HR=1.00)	0.0435	0.0435	0.0435	0.0436	0.045	0.0473
Cumulative Power (HR=0.75)	0.3278	0.3278	0.3279	0.3296	0.4251	0.4713
Cumulative Power (HR=0.65)	0.5726	0.5726	0.5732	0.5795	0.7317	0.7492
Cumulative Power (HR=0.50)	0.9093	0.9094	0.911	0.9231	0.9757	0.9758
Cumulative Power (HR=0.40)	0.9898	0.9898	0.9907	0.9944	0.999	0.999

A2=Columns(4,5,6)-Column(3)

Table 5

The expansion boundary is not crossed at interim 1 and interim 2 but it is crossed at interim 3 while the Phase 3 efficacy boundary is not crossed

	Interim 1	**Interim 2**	**Interim 3**	**Interim 4**	**Interim 5**	**Final Analysis**
Total Number of Events	87	112	131	154	315	432
Z-Statistic (reject the null)	1.711	1.53	3.613	3.439	2.464	1.993
Z statistic (reject the Alt)	0	0	1.432	-4	-4	-4
Hazard Ratio (reject the null)	0.678	0.736	0.512	0.556	0.745	0.816
Hazard Ratio (reject the alt)	1	1	0.767			
Cumulative Power (HR=1.00)	0.0435	0.0752	0.0752	0.0752	0.0761	0.0779
Cumulative Power (HR=0.75)	0.3278	0.4883	0.4883	0.4884	0.5405	0.5742
Cumulative Power (HR=0.65)	0.5726	0.7504	0.7504	0.7505	0.8221	0.8347
Cumulative Power (HR=0.50)	0.9093	0.9757	0.9757	0.9759	0.991	0.9911
Cumulative Power (HR=0.40)	0.9898	0.999	0.999	0.999	0.9998	0.9998

A3=Columns(4,5,6)-Column(3)

Table 6

The probabilities of crossing the Phase 3 efficacy boundary at interims 1, 2 and 3.

	Interim 1	**Interim 2**	**Interim 3**	**Interim 4**	**Interim 5**	**Final Analysis**
Total Number of Events	87	112	131	154	315	432
Z-Statistic (reject the null)	3.938	3.746	3.613	3.439	2.464	1.993
Z statistic (reject the Alt)	0	0	1.432	-4	-4	-4
Hazard Ratio (reject the null)	0.408	0.472	0.512	0.556	0.745	0.816
Hazard Ratio (reject the alt)	1	1	0.767			
Cumulative Power (HR=1.00)	0	1e-04	2e-04			
Cumulative Power (HR=0.75)	0.0038	0.0115	0.0225			
Cumulative Power (HR=0.65)	0.0205	0.0586	0.1071			
Cumulative Power (HR=0.50)	0.1867	0.3953	0.5643			
Cumulative Power (HR=0.40)	0.5362	0.8005	0.913			

A4

Table 7

The probability of Crossing the Phase 3 efficacy boundary accounting for study expansion at interims 1, 2 and 3.

	Interim 1	**Interim 2**	**Interim 3**	**Interim 4**	**Interim 5**	**Final Analysis**
Total Number of Events	87	112	131	154	315	432
Z-Statistic (reject the null)	3.938	3.746	3.613	3.439	2.464	1.993
Z statistic (reject the Alt)	0	0	1.432	-4	-4	-4
Hazard Ratio (reject the null)	0.408	0.472	0.512	0.556	0.745	0.816
Hazard Ratio (reject the alt)	1	1	0.767			
Cumulative Power (HR=1.00)	0	1e-04	2e-04	0.0005	0.0053	0.0127
Cumulative Power (HR=0.75)	0.0038	0.0115	0.0225	0.0444	0.3868	0.5341
Cumulative Power (HR=0.65)	0.0205	0.0586	0.1071	0.1909	0.7762	0.8321
Cumulative Power (HR=0.50)	0.1867	0.3953	0.5643	0.7418	0.9911	0.9914
Cumulative Power (HR=0.40)	0.5362	0.8005	0.913	0.9742	0.9998	0.9998

A1+A2+A3+A4

R code to calculate the probabilities for interim 4 and 5 as well as the final analysis accounting for the expansion boundary.

```
a1<-matrix(c(.0002,.0004,.0029,.0062,.0224,.0425,.2373,.3047,.1065,.1839,.5454,.5712,.5626,.7278,.9094,.9095,.912,.9695,.9897,.9897),byrow=T,ncol=4)
a1<-a1-a1[,1]


a2<-matrix(c(.0435,.0436,.045,.0473,.3279,.3296,.4251,.4713,.5732,.5795,.7317,.7492,.911,.9231,.9757,.9758,.9907,.9944,.999,.999),byrow=T,ncol=4)
a2<-a2-a2[,1]


a3<-matrix(c(.0752,.0752,.0761,.0779,.4883,.4884,.5405,.5742,.7504,.7505,.8221,.8347,.9757,.9759,.991,.9911,.999,.999,.9998,.9998),byrow=T,ncol=4)
a3<-a3-a3[,1]


a<-a1+a2+a3

b<-c(.0002,.0225,.1071,.5643,.913)

final<-b+a
print(final)
```