OncoMed Pharmaceuticals, Inc

M18-007

A 3-Arm Phase 2 Double-Blind Randomized Study of Carboplatin, Pemetrexed Plus Placebo versus Carboplatin, Pemetrexed plus 1 or 2 Truncated Courses of Demcizumab in Subjects with Non-Squamous Non-Small Cell Lung Cancer

10APR2017

Statistical Analysis Plan

Version *1.0*

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ALT (SGPT)110	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thrombplastin Time
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography (Scan)
CTCAE	Common Toxicity Criteria For Adverse Events (National Cancer Institute)
DLL	Delta-like Ligand (dll1, 3, 4)
DOR	Duration of Response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
INR	International Normalized Ratio
ITT	Intent-to-treat (population)
IWRS	Interactive Web Randomization System/Interactive Voice Randomization System
kg	Kilogram(s)
LD	Longest Diameter (of a Lesion)
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
NSCLC	Non-Small Cell Lung Cancer
NE	Not Evaluable

Abbreviation or Term	Definition/Explanation
OS	Overall Survival
PD	Progressive Disease
PK	Pharmacokinetic
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease

1. Introduction

This is a 3-arm, Phase 2, double-blind, randomized study of carboplatin, pemetrexed plus placebo versus carboplatin, pemetrexed plus 1 or 2 truncated courses of demcizumab in subjects with non-squamous non-small cell lung cancer. 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 M18-007 amendment 2 (Effective Date: 4 March 2016).

2. Treatments

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

Arm 1:

- to receive carboplatin, pemetrexed plus placebo every 3 weeks for 4 cycles (last dose on Day 63)
- then, starting on Day 84, to receive pemetrexed alone every 3 weeks for 4 cycles (last dose on Day 147)
- then, starting on Day 168, to receive pemetrexed plus placebo every 3 weeks for 4 cycles (last dose on Day 231)
- then, continue to receive pemetrexed every 3 weeks until disease progression

Arm 2:

- to receive carboplatin, pemetrexed plus demcizumab every 3 weeks for 4 cycles (last dose on Day 63)
- then, starting on Day 84, to receive pemetrexed alone every 3 weeks for 4 cycles (last dose on Day 147)
- then, starting on Day 168, to receive pemetrexed plus placebo every 3 weeks for 4 cycles (last dose on Day 231)
- then, continue to receive pemetrexed every 3 weeks until disease progression

Arm 3:

- to receive carboplatin, pemetrexed plus demcizumab every 3 weeks for 4 cycles (last dose on Day 63)
- then, starting on Day 84, to receive pemetrexed alone every 3 weeks for 4 cycles (last dose on Day 147)
- then, starting on Day 168, to receive pemetrexed plus demcizumab every 3 weeks for 4 cycles (last dose on Day 231)
- then, continue to receive pemetrexed every 3 weeks until disease progression

3. Objectives

Primary Objective:

- To compare the efficacy of Arm 1 to Arm 2 and Arm 3 combined

Secondary Objectives:

- To compare the safety of Arm 1 to Arm 2 and Arm 1 to Arm 3 combined
- To determine the rate of immunogenicity against demcizumab when combined with carboplatin and pemetrexed
- To determine population pharmacokinetics of demcizumab when combined with carboplatin and pemetrexed

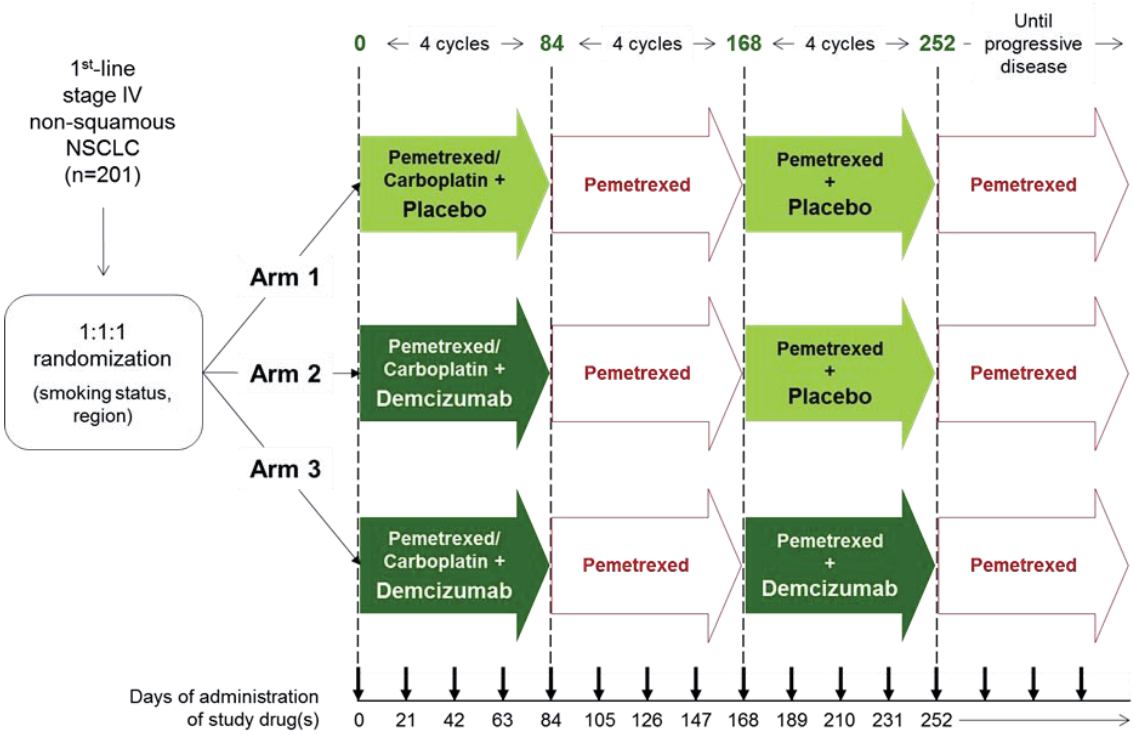
Exploratory Objective:

- To compare the exploratory pharmacodynamics (PD) and predictive biomarkers, such as DLL4 tumor expression, in Arm 1 to Arm 2 and Arm 3 combined

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 first-line Stage IV non-squamous NSCLC. Following determination of study eligibility, at least 201 subjects were to be randomized via an IWRS system to one of 3 arms. Subjects will be stratified according to smoking status (current versus former or never) and region (Australia/Europe versus North America). After randomization of 82 subjects, enrollment was discontinued due to significant difficulties in reaching the projected total subject number in a reasonable timeframe.



Demcizumab (5 mg/kg) or placebo will be administered once every 21 days for a total of 4 cycles (last administration on Day 63). Subjects will only receive their second 4-cycle course (starting on Day 168) of demcizumab (5 mg/kg) or placebo if they meet the original cardiac-related eligibility criteria (see Exclusion Criterion 21 in Protocol Section 6.2), they did not develop pulmonary hypertension or heart failure while on study, and blood pressure is controlled to ≤140/90 mmHg. Subjects who do not meet the criteria to receive the second 4-cycle course of placebo or demcizumab will continue to receive maintenance pemetrexed per protocol without demcizumab or placebo.

Pemetrexed (500 mg/m^2) and carboplatin (area under the concentration-time curve of 6 mg/mL x min) will be administered once every 21 days for a total of 4 cycles (or until toxicity necessitates reducing or holding a dose or terminating treatment). The maintenance pemetrexed (500 mg/m^2) will be given once every three weeks starting at Day 84.

On days of study drug administration, demcizumab or placebo, if applicable, will be administered first, followed by the administration of pemetrexed and then carboplatin (if applicable). To reduce gastrointestinal and hematologic toxicity, subjects must receive oral folic acid of ≥400 µg daily for at least 5 of the 7 days preceding the first dose of pemetrexed and continuing daily during the full course of therapy and for 21 days after the last dose of pemetrexed. Subjects must also receive an intramuscular injection of vitamin B12 1000 µg during the week preceding the first dose of pemetrexed and then every 63 days while being treated with pemetrexed. Unless contraindicated, subjects should also

receive dexamethasone 4 mg orally twice daily on the day before, the day of, and the day after pemetrexed administration to reduce the risk of developing skin rash.

4.2. Study Endpoints

Primary Endpoint

- To compare the Investigator-assessed RECIST v1.1 response rate (unconfirmed) in Arm 1 to Arm 2 and Arm 3 combined

Secondary Endpoints

- To compare the Investigator-assessed RECIST v1.1 clinical benefit rate (i.e., the rate of complete response + partial response + stable disease, all unconfirmed) in Arm 1 to Arm 2 and Arm 3 combined
- To compare the hazard of progression using the Investigator-assessed progression-free survival time as assessed by RECIST v1.1 in Arm 1 to Arm 2 and Arm 3 combined
- To compare the Investigator-assessed PFS at 6 months in Arm 1 to Arm 2 and Arm 3 combined
- To compare the median survival in Arm 1 to Arm 2 and Arm 3 combined To compare the Independent-Review-Facility-assessed RECIST v1.1 response rate and PFS based solely on radiographs in Arm 1 to Arm 2 and Arm 3 combined (optional)
- To determine the half-life, volume of distribution and clearance of demcizumab when combined with carboplatin and pemetrexed
- To compare the safety profile through adverse event (AE) monitoring (including attribution of AEs and serious adverse events [SAEs]), physical examination, vital signs, and clinical laboratory testing between Arm 1 to Arm 2 and Arm 1 to Arm 3
- To determine the incidence of anti-demcizumab antibody development and neutralizing antibody development in Arm*s* 2 and 3

Exploratory Endpoints

To compare the PD and predictive biomarkers for demcizumab and determine their correlation with response in Arm 1 to Arm 2 and Arm 3 combined

4.3. Treatment Modifications

Any subject who has two consecutive BNP values >100 pg/mL at consecutive scheduled BNP assessments or one value >200 pg/mL will be unblinded by the Investigator through

the IWRS system. If the subject is receiving demcizumab, the subject will be started on a cardioprotective agent, either an ACE inhibitor or the β-blocker 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. If deemed necessary and appropriate, the subject should also be evaluated by a cardiologist. 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). Carvedilol is the only option for the drug class of β-blockers. If there are contraindications for both ACE inhibitors and carvedilol, the subject'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
- Left Ventricular Ejection Fraction (LVEF) decline ≥10% from baseline and a LVEF value that is <50%
- Clinically significant pulmonary hypertension (i.e., peak tricuspid velocity >3.4 m/s on Doppler echocardiogram and diagnosed with clinically significant pulmonary hypertension that includes minimal dyspnea by a cardiologist or pulmonologist)
- Signs and symptoms of heart failure

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

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

- BNP <300 pg/mL
- LVEF decline <10% from baseline and LVEF ≥50%
- No clinically significant pulmonary hypertension, and
- No signs or symptoms of heart failure

Subjects with any of the following findings must have demcizumab or placebo permanently discontinued, regardless of relationship to demcizumab or placebo:

- BNP ≥300 pg/mL, LVEF decline ≥10% and LVEF <50%, signs or symptoms of heart failure or clinically significant pulmonary hypertension (i.e., peak tricuspid velocity >3.4 m/s on Doppler echocardiogram and diagnosed with clinically significant pulmonary hypertension that includes minimal dyspnea by a cardiologist or pulmonologist) that persists for 9 weeks
- BNP ≥400 pg/mL
- Grade ≥2 pulmonary hypertension
- Grade ≥2 bronchopulmonary or gastrointestinal bleeding (except for readily manageable local bleeding, such as hemorrhoidal bleeding)

- Hypertensive crisis
- Hypertensive encephalopathy
- Blood pressure ≥200/120 mmHg (i.e.both systolic and diastolic criteria are met), despite maximum treatment with at least three anti-hypertensive drugs
- Need for therapeutic anti-coagulation

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

Chemotherapy should be continued until disease progression, unless contraindicated.

5. General Statistical Considerations

5.1. Sample Size

The KEYNOTE-021 Cohort G trial reported a confirmed response rate in the chemotherapy alone arm of 29% (Ref 2). Here, we will assume that the unconfirmed response rate for chemotherapy alone is 40 percent. With 82 subjects and the type 1 error controlled at 0.10 1-sided, there is greater than 80 percent power to detect an increase in the response rate from 0.40 in the control arm to 0.65 in the pooled demcizumab arms. With 82 subjects and the type 1 error controlled at 0.40 1-sided, there is greater than 80 percent power to detect an increase in the response rate from 0.40 in the control arm to 0.55 in the pooled demcizumab arms, which is still a clinical important improvement in the response rate.

In the Phase 1b trial M18-004, an ongoing open-label study of carboplatin and pemetrexed plus demcizumab in subjects with unresectable locally advanced, recurrent, or metastatic non-squamous NSCLC, the observed OS survival curve suggested that the hazard of death is greatly reduced beyond 10 months in first-line NSCLC subjects treated with demcizumab. The median OS is assumed to be 10 months prior to 10 months and 12 months post 10 months to account for treatment with checkpoint inhibitors, such as nivolumab. With a total study duration of 30 months, we expect to see 5 deaths in the control arm beyond 10 months. If the hazard ratio beyond 10 months is 0.25, there will be 81 percent power to detect a difference in hazards between the control arm and the pooled demcizumab arms of the trial beyond 10 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 smoking status (current versus former or never) and region (Australia/Europe versus North America). At least 201 subjects will be randomized via an IWRS system to one of the 3 arms.

5.3. Subject Populations for Analysis

Per protocol 201 subjects were planned to be randomized in the trial. After randomization of 82 subjects, enrollment was discontinued due to significant difficulties in reaching the projected total subject number in a reasonable timeframe.

Intent-to-Treat (ITT) Population:

The ITT Population comprises all subjects who are randomized. Subjects will be analyzed as they were randomized. All baseline characteristics and demographic, efficacy, immunogenicity, and biomarker data will be analyzed using the ITT Population.

Per-Protocol (PP) Population:

The PP Population comprises all subjects who receive at least one dose of study drug and who have at least one postbaseline tumor assessment. Subjects will be analyzed as they were treated. Efficacy, immunogenicity and biomarker data will be analyzed using the per-protocol population as well as the ITT population.

Safety 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. Subjects will be analysed as they were treated. All safety endpoints will be summarized using the Safety Population.

Pharmacokinetic (PK) Population:

The 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 will be analyzed as they were treated. Subjects with protocol violations will be assessed on a subject-by-subject basis for inclusion in the PK Population. All the PK analyses will be conducted using the PK Population.

Response Evaluable 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. The 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 completed follow up. All percentages will be based on the number of patients randomized.

The reasons for discontinuing the study and follow-up will also be summarized in this summary table. Analysis population will be summarized for all subjects.

Subject disposition data will also be presented in a listing.

6.2. Protocol Deviations

The following protocol deviations will be recorded and summarized for the ITT population: 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 deviations will also be 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. Subject demographic data will also be presented in a listing.

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, Histologic subtype, KRAS Status, EGFR Mutation Status, and ALK Rearrangement Status will be tabulated.

A listing of cancer diagnosis history will be presented.

7.2.3. Prior Cancer Treatments and Therapies

The number and percentage of subjects who have received prior cancer treatments including prior adjuvant systemic therapy, prior surgery to treat their cancer, and prior radiotherapy will be summarized by treatment arm.

Prior cancer treatments including prior adjuvant systemic therapy, prior surgical treatment, and prior radiotherapy treatment will also be presented in listings.

Systemic therapy for lung 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 the 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 for the ITT Population.

Prior medications are defined as medications with a stop date occurring before the 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 and anti-hypertensive concomitant medications will be tabulated by WHO drug generic term. Folic acid, Dexamethasone, and Vitamin B12, which are required during study will not be included in prior or concomitant summary tables or listings and will be presented in separated tables and listingsMissing date of prior and concomitant medication will be imputed as in Appendix B.

Prior and concomitant medications and procedures will be presented in a by-patient listing.

Concomitant medications and procedures will be also presented in listings.

8.2. Study Treatments

Study treatment will be analyzed for the Safety Population.

8.2.1. Extent of Exposure

Treatment exposure will be summarized as duration on treatment and extent of exposure to demcizumab/placebo 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 infusions 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 according to the protocol defined schedule of drug administration. Planned dose per cycle= 5 mg/kg *baseline weight, where baseline weight is the Day 0 weight throughout the 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 PFS, best overall response, duration of response, and overall survival. 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.

9.1. Primary Efficacy Endpoint

The primary endpoint of response rate will be based on Investigator-assessed best overall response and is defined as the best unconfirmed 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 35 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.

Response rate based on the IRF (optional) assessment of tumor response will be similarly defined. The optional IRF assessment will be performed if the Investigator-assessed best overall data show a sufficiently positive trend in favor of the combined demcizumab arms.

The response rate will be assessed as well and 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 arms and control will be

calculated for the two groups using a logistic regression model with performance status, and region as factors in the model. A similar comparison will be made between each individual demcizumab arm and control.

9.2. Progression-free Survival

The secondary endpoint of PFS is defined as the number of days from randomization until death or disease progression as defined by the 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 42 + 7 days (Tumor assessments are 6 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 98 days (2*6*7+14 tumor assessments occur every 6 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 randomization + 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	Date of scan or clinical	Event

at or between scheduled visits	assessment of progression	
No Progression	Date of last adequate on study assessment	Censored
Death due to any cause before first scheduled post baseline assessment+ 7 days	Date of Death	Event
Death less than 42 +7days from the last tumor assessment without prior progression	Date of Death	Event
Death greater than 42+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 overtime and the median progression-free survival time. The 95% confidence intervals for median progression-free survival time will also be calculated for 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 will be generated using a stratified log rank test. A stratified Cox proportional hazards regression model will be used to estimate the hazard ratio. The stratification factors will be smoking status (current versus former or never) and region (Australia/Europe versus North America). 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 stratified Cox regression analysis will be fit to the ITT population. 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. Specifically the model will be

log(hr)=I{Randomized to Dem} + I{Received Second Course of Dem}

where I{Received Second Course of Dem} is a time dependent covariate and the model is stratified on smoking status (Current vs former or never) and region (Australia/Europe vs North America). The coefficient of I{Received Second Course of Dem} will be used to assess the impact of the second course of Dem on PFS.

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.

9.3. Other Efficacy Endpoints and Analysis

9.3.1 Continuous Variable Assessment of Tumor Length

The tumor length will be calculated as the sum of the longest diameters for the target lesions (as defined by RECIST v1.1 criteria and determined by the Investigator). Summary statistics including mean, standard deviation, median, minimum, and maximum for tumor length will be presented for baseline, as well as 6, 12 and 18 weeks post baseline. These summary statistics will also be presented for changes and percent changes from baseline at 6, 12 and 18 weeks post baseline. Along with the summary statistics, the 95% confidence intervals of the mean tumor length for each treatment arm 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) with regard to changes and percent changes from baseline tumor length at scheduled tumor assessments. Smoking status 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.

9.3.2 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. DOR will be determined for the 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 response (CR or PR) assessment	Date of Death	Event
Death less than 42 +7days from the last tumor assessment without prior progression	Date of Death	Event
Death greater than 42+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 the median 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). Waterfall plot of investigator-assessed duration of response will be also graphed.

9.3.3 Overall Survival

A comparison of the overall survival (OS) for the combined demcizumab arms with control will be performed. The following algorithm will be applied for the final delivery.

The data cutoff date is 16DEC2017, which is set up for data cleaning in the original database lock. 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 below.

Table 3: Censoring Conventions for OS

Situation	Date of 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

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 Cox proportional hazards model. The stratification factors will be smoking status (current versus former or never) and region (Australia/New Zealand versus Europe versus North America). The number and percentage of these subjects who are treated as an event and as a censor will be displayed. If there is a disparity in discontinuation rates between treatment arms, a sensitivity analysis will be performed to assess the impact.

Two analyses of survival will be undertaken, one at the time of the final analysis for PFS and the second 9 months after the time of the PFS analysis.

A number of secondary analyses for OS will be undertaken. First, the log rank test and the hazard ratio estimate will be determined using only patients who survived beyond 10 months. Next, a robust test procedure which adaptively weights which time points receive the greatest weights in the construction of the test will be applied (Ref 3). This test is based on weighted KM curve differences, and the weighting is data-dependent. To supplement the model-based hazard ratio estimate, we will calculate the difference in the area under the KM curves between

the control arm and the pooled demcizumab arms restricted up to the time point T, which is the minimum of the two largest observed death times from the two arms combined. Finally we will compare the hazard of death in the pooled demcizumab arms of the trial between those subjects who lived past 10 months and those subjects who did not. The estimate of the hazard will be simply the number of events observed divided by the amount of follow-up time. Testing will be based on a Z test using 1/number of events as the variance for the log(hazard).

In addition to the analyses described above, OS analyses will be undertaken to identify a subgroup of subjects who may derive a large benefit from the experimental treatment. First we will evaluate OS between the control arm and the pooled demcizumab arms of the trial in those subjects whose baseline albumin level is greater than 0.7*LLN + 0.3*ULN. Then we will cast a wider net by applying the method of Li et al (Ref 4) to the following list of baseline covariates, baseline albumin, LDH, alkaline, phosphatase, ECOG, PS, and smoking status (others may be added).

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Kaplan-Meier curves of OS will be plotted for each individual arm (Arm 1, 2, and 3) by stratification factors, ECOG status, 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, ECOG status, and overall.

9.3.4 Tumor Assessment

In addition to the efficacy tables for PFS and Response described above, radiographic evaluation for target lesions, non-target lesions, and new lesions treatment data will be presented in listings.

9.3.5 Exploratory Endpoints

Biomarker and pharmacogenomics blood samples will be presented in a listing. Exploratory biomarkers will be reported in a separate appendix to the CSR.

9.3.6 FFPE Tissue Sample and Tumor Marker CEA

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

Tumor marker CEA 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 CEA over time will be also presented.

Both FFPE tissue sample and tumor marker CEA will be presented in listings.

9.3.7 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. Baseline for safety analysis is the last assessment prior to treatment.

10.1 Adverse Events

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

An 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 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 Case Report Form (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.

An overall summary of TEAEs will include number and percent of subjects with any TEAEs, serious TEAEs, Demcizumab/Placebo related TEAEs, Carboplatin related TEAEs, Pemetrexed 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. All these 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 listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented.

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

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

10.1.1 Death

Total number of deaths and cause 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 or cannot be converted into standard unit 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) 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, AST [SGOT], ALT [SGPT], sodium etc.) 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 21 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 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 listings respectively. Listing for hepatitis will be also presented.

Box plots for chemistry, hematology and BNP will be presented. In addition , 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 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 along with interpretation (abnormal or not) will be presented in a listing. For the summary table, if a physical system for a subject has at least one visit with abnormal result, then it would be counted as abnormality.

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 at baseline, minimum post-baseline, maximum post-baseline, and the last available measurement by 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 along with interpretation (abnormal or not) 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 Brain CT/MRI Scan

Brain 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 samples for PK analysis will be obtained prior to the demcizumab (or placebo) infusion on Days 0, 42, 84, 126, 168, 210, 252, 294 and 336, and at the end of the

demcizumab (or placebo) infusion (prior to chemotherapy infusion, if applicable) on Days 0, 42, 168 and 210, and at the 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.

Impact of ADA and/or NAb formation on PK will be assessed when possible.

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/palcebo at any time and for the OncoMed M18-007 study patients have received at least 2 doses of demcizumab/palcebo 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 Reference

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5.

16 Appendices

APPENDIX A:

16.1 Listing of Tables

Number	Title
Table 14.1.1.1	Summary of Overall Disposition - ITTPopulation
Table 14.1.2.1	Summary of Protocol Deviations - ITTPopulation
Table 14.1.3.1	Summary of Demographics - ITTPopulation
Table 14.1.3.2	Summary of Cancer Diagnosis History and Stratification Factors - ITTPopulation
Table 14.1.4.1	Summary of Prior Cancer Treatment - ITTPopulation
Table 14.1.4.2	Summary of General Medical History - ITTPopulation
Table 14.1.4.3a	Concomitant Medications - Alphabetic Order - ITTPopulation
Table 14.1.4.3b	Concomitant Medications - Descending Order of Frequency - ITTPopulation
Table 14.1.4.4a	Anti-hypertensive Concomitant Medications – at Screening - ITTPopulation
Table 14.1.4.4b	Anti-hypertensive Concomitant Medications – on Study - ITTPopulation
Table 14.1.4.5	Folic Acid Administation - ITTPopulation
Table 14.1.4.6	Vitamin B12 Administration - ITTPopulation
Table 14.1.4.7	Dexamethasone Administration - ITTPopulation
Table 14.1.5.1	Summary of Extent of Exposure to Blinded Study Drug - Safety Population
Table 14.1.6.1	Descriptive Statistics for Demcizumab Concentration - PK Population
Table 14.1.7.1	Incidence of Anti-Drug Antibodies (ADA) and Neutrolizing Antibodies (Nab) - ITT Population
Table 14.2.3.1	Summary of Investigator-Assessed Kaplan-Meier Estimates of Progression-Free Survival for Arm 1 and Pooled Demcizumab Arms - ITT Population
Table 14.2.3.2	Summary of Investigator-Assessed Kaplan-Meier Estimates of Progression-Free Survival for Each Treatment Arm - ITT Population
Table 14.2.3.3	Summary of Investigator-Assessed Kaplan-Meier Estimates of Progression-Free Survival for Arm 1 and Pooled Demcizumab Arms - PP Population
Table 14.2.3.4	Summary of Investigator-Assessed Kaplan-Meier Estimates of Progression-Free Survival for Each Treatment Arm - PP Population

Table 14.2.3.5	Sensitivity Analysis of Progression-Free Survival - ITT Population
Table 14.2.3.6	Summary of Best Overall Response for Arm 1 and Pooled Demcizumab Arms - ITT Population
Table 14.2.3.7	Summary of Best Overall Response for Each Arm - ITT Population
Table 14.2.3.8	Summary of Best Overall Response for Arm 1 and Pooled Demcizumab Arms - PP Population
Table 14.2.3.9	Summary of Best Overall Response for Each Treatment Arm - PP Population
Table 14.2.3.10	Summary of Tumor Marker CEA - ITT Population
Table 14.2.3.11	Summary of Tumor Length - ITT Population
Table 14.2.3.12	Analysis of Tumor Length Change for Arm 1 and Pooled Demcizumab Arms - ITT Population
Table 14.2.3.13	Analysis of Tumor Length Change for Each Treatment Arm - ITT Population
Table 14.2.3.14	Analysis of Percent Change of Tumor Length for Arm 1 and Pooled Demcizumab Arms - ITT Population
Table 14.2.3.15	Analysis of Percent Change of Tumor Length for Each Treatment Arm - ITT Population
Table 14.2.3.16	Summary of Rate of Change in Tumor Volume at Progression - ITT Population
Table 14.2.3.17	Summary of Rate of Change in Tumor Volume at Progression - PP Population
Table 14.2.3.18	Summary of Investigator-Assessed Kaplan-Meier Estimates of Duration of Response for Arm 1 and Pooled Demcizumab Arms - Response Evaluable Population
Table 14.2.3.19	Summary of Investigator-Assessed Kaplan-Meier Estimates of Duration of Response for Each Treatment Arm - Response Evaluable Population
Table 14.2.3.20	Summary of Kaplan-Meier Estimates of Overall Survival for Arm 1 and Pooled Demcizumab Arms - ITT Population
Table 14.2.3.21	Summary of Kaplan-Meier Estimates of Overall Survival for Each Treatment Arm - ITT Population
Table 14.2.3.22	Summary of Kaplan-Meier Estimates of Overall Survival for Arm 1 and Pooled Demcizumab Arms - PP Population
Table 14.2.3.23	Summary of Kaplan-Meier Estimates of Overall Survival for Each Treatment Arm - PP Population
Table 14.2.3.24	Summary of Kaplan-Meier Estimates of Overall Survival among Patients Survived beyond 10 Months for Arm 1 and Pooled Demcizumab Arms - ITT Population
Table 14.2.3.25	Summary of Kaplan-Meier Estimates of Overall Survival among Patients Survived beyond 10 Months for Each Treatment Arm - ITT Population

Table 14.2.3.26	Summary of Kaplan-Meier Estimates of Overall Survival among Patients with Baseline Albumin Level Greater than 0.7*LLN + 0.3*UNL for Arm 1 and Pooled Demcizumab Arms - ITT Population
Table 14.2.3.27	Summary of FFPE Tissue Sample - ITT Population
Table 14.3.1.1	Summary of Treatment-Emergent Adverse Events - Safety Population
Table 14.3.1.2	All Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Population
Table 14.3.1.3	Treatment-Emergent Adverse Events in Descending Order of Frequency by Preferred Term - Safety Population
Table 14.3.1.4	Demcizumab or Placebo Drug Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Population
Table 14.3.1.5	Drug Related Treatment-Emergent Adverse Events in Descending Order of Frequency - Safety Population
Table 14.3.1.6	Treatment-Emergent Grade 3 or Higher Adverse Events by System Organ Class and Preferred Term - Safety Population
Table 14.3.1.7	Demcizumab or Placebo Drug Related Treatment-Emergent Grade 3 or Higher Adverse Events by System Organ Class and Preferred Term - Safety Population
Table 14.3.1.8	All Treatment-Emergent Serious Adverse Events - Safety Population
Table 14.3.1.9	Demcizumab or Placebo Drug Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term - Safety Population
Table 14.3.1.10	Treatment-Emergent Adverse Events Resulting in Study Discontinuation - Safety Population
Table 14.3.1.11	Summary of Deaths - Safety Population
Table 14.3.1.12	Demcizumab or Placebo Drug Related Deaths - Safety Population
Table 14.3.4.1	Summary of ECOG Performance Status - Safety Population
Table 14.3.4.2	Summary of ECOG Performance Score Shift from Baseline to Worst - Safety Population
Table 14.3.4.3	Summary of ECOG Performance Score Shift from Baseline to Last - Safety Population
Table 14.3.4.4	Summary of Chemistry Data - Safety Population
Table 14.3.4.5	Summary of Chemistry Shifts from Baseline to Worst on Study Based on CTCAE Grade - Safety Population
Table 14.3.4.6	Summary of Hematology Data - Safety Population
Table 14.3.4.7	Summary of Hematology Shifts from Baseline to Worst on Study Based on CTCAE Grade - Safety Population
Table 14.3.4.8	Summary of B-type Natriuretic Peptide (BNP) Collection - Safety

	Population
Table 14.3.4.9	Summary of Transthoracic Doppler Echocardiogram - Safety Population
Table 14.3.4.10	Summary of Pulmonary Hypertension Adverse Event - Safety Population
Table 14.3.4.11	Summary of Heart Failure Adverse Event - Safety Population
Table 14.3.4.12	Summary of Adverse Bleeding Events - Safety Population
Table 14.3.5.1	Summary of Vital Signs - Safety Population
Table 14.3.5.2a	Summary of Physical Exam – at Screening - Safety Population
Table 14.3.5.2b	Summary of Physical Exam – on Study - Safety Population
Table 14.3.5.3	Summary of 12-Lead ECG - Safety Population
Table 14.3.6.1	Summary of CT Pulmonary Angiogram - Safety Population
Table 14.3.7.1	Summary of Systemic Therapy for Lung Cancer during Follow-up Period - ITT Population

16.2 Listing of Listings

Number	Title
Listing 16.2.1.1	Overall Disposition - ITT Population
Listing 16.2.1.2	Demographics - ITT Population
Listing 16.2.1.3	16.2.2.1 Inclusion/Exclusion Criteria - ITT Population
Listing 16.2.3.1	Protocol Deviations - ITT Population
Listing 16.2.4.1	General Medical History - ITT Population
Listing 16.2.4.2a	Cancer Diagnosis History and Stratification Factors - ITT Population
Listing 16.2.4.2b	Cancer Diagnosis Metastasis - ITT Population
Listing 16.2.4.2c	Stratification Factors and NLR - ITT Population
Listing 16.2.4.3	Prior Systematic Therapy - ITT Population
Listing 16.2.4.4	Prior Radiotherapy Treatment - ITT Population
Listing 16.2.4.5	Prior Surgical - ITT Population
Listing 16.2.4.6	Prior and Concomitant Medication - ITT Population
Listing 16.2.4.7	Antihypertensive Medication - ITT Population
Listing 16.2.4.8	Folic Acid Administration - ITT Population
Listing 16.2.4.9	Vitamin B12 Administration - ITT Population
Listing 16.2.4.10	Dexamethasone Administration - ITT Population
Listing 16.2.5.1	Study Drug Dose Administration - Safety Population
Listing 16.2.5.2	Demcizumab Concentration - PK Population
Listing 16.2.5.3	Anti-Drug Antibodies (ADA) - ITT Population
Listing 16.2.5.4	Neutralizing Antibodies (Nab) - ITT Population
Listing 16.2.6.1	Radiographic Evaluation Target Lesions - ITT Population
Listing 16.2.6.2	Radiographic Evaluation Non-Target Lesions - ITT Population

Listing 16.2.6.3	Radiographic Evaluation New Lesions - ITT Population
Listing 16.2.6.4	Overall Response - ITT Population
Listing 16.2.6.5	Tumor Marker CEA - ITT Population
Listing 16.2.6.6	Progression-Free Survival - ITT Population
Listing 16.2.6.7	Duration of Response - Response Evaluable Population
Listing 16.2.6.8	Overall Survival - ITT Population
Listing 16.2.6.11	FFPE Tissue Sample - ITT Population
Listing 16.2.6.9	Surgery for Lung Cancer during Follow-up Period - ITT Population
Listing 16.2.6.10	Radiotherapy for Lung Cancer during Follow-up Period - ITT Population
Listing 16.2.6.11	Systemic Therapy for Lung Cancer during Follow-up Period - ITT Population
Listing 16.2.6.15	Anti-demcizumab Collection - ITT Population
Listing 16.2.7.1	Adverse Events - Safety Population
Listing 16.2.7.2	Serious Adverse Events - Safety Population
Listing 16.2.7.3	CTCAE Grade 3 or Higher Heart Failure or Pulmonary Hypertension - Safety Population
Listing 16.2.7.5	All Adverse Events that Resulted in Study Discontinuation - Safety Population
Listing 16.2.7.6	All Adverse Events that Resulted in Death - Safety Population
Listing 16.2.8.1	Laboratory Results: Chemistry - Safety Population
Listing 16.2.8.2	Laboratory Results: Coagulation - Safety Population
Listing 16.2.8.3	Laboratory Results: Hematology - Safety Population
Listing 16.2.8.4	B-type Natriuretic Peptide (BNP) Collection - Safety Population
Listing 16.2.8.5	Laboratory Results: Urinalysis - Safety Population
Listing 16.2.8.6	12-Lead ECG - Safety Population
Listing 16.2.8.7	Transthoracic Doppler Echocardiogram - Safety Population
Listing 16.2.8.8	Vital Signs - Safety Population
Listing 16.2.9.1	Physical Exam - Safety Population
Listing 16.2.9.2	CT Pulmonary Angiogram - Safety Population
Listing 16.2.9.3	Colonoscopy and Upper Gastrointestinal Endoscopy - Safety Population
Listing 16.2.9.4	Head CT/MRI Scan - Safety Population
Listing 16.2.9.5	Serum Pregnancy Test - Safety Population
Listing 16.2.9.6	ECOG Performance Status - Safety Population
Listing 16.2.10.1	Follow-up after Termination Visit - Safety Population
Listing 16.2.11.1	Biomarker Blood Samples - ITT Population
Listing 16.2.11.2	Pharmacogenomics Blood Samples - ITT Population

16.3 Listing of Figures:

Number	Title

Figure 14.2.1.1	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Arm 1 and Pooled Demcizumab Arms - ITT Population
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
Figure 14.2.1.3b	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Arm 1 and Pooled Demcizumab Arms by Stratification Factors – Single Level - ITT Population
Figure 14.2.1.3c	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Arm 1 and Pooled Demcizumab Arms by ECOG Status - ITT Population
Figure 14.2.1.4a	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Each Treatment Arm by Stratification Factors - Combination - ITT Population
Figure 14.2.1.4b	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Each Treatment Arm by Stratification Factors - Single level - ITT Population
Figure 14.2.1.4c	Kaplan Meier Plot of Investigator-Assessed Progression-Free Survival for Each Treatment Arm by ECOG Status - ITT Population
Figure 14.2.1.5	Kaplan Meier Plot of Overall Survival for Arm 1 and Pooled Demcizumab Arms - ITT Population
Figure 14.2.1.6	Kaplan Meier Plot of Overall Survival for Each Treatment Arm - ITT Population
Figure 14.2.1.7a	Kaplan Meier Plot of Overall Survival for Arm 1 and Pooled Demcizumab Arms by Stratification Factors - Combination - ITT Population
Figure 14.2.1.7b	Kaplan Meier Plot of Overall Survival for Arm 1 and Pooled Demcizumab Arms by Stratification Factors - Single Level - ITT Population
Figure 14.2.1.7c	Kaplan Meier Plot of Overall Survival for Arm 1 and Pooled Demcizumab Arms by ECOG Status - ITT Population
Figure 14.2.1.8a	Kaplan Meier Plot of Overall Survival for Each Treatment Arm by Stratification Factors - Combination - ITT Population
Figure 14.2.1.8b	Kaplan Meier Plot of Overall Survival for Each Treatment Arm by Stratification Factors – Single Level - ITT Population
Figure 14.2.1.8c	Kaplan Meier Plot of Overall Survival for Each Treatment Arm by ECOG - ITT Population
Figure 14.2.1.9	Waterfall Plot of Tumor Response Best Percent Change for Each Treatment Arm - ITT Population
Figure 14.2.1.10	Box Plot of Tumor Marker CEA Over Time - ITT Population
Figure 14.3.1.1	Swimmer Plot for Serious Treatment-Emergent Adverse Events -

	Safety Population
Figure 14.3.1.2	Box Plot of Chemistry Data Over Time - Safety Population
Figure 14.3.1.3	Scatter Plot of Baseline vs. Worst Post-baseline in Chemistry Data - Safety Population
Figure 14.3.1.4	Box Plot of Hematology Data Over Time - Safety Population
Figure 14.3.1.5	Scatter Plot of Baseline vs. Worst Post-baseline in Hematology Data - Safety Population
Figure 14.3.1.6	Box Plot of B-type Natriuretic Peptide (BNP) Collection Over Time - Safety Population

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

OncoMed M18-007

A 3-Arm Phase 2 Double-Blind Randomized Study of Carboplatin, Pemetrexed Plus Placebo versus Carboplatin, Pemetrexed plus 1 or 2 Truncated Courses of Demcizumab in Subjects with Non-Squamous Non-Small Cell Lung Cancer

Signature Page for Statistical Analysis Plan (SAP)

Approval of SAP – Version 1.0

April 6, 2017

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