CLINICAL PROTOCOL

Protocol No.	M18-007
Title:	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 **DENALI**: A 3-Arm Phase 2 **D**ouble-Blind Randomiz**E**d Study of Carboplati**N**, Pemetrexed Plus Placebo versus Carbopl**A**tin, Pemetrexed p**L**us 1 or 2 Truncated Courses of Demcizumab **I**n Subjects with Non-Squamous Non-Small Cell Lung Cancer
Version:	12 September 2014 Amendment 1: 8 October 2014 Amendment 2: 4 March 2016 Amendment 3: 29 November 2016
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Sponsor:	OncoMed Pharmaceuticals, Inc. 800 Chesapeake Drive Redwood City, CA 94063 Phone: 650-995-8200

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OncoMed Pharmaceuticals

Protocol No. M18-007, Amendment 3

29 November 2016

I will provide copies of the protocol, any subsequent protocol amendments, and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol. I also agree to conduct this study in compliance with Good Clinical Practice (GCP), all federal, state, and local regulations as well as with the requirements of the appropriate Institutional Review Board or Ethics Committee and any other institutional requirements.

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OncoMed Pharmaceuticals, Inc.

Protocol No. M18-007, Amendment 3

29 November 2016

This study protocol has been reviewed and approved by the undersigned person. It is confirmed that the information and guidance given in this protocol complies with the scientific principles, the guideline of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

[redacted]

21 Dec 2016

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SYNOPSIS

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	
Study Period: Approximately 30-36 months	**Development Phase:** Phase 2

Objectives:
All objectives apply to the study population of subjects with 1st-line stage IV non-squamous non-small cell lung cancer (NSCLC).

Primary Objective:

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

Secondary Objectives:

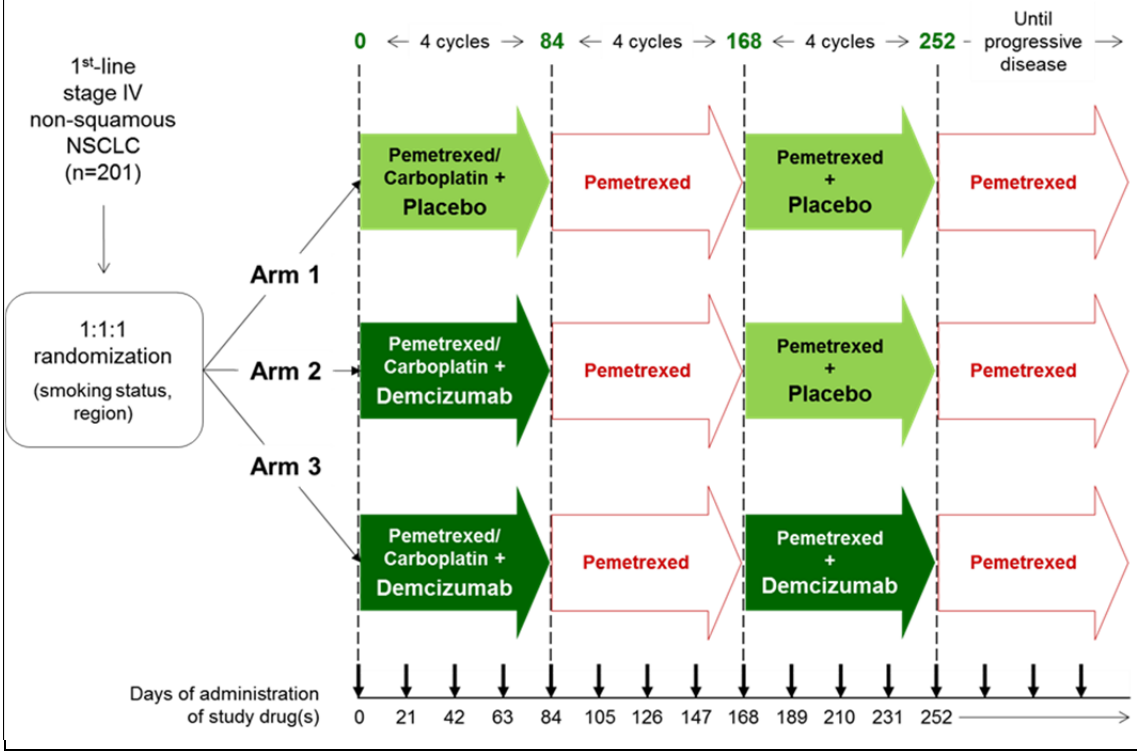
- To compare the safety of Arm 1 to Arm 2 and Arm 1 to Arm 3
- To determine the rate of immunogenicity against demcizumab when combined with carboplatin and pemetrexed
- To determine population pharmacokinetics of demcizumab when combined with carboplatin and pemetrexed

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

Study Design:

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 two-hundred and one subjects were to be randomized via an IWRS system to one of three arms. After randomization of 82 subjects, enrollment was discontinued due to significant difficulties in reaching the projected total subject number in a reasonable timeframe.



Study Design: (Cont'd)

Demcizumab (5 mg/kg) or placebo will be administered once every 21 days for a total of 4 cycles (i.e., 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 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 ≥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.

In the absence of unacceptable toxicities or disease progression per RECIST v1.1, subjects should continue to receive study treatment. Regardless of discontinuation of one, two or all three study drugs, subjects should continue on study with assessments as outlined in Section 12.0 and Appendix A). Once discontinuation criteria for the study are met (disease progression, use of other anti-cancer therapy, subject or investigator decision or protocol non-compliance, see Section 7.0), a termination visit should occur ≤14 days later. The termination visit may occur later after discussion with the OncoMed Medical Monitor for specific circumstances, such as prolonged hospitalization. After the termination visit, subjects should have regular follow-up for survival, subsequent anti-cancer therapies and other assessments as required per protocol (see Section 12.4). Study procedures and assessments are further detailed in Appendix A.

Diagnosis and Main Criteria for Eligibility (for *c*omplete *e*ligibility *c*riteria, *s*ee Section 6.0)

Inclusion Criteria

1. Signed Informed Consent Form
2. Histologically or cytologically confirmed Stage IV non-squamous NSCLC
3. If available, agreement to provide archival FFPE tumor tissue (obtained by core biopsy or surgical resection) for exploratory biomarker analyses
4. Age ≥21 years
5. ECOG performance status of 0 or 1 (see Appendix B)
6. Disease that is measurable per RECIST v1.1 (Appendix C)
7. Adequate organ and marrow function
8. For women of childbearing potential and men with partners of childbearing potential, agreement to use two effective forms of contraception

Exclusion Criteria

1. Histologically or cytologically documented, advanced, mixed non-small cell and small cell tumors or mixed adenosquamous carcinomas
2. NSCLC with EGFR mutation or anaplastic lymphoma kinase (ALK) gene translocation (such as EML4-ALK)
3. Prior or ongoing therapy (including chemotherapy, antibody therapy, tyrosine kinase inhibitors, radiotherapy, immunotherapy, hormonal therapy, or investigational therapy) for the treatment of Stage IV non-squamous NSCLC
4. Evidence of tumor invading major blood vessels, cavitation of one or more pulmonary tumor mass(es) or tracheo-esophageal fistula
5. Brain metastases, leptomeningeal disease, uncontrolled seizure disorder, or active neurologic disease
6. Metastases involving the lumen of the gastrointestinal tract
7. Malignancies other than non-squamous NSCLC successfully treated within 3 years prior to randomization (with the exception of certain early-stage cancers)
8. Prior radiation to the chest wall or mediastinum if the radiation field involved the heart
9. History of a significant allergic reaction attributed to humanized or human monoclonal antibody therapy
10. Significant intercurrent illness defined as an illness that may result in the subject's death prior to their death from non-squamous NSCLC and/or significantly limit their ability to comply with the requirements of this study
11. Recent hemoptysis >2.5 mL or serious bleeding from another site, known bleeding disorder or coagulopathy or therapeutic anti-coagulation
12. History of cerebral vascular accident (CVA) or transient ischemic attacks (TIAs) within 6 months of randomization
13. Clinically significant arterial aneurysm
14. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of need for major surgical procedure during the course of the study
15. Blood pressure (BP) of >140/90 mmHgHistory, signs or symptoms indicative of an increased cardiac risk, including, but not limited to BNP value of >100 pg/mL, left ventricular ejection fraction (LVEF) <50%, peak tricuspid velocity >3.0 m/s on Doppler echocardiogram, history of or current cardiac ischemia or congestive heart failure
16. History of interstitial lung disease or pneumonitis that required oral or intravenous corticosteroids

Test Product, Dose, and Mode of Administration

Demcizumab is an IgG2 humanized monoclonal antibody that is directed against the Delta-Like Ligand 4 (DLL4). Demcizumab is supplied at a concentration of 10 mg/mL in 25-mL single-use glass vials filled to 20 mL to deliver a total of 200 mg per vial. Demcizumab vials must be stored at 2°–8°C. DO NOT FREEZE. DO NOT SHAKE. Placebo is a clear to slightly opalescent, colorless to slightly yellow liquid formulation of 50 mM Histidine, 100mM Sodium Chloride, 45mM Sucrose and 0.01% (v/v) Polysorbate-20, pH 6.0. Study drug (demcizumab at 5 mg/kg or placebo) will be administered as an intravenous infusion over 30 *(+5)* minutes once every 3 weeks for 4 cycles (i.e., last *administration* on Day 63). A second course of study drug (demcizumab at 5 mg/kg or placebo) will be administered once every 3 weeks for 63 days starting at Day 168 if the criteria outlined in Study Design are met.

Duration of Treatment:

Subjects should be treated until they develop unacceptable toxicities or disease progression per the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.

Safety Evaluation: Safety will be assessed by adverse event monitoring (including attribution of adverse events and serious adverse events), physical examination, vital signs, clinical laboratory testing including assessment of BNP, Doppler echocardiogram, anti-demcizumab testing, and subject interview on an ongoing basis (as outlined in Appendix A) from randomization through 30 days following the discontinuation of treatment. Subjects who have two consecutive BNP values >100 pg/mL or one value ≥200 pg/mL will have their treatment unblinded and, if they are receiving demcizumab, will be started on a cardioprotective agent, either an ACE inhibitor or carvedilol. In addition, any subject who develops a BNP ≥300 pg/mL, a LVEF decline ≥10% from baseline and LVEF <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) and/or symptoms of heart failure must have their dose of demcizumab held. Demcizumab must be discontinued for BNP ≥400 pg/mL, Grade ≥2 pulmonary hypertension, Grade ≥2 bronchopulmonary or gastrointestinal bleeding, hypertensive crisis or encephalopathy, blood pressure ≥200/120 mmHg despite maximum treatment and/or need for therapeutic anti-coagulation. Administration of chemotherapy should be continued, unless contraindicated, when demcizumab/placebo is held or discontinued (see Section 8.1.6).
Efficacy Evaluation: Subjects will be assessed for response using RECIST criteria v1.1 during screening, then every 6 weeks, and at the termination visit (unless performed within 14 days of the termination visit or at a prior response evaluation that documented progressive disease). Investigator-assessed progression-free survival, response rates, duration of response, and survival will be evaluated.
Immunogenicity: Serum samples for immunogenicity analysis will be obtained at Day 0, every 6 weeks during the study, and at *the* termination visit.
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.
Biomarker Evaluation: Whole blood will be obtained for biomarker evaluations on Study Days 0 and 28, and at the termination visit as outlined in Appendix A. In addition, a pharmacogenomics sample will be collected at baseline from subjects who give informed consent. If available, archival FFPE tumor tissue (from either the primary tumor, locoregional disease or a metastatic site) obtained by core biopsy or surgical resection will be collected. Analysis of candidate genes and/or proteins relevant to the Notch pathway may be performed (e.g., DLL4, Notch1, Hey1, FBXW7).

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2.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALT (SGPT)	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
CRA	Clinical Research Associate
CRF	Case Report Form
CT	computed tomography (scan)
CTC	circulating tumor cell
CTCAE	Common Toxicity Criteria for Adverse Events (National Cancer Institute)
dL	deciliter(s)
DLL	Delta-like ligand (DLL1, 3, 4)
DLT	dose-limiting toxicity
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FACS	Fluorescent-activated cell sorting
GI	gastrointestinal
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
IMP	Independent Medicinal Product
IEC	Independent Ethics Committee
IGS	Invasiveness gene signature
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	intent-to-treat (population)
IV	intravenous
IWRS	Interactive web randomization system/Interactive voice randomization system
kg	kilogram(s)
LD	longest diameter (of a lesion)
LDH	lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)

Abbreviation or Term	Definition/Explanation
mL	milliliter(s)
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NOAEL	no observed adverse effect level
PD	progressive disease
POC	point of care
PR	partial response
RDC	remote data capture
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
ULN	upper limit of normal
US	ultrasound
VEGF	vascular endothelial growth factor

3.0 BACKGROUND

3.1 Investigational Medicinal Product

Demcizumab is an IgG2 humanized monoclonal antibody directed against Delta-Like Ligand 4 (DLL4), which is one of the ligands that bind to the Notch 1, 2, 3, and 4 receptors.

3.2 Stage IV Non-Small Cell Lung Cancer

Lung cancer is the leading cause of malignancy-related mortality worldwide. Over 1,000,000 new cases of lung cancer are diagnosed annually, and more than 900,000 people die of the disease every year (Ref 1, Ref 2). Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers, with the major histologic subtypes being adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma. The prognosis for subjects with Stage IV NSCLC is particularly poor with only approximately 2% of these subjects alive 5 years after diagnosis (Ref 3).

Platinum-based combination chemotherapy is the standard first-line treatment for subjects with Stage IV NSCLC. For subjects with good performance status, platinum-based chemotherapy has demonstrated prolongation of survival and improvement in quality-of-life compared with best supportive care (Ref 4, Ref 5, and Ref 6). More recently, it was demonstrated that, in chemotherapy-naïve subjects with NSCLC, overall survival with a cisplatin + pemetrexed doublet was statistically non-inferior to that achieved with cisplatin + gemcitabine; additionally, in subjects with non-squamous histology, overall survival was superior with cisplatin + pemetrexed as compared to cisplatin + gemcitabine (Ref 7). The combination of pemetrexed with a platinum, typically carboplatin, has emerged as a popular regimen for non-squamous NSCLC because of its efficacy and its superior toxicity profile (Ref 8).

In subjects who achieve disease stabilization or an objective response, the use of maintenance therapy with continued administration of a single drug until disease progression has also resulted in improved survival (Ref 9). Pemetrexed is one of the drugs used in this setting (Ref 10).

For a small subset of NSCLC subjects with specific genetic tumor alterations, these general treatment guidelines do no longer apply in their entirety. Subjects whose tumor has an activating EGFR mutation should receive a tyrosine kinase inhibitor (TKI), either erlotinib or gefitinib. Subjects whose tumor has a rearrangement of the anaplastic lymphoma kinase (ALK) gene should receive the TKI crizotinib (Ref 11; and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-small cell lung cancer, Version 2.2013).

More recently, immunomodulatory antibodies targeting the programmed death-1 pathway have emerged as an important treatment option for previously treated NSCLC subjects (Ref 12, Ref 13).

3.3 Nonclinical Background

Notch signaling controls various cellular processes including stem cell self-renewal, cell fate specification, differentiation, proliferation and survival (Ref 14). Evidence has accumulated that tumors are composed of heterogeneous cell types and that tumor growth is driven by a subset of cells termed cancer stem cells (CSCs) or tumor initiating cells (Ref 15). DLL4 is an important component of Notch-mediated stem cell self-renewal and vascular development. DLL4 over-expression is found in tumor vasculature and tumor cells and has been shown to activate Notch signaling in CSCs. Inhibition of DLL4 in epithelial tumors resulted in an anti-tumor effect through an increase of vasculature sprouting resulting in dysfunctional vasculature (Ref 16, Ref 17). We have shown anti-tumor activity in a variety of epithelial tumors including breast, colon, and pancreatic cancers (Ref 18, Ref 19, Ref 20). These experiments demonstrated that anti-DLL4 reduces tumor growth through at least two mechanisms of action – disrupting tumor angiogenesis and reducing tumorigenic cell frequency.

3.3.1 Activity of Anti-DLL4 in Non-Small Cell Lung Cancer Xenografts

Notch signaling has been implicated in cancer stem cell function and disease progression in NSCLC (Ref 21, Ref 22). In order to evaluate the potential of demcizumab for the treatment of NSCLC, we have tested anti-DLL4 in a variety of patient-derived NSCLC tumor xenografts and found that this treatment is efficacious as a single agent and in combination with various chemotherapeutic regimens including pemetrexed, carboplatin plus pemetrexed, or paclitaxel (Table 1).

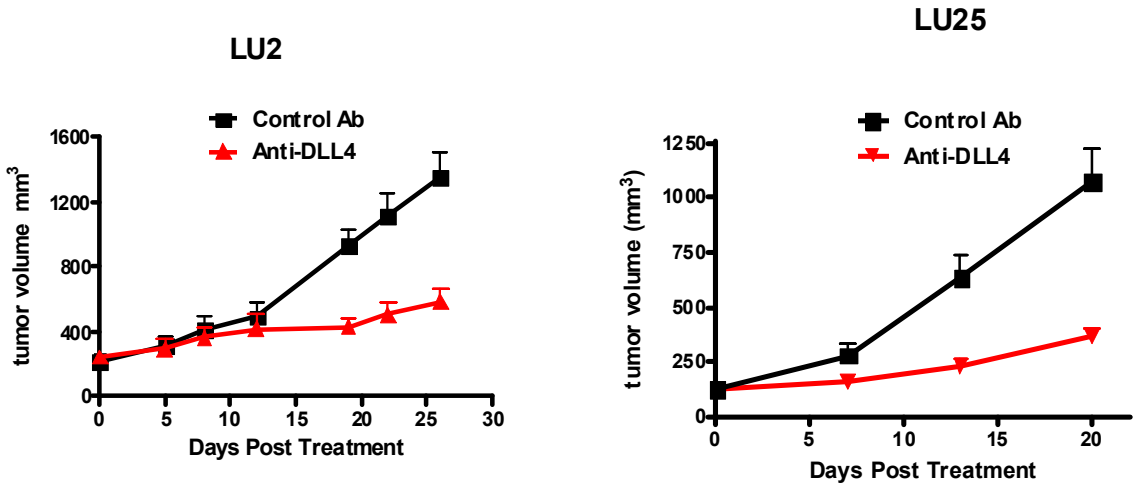
Table 1: Activity of Anti-DLL4 in NSCLC Tumor Xenografts

Tumor	Path	Anti-DLL4 Single Agent	Anti-DLL4 Combination
LU2	Large cell (met to colon)	+	**+ (paclitaxel)**
LU11	Squamous (Primary)	+	**+ (paclitaxel)**
LU24	Squamous (primary)	+	**- (pemetrexed)**
LU25	Squamous (primary)	+	**- (paclitaxel)**
LU45	Adeno (primary)	-	**+ (pemetrexed)**
LU53	Squamous (primary)	+	**+ (paclitaxel)**
LU56	Squamous (primary)	+	**+ (carbo/pem)**

Anti-DLL4 (OMP-21M18 + 21R30) was tested as a single agent and in combination in NSCLC tumors. The activity of anti-DLL4 treatment as a single agent or in combination with either paclitaxel or pemetrexed is indicated. A "+" for the single agent activity indicates that tumor volume was less than the control antibody treated group, while "+" in the combination activity column indicates the effect on tumor volume relative to combination agent group ($p < 0.05$).

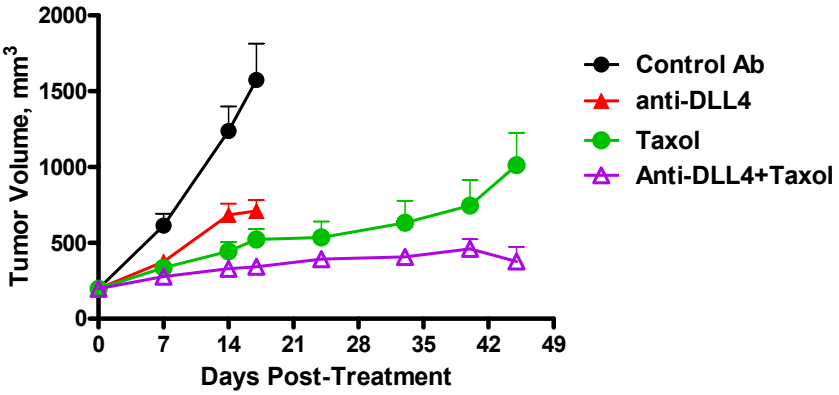
Examples of the single-agent activities of anti-DLL4 are shown in Figure 1. Established LU2 or LU25 NSCLC tumor xenografts were treated with the combination of anti-human DLL4 (OMP-21M18) and anti-mouse (21R30) DLL4. Blockade of DLL4-Notch signaling significantly delayed tumor growth in both models (Figure 1). In addition, we have seen evidence of anti-DLL4 combination activity with either pemetrexed (Figure 2) or paclitaxel (Figure 3).

Figure 1: Activity of Anti-DLL4 in LU2 (left panel) and LU25 (right panel) NSCLC Tumors



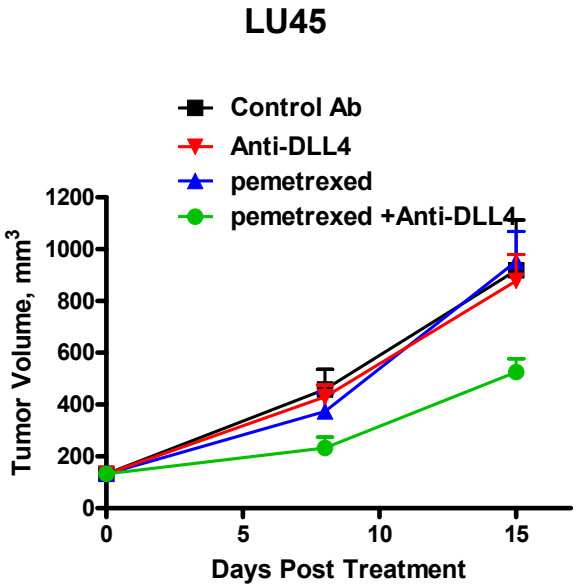
LU2 (left panel) or LU25 (right panel) patient-derived xenograft NSCLC tumors were treated with control antibody (Ab) or anti-DLL4 (OMP-21M18 + 21R30).

Figure 2: Activity of Anti-DLL4 in Combination with Paclitaxel in LU53 NSCLC Tumors



LU53 patient-derived xenograft NSCLC tumors were treated with control antibody (Ab), anti-DLL4 (OMP-21M18 + 21R30), paclitaxel (Taxol) alone, or the combination of anti-DLL4 plus paclitaxel (Taxol). The antibodies and paclitaxel (Taxol) were administered at 10 mg/kg weekly.

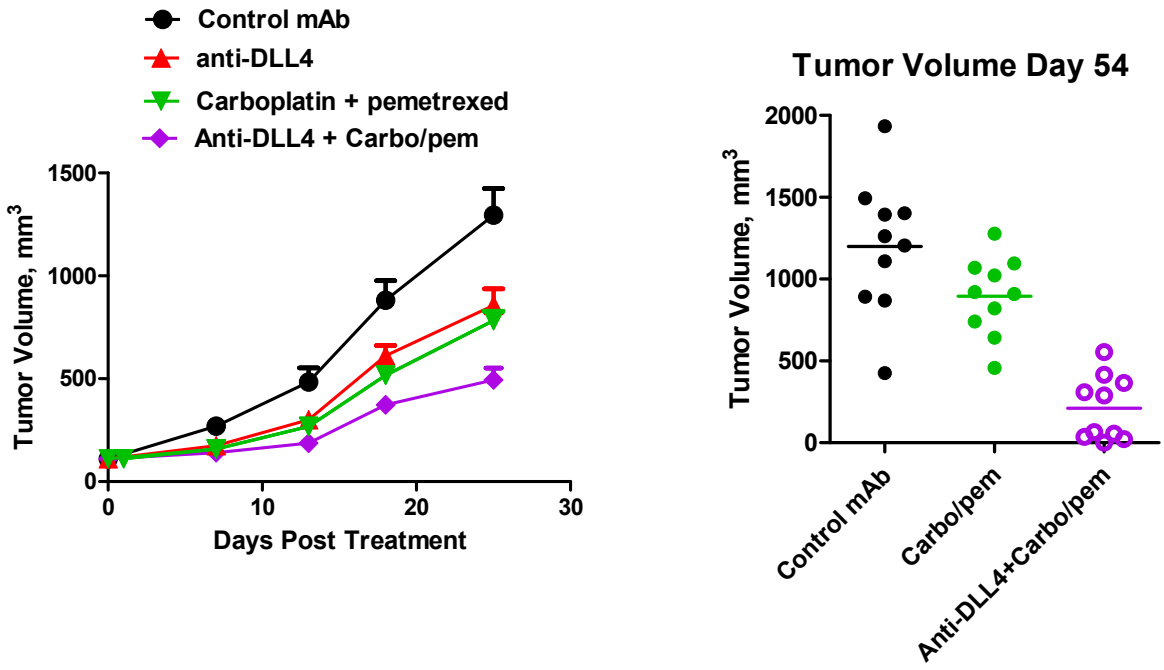
Figure 3: Activity of Anti-DLL4 in Combination with Pemetrexed in LU45 NSCLC Tumors



LU45 patient-derived xenograft NSCLC tumors were treated with control antibody (Ab), anti-DLL4 (OMP-21M18 + 21R30), pemetrexed alone, or the combination of anti-DLL4 plus pemetrexed. The antibodies were administered at 10 mg/kg weekly, and pemetrexed was dosed at 150 mg/kg five times per week.

The activity of anti-DLL4 in combination with carboplatin plus pemetrexed was also tested. Anti-DLL4 was effective in reducing both tumor volume and tumorigenic cell frequency (Figure 4). The reduction in tumorigenic cell frequency was determined by a serial transplantation experiment. These data indicate that, as in other tumor types, anti-DLL4 treatment results in a long-term effect on NSCLC cells that limits their proliferative capacity and ability to propagate tumor growth.

Figure 4: Reduction of Tumor Growth and Tumorigenic Cell Frequency by Anti-DLL4 in Combination with Carboplatin plus Pemetrexed

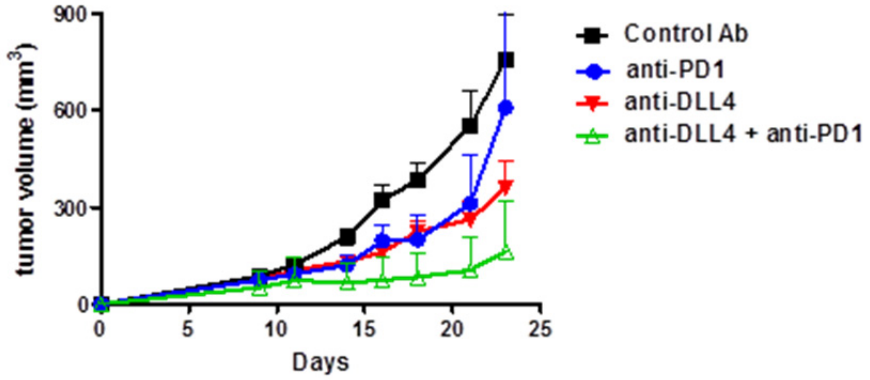


LU56 patient-derived xenograft NSCLC tumors were treated with control antibody (Ab), anti-DLL4 (OMP-21M18 + 21R30), carboplatin plus pemetrexed, or the triple combination of anti-DLL4, carboplatin (carbo) and pemetrexed (pem). The antibodies were administered at 10 mg/kg weekly, carboplatin at 25 mg/kg weekly, and pemetrexed at 100 mg/kg three times per week. Tumor volumes are shown in the left panel. Following treatment, human tumor cells were isolated from the control antibody, carboplatin/pemetrexed and anti-DLL4 plus carboplatin/pemetrexed groups. Fifty tumor cells were injected into 10 mice each and allowed to grow for 54 days without further treatment (right panel). Tumor cells from animals previously treated with anti-DLL4 + carboplatin/pemetrexed had a reduced rate of tumor growth compared to controls, indicating a reduction in tumor initiating cell frequency.

3.3.2 Potential for Immune-Mediated Mechanism of Action for Anti-DLL4

Evidence has accumulated that Notch signaling plays a significant role in various aspects of the immune response, including the generation of IL-17 producing T cells (Ref 23, Ref 24). Based on the emerging understanding of the activity of DLL4-Notch signaling in immune function, we wanted to determine if inhibition of DLL4-Notch signaling might augment anti-tumor immune response. To address this question, we have carried out pre-clinical experiments with murine tumors in immunocompetent mice. Initial experiments showed that anti-DLL4 increased cytotoxic T cell activity in tumors comparable to IL-2 treatment (data not shown). Subsequently, we tested anti-DLL4 in combination with anti-PD1 and found that both anti-DLL4 and anti-PD1 treatments reduced tumor growth, and the combination produced an additive effect (Figure 5).

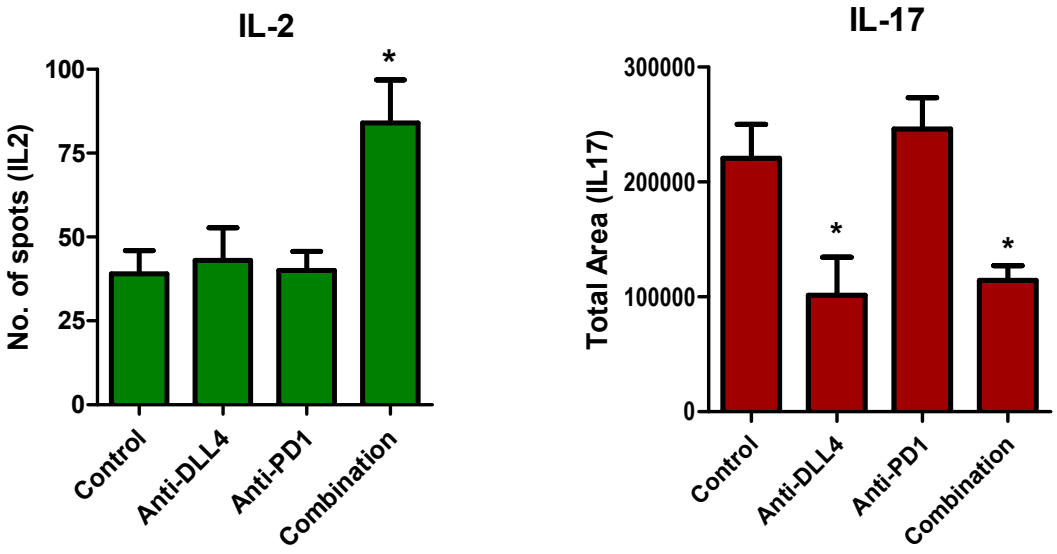
Figure 5: Inhibition of Tumor Growth by the Combination of Anti-DLL4 and Anti-PD1



CT26 murine tumors were grown in Balb/c mice and treated with either control Ab, anti-PD1, anti-DLL4 (OMP-21R30), or the combination of anti-DLL4 and anti-PD1 (n = 10/group). Antibodies were administered at 20 mg/kg, IP, twice per week. Mean tumor volumes (+SEM) are shown on the indicated days.

Following the treatment phase of the experiment shown in Figure 5, splenocytes from tumor-bearing mice were tested for their ability to produce various cytokines in response to an antigenic peptide derived from the CT26 tumor. Anti-PD1 increased IFN-γ production, as expected, whereas anti-DLL4 treatment had no effect (data not shown). The combination of anti-DLL4 and anti-PD1 increased IL-2 production and, of most interest, anti-DLL4 treatment reduced IL-17 production, either as a single agent or in combination with anti-PD1 (Figure 6). Higher levels of IL-17 production in tumors have been shown to be associated with poor clinical outcome in cancer patients (Ref 25); therefore inhibiting IL-17 is expected to be beneficial.

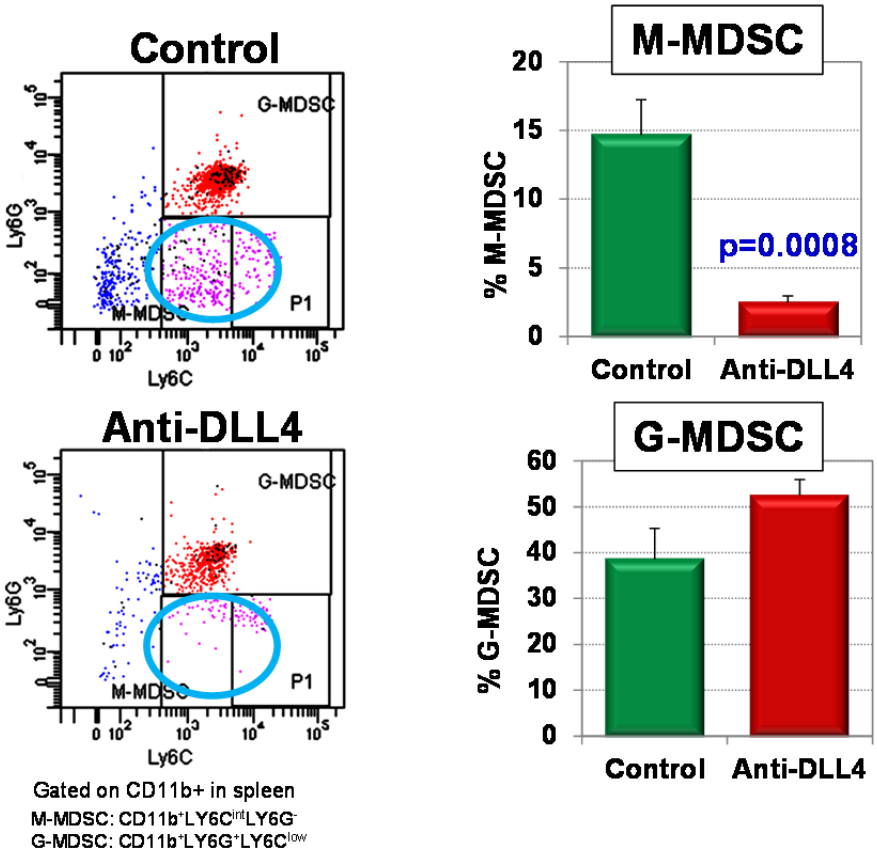
Figure 6: Effects of Anti-DLL4 and Anti-PD1 on Cytokine Production



Cytokine production in splenoctyes was measured by ELISPOT assay. Spleen cells from each group were cultured with and without tumor-specific peptide (AH1) for 2 days, and AH1-specific cytokine was determined. IL-2 production was increased by the combination of anti-DLL4 and anti-PD1 (left panel). IL-17 production was decreased by single-agent anti-DLL4 and combination treatment (right panel).

IL-17 has been identified as a key factor inducing myeloid-derived suppressor cells (MDSCs), and these cells are critical in promoting an immunosuppressive environment in tumors (Ref 26). Anti-DLL4 treatment was found to significantly reduce MDSCs, specifically the monocytic MDSCs, in tumor-bearing mice as shown by flow cytometry (Figure 7).

Figure 7: Anti-DLL4 Selectively Reduces the Frequency of Monocytic Myeloid-Derived Suppressor Cells



The frequency of sub-classes of myeloid-derived suppressor cells (MDSCs) was investigated by flow cytometry. CD11b positive cells were analyzed for Ly6G and Ly6C expression. The percentage of monocytic MDSCs (M-MDSC), but not granulocytic MDSCs (G-MDSC), was reduced by anti-DLL4 treatment. The results are quantified in the graphs on the right.

These data show that anti-DLL4 may inhibit tumor growth by promoting anti-tumor immunity. Our data indicate that anti-DLL4 operates through distinct mechanisms in the immune system compared with immune checkpoint blockers such as anti-PD1. Inhibition of DLL4 signaling reduces IL-17 production and the prevalence of monocytic MDSCs. Thus, in addition to its well established activities in maintaining functional tumor vasculture and self-renewal of cancer stem cells, DLL4 appears to play a key role in regulating the immune response in the tumor microenvironment.

3.4 Clinical Background

Five clinical studies (M18-001, M18-002, M18-003, M18-004 and M18-005) have been or are being conducted with de*mci*zumab. M18-001 was a Phase 1a single-agent dose escalation trial of demcizumab in subjects with previously treated advanced solid tumors. Study M18-002 is an ongoing open-label Phase 1b study of gemcitabine or gemcitabine and nab-paclitaxel plus demcizumab in subjects with locally advanced or metastatic pancreatic cancer. Study M18-003 was an open-label Phase 1b study of 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) plus demcizumab in subjects with metastatic colorectal cancer that was closed after seven subjects were treated on the trial due to changing corporate priorities. Study M18-004 is an ongoing open-label Phase 1b study of carboplatin and pemetrexed plus demcizumab in subjects with unresectable locally advanced, recurrent, or metastatic non-squamous NSCLC. Finally, study M18-005 is an ongoing Phase 1b/2 study of paclitaxel plus demcizumab in subjects with platinum-resistant ovarian cancer.

3.4.1 Phase 1a Study M18-001

M18-001 was a Phase 1a single-agent dose escalation trial of demcizumab in subjects with previously treated advanced solid tumors. This trial was conducted to determine the maximum tolerated dose (MTD), safety, pharmacokinetics, immunogenicity, and preliminary efficacy of demcizumab. A total of 61 subjects were enrolled in the trial, and 55 subjects received treatment. In the dose-escalation phase of the study, 39 subjects received treatment at 0.5 (n=3), 1.0 (n=3), 2.5 (n=6), and 5.0 (n=3) mg/kg once weekly for the first 56 days and then once every other week, and 2.5 (n=6), 5 (n=6) and 10 (n =12) mg/kg once every other week until disease progression. In the expansion phase of the study, an additional 15 subjects were treated with 10 mg/kg once every other week. Finally, one subject was treated with 10 mg/kg weekly on Day 0, 7, and 14 (as a loading dose) and then 10 mg/kg once every other week.

The MTD as assessed by DLTs observed over the first 28 days was not reached at 10 mg/kg once every other week. Hypertension or blood pressure increased that was managed with oral antihypertensives was the most frequent related event occurring in 55% of subjects. Other common related events included fatigue, anemia, headache, hypoalbuminemia, and dyspnea. A decline in hemoglobin of $\geq$2 g/dL was also observed in 17 of the 55 (31%) treated subjects. During the conduct of the study, cardiotoxicity was identified as a potential toxicity in the ongoing 6-month cynomolgus monkey study. As a result, the protocol was amended to include monitoring with brain natriuretic peptide (BNP) and echocardiograms. Increases in BNP to >400 pg/mL (or NT-pro-BNP >800 pg/mL) considered to be possibly related to study drug were observed in 6 subjects who received 10 mg/kg once every other week. This toxicity is considered dose-, schedule- and duration-related. High doses of demcizumab administered frequently for prolonged periods of time can result in the emergence of cardiotoxicity as was seen on study M18-001 in the subjects treated at 10mg/kg dosed every other week for a prolonged period of time (>100 days). Three of the subjects who had a screening left ventricular ejection fraction of at least 50% subsequently had a value that was $\leq$40% after receiving therapy for >100 days.

Four subjects who received 10 mg/kg once every other week developed congestive heart failure (3 Grade 3 and 1 Grade 4). A rise in BNP above 250 pg/mL occurred prior to the development of congestive heart failure in 3 of these 4 subjects. In addition, 1 subject who received 2.5 mg/kg once every week developed Grade 3 right ventricular failure. In all 5 subjects, demcizumab therapy was discontinued, and the subjects were started on medication to treat their heart failure when the event occurred. The symptoms of heart failure subsequently diminished in all 5 subjects. In addition, 2 subjects developed pulmonary hypertension. One of these subjects received 2.5 mg/kg once every week and developed Grade 1 pulmonary hypertension. Enrollment in the study was stopped early due to an unacceptably high rate of congestive heart failure in subjects treated at 10 mg/kg once every other week for longer than 100 days. The data from this trial suggest that high (i.e., 10 mg/kg) doses of demcizumab administered for a prolonged period of time (i.e., >100 days) results in an increased incidence of heart failure.

One unconfirmed partial response as per RECIST version 1.1 (v1.1) was observed in a refractory pancreatic cancer subject treated at 10 mg/kg once every other week. In addition, a number of subjects with a variety of solid tumors including NSCLC, renal cell carcinoma, colorectal cancer, and pancreatic cancer, had a reduction in the size of their target lesions of <30%. A high percentage of subjects (59%; 16 of 27) treated at 10 mg/kg once every other week had stable disease (n=15) or a partial response (n=1). One subject at 10 mg/kg once every other week with a refractory ovarian cancer (granulosa cell) who had progressed through 12 prior treatment regimens remained on therapy with disease control for 518 days.

3.4.2 Phase 1b Studies M18-002, M18-003, and M18-004 and Phase 1b/2 Study M18-005

Three Phase 1b studies (M18-002, M18-003, and M18-004) and one Phase 1b/2 study (M18-005) of demcizumab plus chemotherapy have been or are being conducted. As of the cut-off dates of 23 July 2013 (M18-003), 25 July 2014 (M18-002 and M18-004), and 21 August 2014 (M18-005), 99 subjects have been treated in these trials. Study M18-002 is an ongoing open-label Phase 1b study of gemcitabine or gemcitabine and nab-paclitaxel plus demcizumab in subjects with locally advanced or metastatic pancreatic cancer. Study M18-003 was an open-label Phase 1b study of 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) plus demcizumab in subjects with metastatic colorectal cancer that was closed after seven subjects were treated on the trial due to changing corporate priorities. Study M18-004 is an ongoing open-label Phase 1b study of carboplatin and pemetrexed plus demcizumab in subjects with unresectable locally advanced, recurrent, or metastatic non-squamous NSCLC. Finally, study M18-005 is an ongoing Phase 1b/2 study of paclitaxel plus demcizumab in subjects with platinum-resistant ovarian cancer.

3.4.2.1 Phase 1b Efficacy Data

Response Data for All Three Phase 1b Studies

Study M18-002 is an ongoing Phase 1b trial of demcizumab in combination with gemcitabine or gemcitabine and nab-paclitaxel in subjects with previously untreated adenocarcinoma of the pancreas. Thirty-eight of the 47 subjects were evaluable for response. Four of the 16 (25%) evaluable subjects treated with gemcitabine and demcizumab had a partial response, and 7 (44%) had stable disease. Nine of the 22 (41%) evaluable subjects treated with nab-paclitaxel, gemcitabine and demcizumab had a partial response, and 10 (45%) had stable disease. Table 2 summarizes the RECIST v1.1 response data for this study.

Table 2: Overall Response Assessment for Subjects Enrolled in Study M18-002 (n=47)

	Cohort 1 5 mg/kg q2w (n=8)	Cohort 2 2.5 mg/kg q4w (n=8)	Cohort 3 5 mg/kg q4w (n=8)	TOTAL Gem + Dem (evaluable: n=16)	Cohort 4 Tr. Dem 2.5 mg/kg q2w (n=6)	Cohort 5 Tr. Dem 5 mg/kg q2w (n=8)	Cohort 6 Tr. Dem 3.5 mg/kg q2w (n=9)	TOTAL Nab/Gem + Dem (evaluable: n=22)
Complete Response	-	-	-	-	-	-	-	-
Partial Response	1	1	2	4 (25%)	4	3	2	9 (41%)
Stable Disease	4	2	1	7 (44%)	1	4	5	10 (45%)
Progressive Disease	-	3	2	5 (31%)	1	1	1	3 (14)%
Not evaluable	3	2	3	8	-	-	1	1

Dem = demcizumab; Gem = gemcitabine; Nab = nab-paclitaxel; q2w = every 2 weeks; q4w = every 4 weeks; Tr. Dem = truncated demcizumab dosing regimen (last demcizumab dose on Day 70; see Section 3.4.2.2). Subjects in Cohorts 1-3 received gemcitabine plus demcizumab. Subjects in Cohorts 4-6 received nab-paclitaxel, gemcitabine and demcizumab (truncated dosing regimen).

Figure 8 and Figure 9 are the waterfall plots showing the best % reduction in target lesion size for all of the subjects on the study and those who received demcizumab, gemcitabine and nab-paclitaxel, respectively.

Figure 8: Percent Change in Tumor Target Lesion Size - Study M18-002

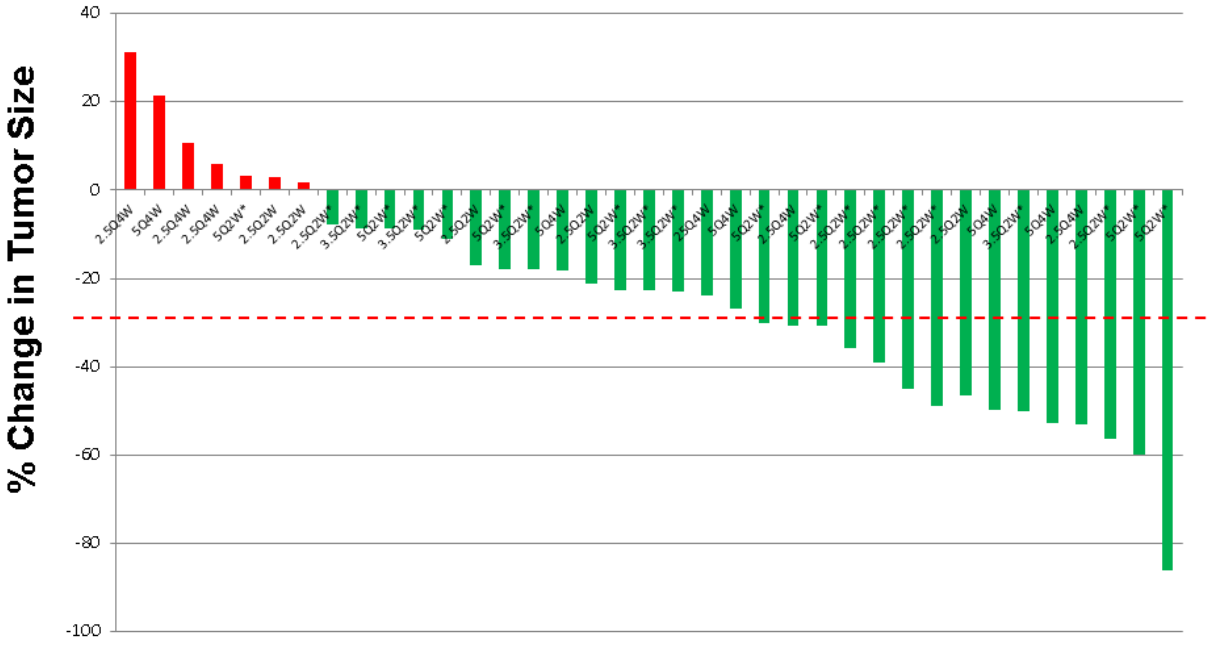
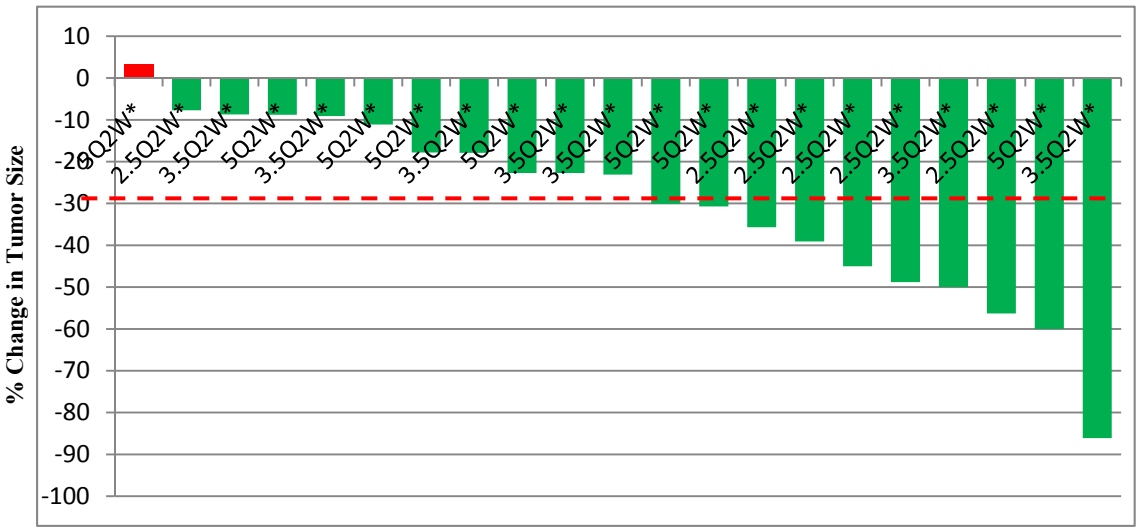


Figure 8 provides the best % change in tumor target lesion size for all subjects (i.e., subjects treated with gemcitabine and demcizumab and subjects treated with nab-paclitaxel, gemcitabine and demcizumab) enrolled in study M18-002. Thirty-one of the 38 evaluable subjects had a reduction in the size of their target lesions, and 7 subjects had an increase in the size of their target lesions. Each bar represents an individual subject. Subjects were dosed either once every 2 weeks or every 4 weeks.

Figure 9: Percent Change in Tumor Target Lesion Size of the Nab-paclitaxel/Gemcitabine/Demcizumab Subjects - Study M18-002



Only 7 1st- or 2nd-line colorectal cancer subjects were enrolled in study M18-003, and their treatment was stopped early. Thus, response data are not displayed.

Table 3 summarizes the RECIST v1.1 response data for study M18-004 that is an ongoing Phase 1b study in subjects with 1st-line NSCLC who were treated with demcizumab in combination with pemetrexed and carboplatin. Thirty-three of the 40 subjects were evaluable for response. Sixteen of the 33 (48%) evaluable subjects had a response, and 13 (39%) subjects had stable disease.

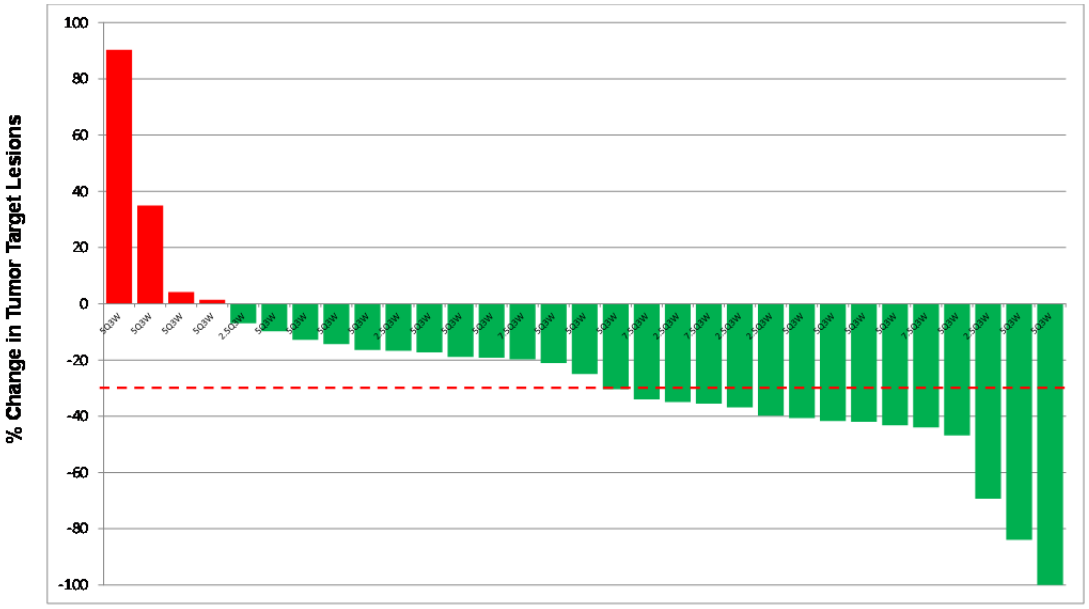
Table 3: Overall Response Assessment for Subjects in Study M18-004 (n =40)

	Cohort 1 5 mg/kg q3w (n=6)	Cohort 2 2.5 mg/kg q3w (n=6)	Cohort 3 5 mg/kg q3w (n=8)	Cohort 4 (Expansion) 5 mg/kg q3w (n=6)	Cohort 5 Trunc Dem 7.5 mg/kg q3w (n=6)	Cohort 6 Trunc Dem 5 mg/kg q3w (n=7)	Cohort 7 (Expansion) Trunc Dem 5 mg/kg q3w (n=1)	TOTAL (evaluable: n=33)
Best Overall Response, n (%)								
Complete Response	-	-	-	1	-	-	-	1 (3%)
Partial Response	2	4	2	-	4	3	-	15 (45%)
Stable Disease	2	2	4	2	1	2	-	13 (39%)
Progressive Disease	-	-	1	2	1	-	-	4 (12%)
Not evaluable	2	-	1	1	-	2	1	7

q3w = every 3 weeks; Trunc Dem = truncated demcizumab dosing regimen (last demcizumab dose on Day 63, see Section 3.4.2.2).

Figure 10 provides the best percent change in tumor target lesion size for study M18-004. Twenty-seven of the 31 evaluable subjects had a reduction the size of their target lesions.

Figure 10: Percent Change in Tumor Target Lesion Size - Study M18-004

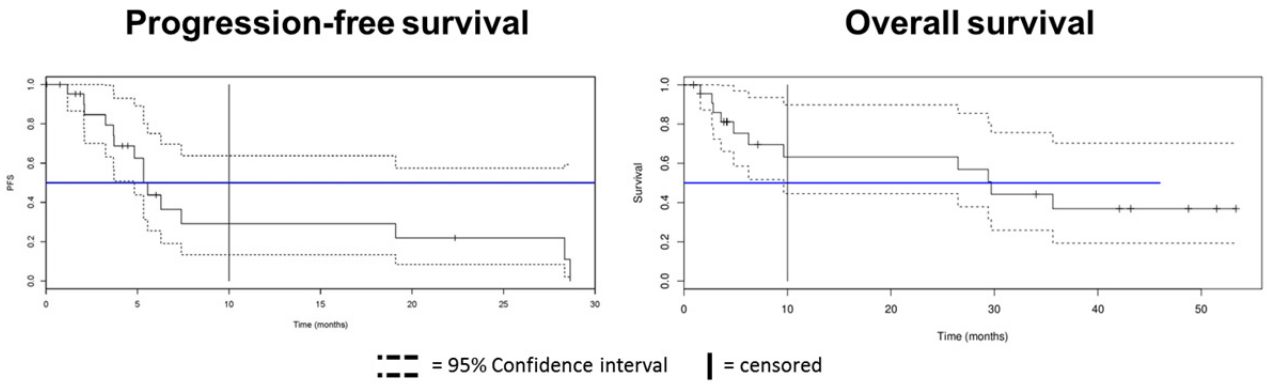


Each bar represents an individual subject. All subjects were dosed once every 3 weeks.Five subjects with platinum-resistant ovarian cancer have been enrolled in study M18-005 and were treated with paclitaxel and demcizumab. Two of these subjects had stable disease, and 3 had progressive disease.

Progression-free Survival and Overall Survival Data for M18-004 (NSCLC Phase 1b)

The Phase 1b study for NSCLC subjects (M18-004) was analyzed for progression-free survival and overall survival using on- and off-study data. Figure 11 shows the results for the first group of 23 subjects who received continuous demcizumab dosing.

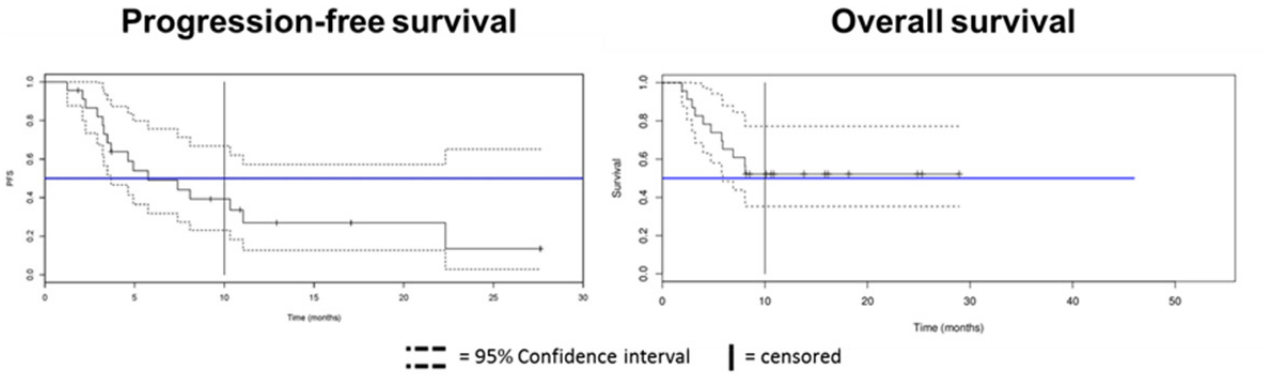
Figure 11: Progression-free and Overall Survival for Subjects with Continuous Demcizumab Dosing - Study M18-004



Data as of 17 June 2015. 23 subjects who received 6 cycles of demcizumab, carboplatin and pemetrexed followed by demcizumab maintenance. Excludes 3 patients from Cohort 4.

Figure 12 shows the results for the second group of 23 subjects who received truncated demcizumab dosing.

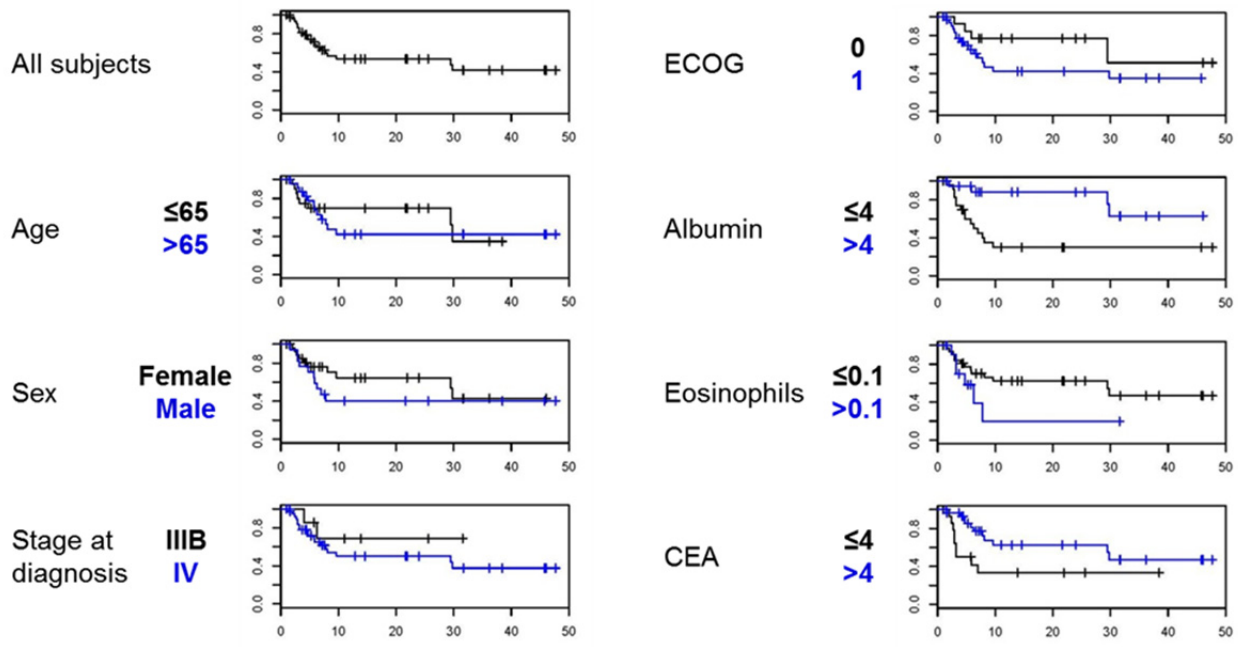
Figure 12: Progression-free and Overall Survival for Subjects with Truncated Demcizumab Dosing - Study M18-004



Data as of 17 June 2015. 23 subjects who received 4 cycles of demcizumab, carboplatin and pemetrexed followed by pemetrexed maintenance. Includes 3 patients from Cohort 4.

In a combined analysis for all 46 subjects, subject demographics and laboratory parameters were assessed to determine which factors were associated with the prolonged survival tail on the Kaplan-Meier curves. Across all these subject variables the survival tail on the Kaplan-Meier curves remained evident (Figure 13).

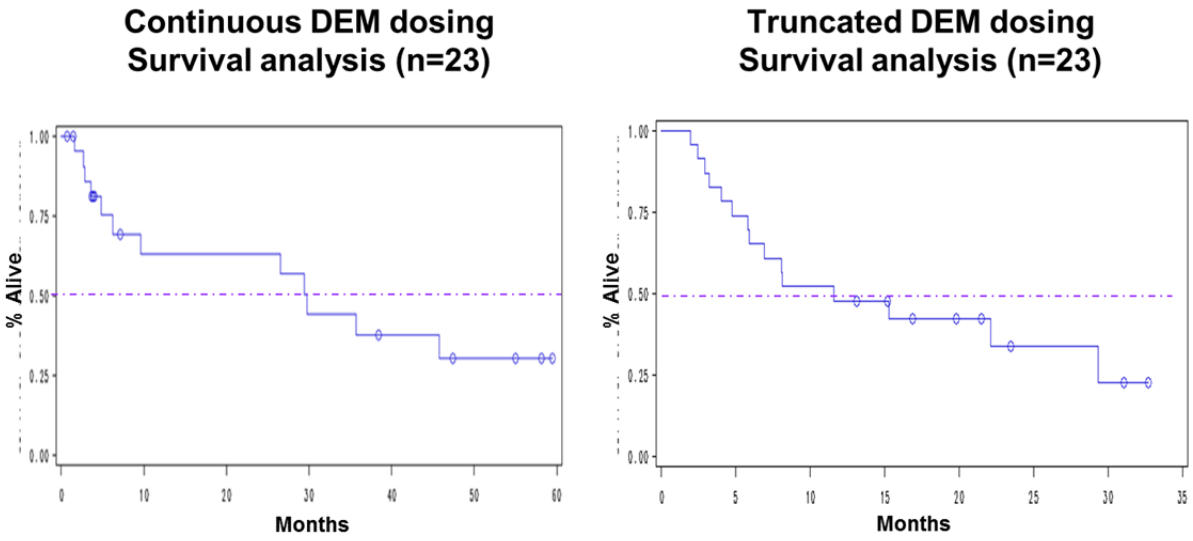
Figure 13: Exploratory Subset Analysis for Overall Survival - Study M18-004



(Ref 27)

Figure 14 shows the results for overall survival with additional follow-up for both groups of subjects.

Figure 14: Overall Survival for Subjects with Continuous and Truncated Demcizumab (DEM) Dosing - Study M18-004



Data as of 8 December 2016

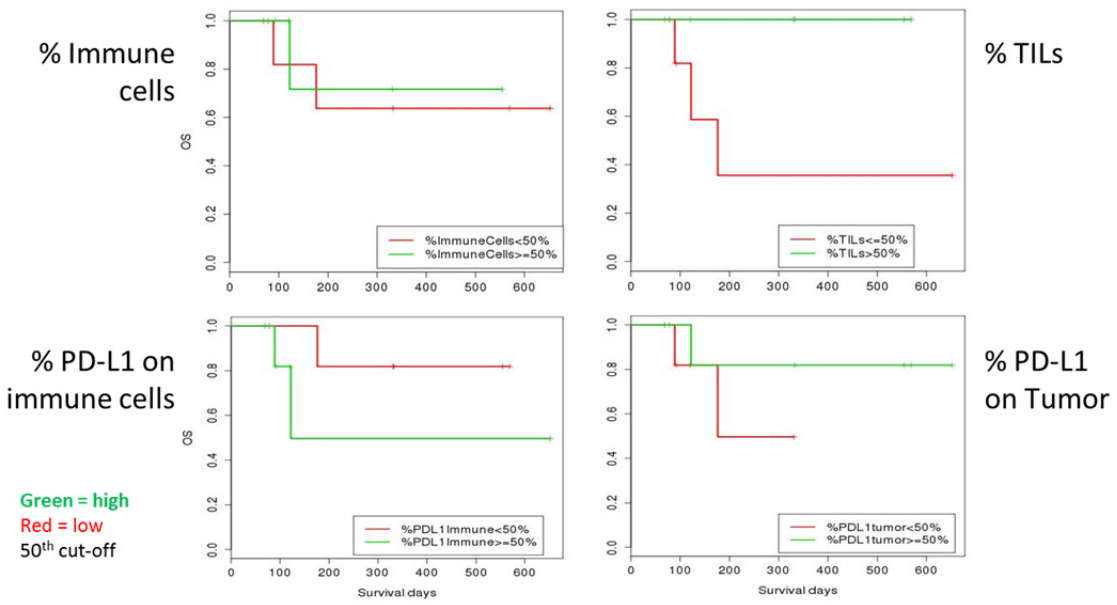
Subjects were assessed for subsequent therapies after participation in M18-004. Comparison of subjects who lived or did not live beyond 10 months did not reveal significant differences (Table 4).

Table 4: Subsequent Anti-Cancer Therapies for Subjects after Discontinuation from Study M18-004

	Continuous Demcizumab		Truncated Demcizumab	
	Alive <10 mths (n=13)	Alive ≥10 mths (n=10)	Alive <10 mths (n=11)	Alive ≥10 mths (n=12)
Ongoing	0	0	0	3
No 2nd-line treatment	5	5	10	6
2nd-line treatment unknown	7	1	1	0
2nd-line chemotherapy	0	3	0	3
2nd-line checkpoint inhibitor	0	0	0	0
2nd-line ALK inhibitor	0	0	0	0
2nd-line EGFR inhibitor	1	1	0	0
3rd line EGFR inhibitor	0	1	0	0
3rd- line chemotherapy	0	2	0	0
4th-line checkpoint inhibitor	0	1	0	0

Twelve of the 23 subjects receiving truncated demcizumab had tumor tissue available for further analyses. Figure 15 shows the exploratory overall survival analysis for several immune biomarkers.

Figure 15: Exploratory Overall Survival Analysis for Immune Biomarkers - Study M18-004



TILs = tumor-infiltrating lymphocytes. FFPE tumors from truncated patients were evaluated for % immune cells/tumor area, % TILs/tumor area, % PDL-1 positivity (membrane plus cytoplasm) on infiltrating immune cells and % PDL-1 positivity on tumor cells (Ref 28).

In summary, two separate cohorts of M18-004 subjects (continuous versus truncated demcizumab dosing) showed prolonged survival tails on the Kaplan-Meier curves, and these tails persisted regardless of associated demographic or laboratory parameters. The exploratory analysis of available tumor tissue demonstrated that a high number of tumor-infiltrating lymphocytes was associated with long-term survival, suggesting that immunomodulatory mechanisms may contribute to the observed subject benefit.

3.4.2.2 Phase 1b Safety Data

The treatment-emergent adverse events (AEs) in the 3 Phase 1b studies and the 1 Phase 1b/2 study considered to be related or possibly related to demcizumab by the Investigators and that occurred in >10 % of subjects were fatigue (45.5%), nausea (41.4%), hypertension/blood pressure increased (32.3%), vomiting (26.3%), edema peripheral (21.2%), diarrhea (22.2%), appetite decreased (18.2%), increased BNP (17.2%), anemia (15.2%), thrombocytopenia (15.2%), neutropenia (14.1%), dyspnea (12.1%), headache (11,1%), pulmonary hypertension (11.1%), constipation (10.1%), and rash (10.1%).

The Grade 3-5 treatment-emergent AEs considered to be related to demcizumab that occurred in >5% of subjects were neutropenia (27.2%), hypertension/blood pressure increased (16.2%) and thrombocytopenia (7.1%).

While subjects were being dosed in the first cohorts of the Phase 1b studies (M18-002, M18-003 and M18-004), some subjects in the Phase 1a single-agent study (M18-001) developed congestive heart failure, and, thus, the enrollment and treatment of subjects in the first dose cohort of the Phase 1b trials was stopped while the data for the subjects with congestive heart failure were analyzed. A decision was made to close study M18-003, but, subsequently, enrollment was resumed in studies M18-002 and M18-004 after the protocols were amended to include the following changes: 1) modified demcizumab dosing approach to include less frequent and lower doses; 2) standard bed-side Alere Triage BNP testing, 3) exclusion of subjects with a screening BNP of >100 pg/mL, 4) exclusion of subjects with a left ventricular ejection fraction (LVEF) of <50% or with pulmonary hypertension defined as a peak tricuspid velocity >3.4 m/s on Doppler echocardiogram, and 5) implementation of a dosing risk mitigation strategy including the administration of a cardioprotective agent (ACE inhibitor or carvedilol) to subjects with one BNP value >200 pg/mL or two values >100 pg/mL. As 3 subjects in the 2 ongoing Phase 1b studies (M18-002 and M18-004) subsequently developed pulmonary hypertension and/or heart failure between Days 168-184, further modifications were made including the utilization of truncated dosing with the last dose of demcizumab being administered on Day 63 in the NSCLC trial and on Day 70 in the pancreatic cancer trial. The use of truncated dosing allowed for washout of the drug prior to the timeframe when cardiopulmonary events had been observed. The utilization of truncated demcizumab dosing and further modifications of the risk mitigation strategy have resulted in none of the subsequent 5*1* subjects developing Grade $\geq$2 pulmonary hypertension or heart failure; i.e., only 1 subject has developed Grade 1 asymptomatic pulmonary hypertension, and none have developed heart failure.

These data demonstrate that the risk mitigation strategy that was employed in the Phase 1b studies was successful in preventing any clinically significant cases of pulmonary hypertension or heart failure.

3.5 Dose Rationale

In the Phase 1b study of demcizumab, pemetrexed and carboplatin in 1st-line non-squamous NSCLC subjects (study M18-004), subjects in the 1st 4 dose cohorts received demcizumab doses of either 2.5 or 5 mg/kg once every 3 weeks until disease progression. As 2 of these subjects developed Grade 3 pulmonary hypertension and heart failure at approximately Day 168, the 20 subjects in the subsequent 3 cohorts received a truncated dosing regimen (i.e., 4 doses over 63 days) of either 5 or 7.5 mg/kg once every 3 weeks. Whereas no cases of Grade ≥2 pulmonary hypertension or heart failure were observed in any of these subjects, the data safety monitoring board (DSMB) for the study felt that the BNP and peak tricuspid velocity data of subjects in the 7.5 mg/kg cohort suggested that the dose may be too high and thus recommended that the truncated dosing regimen of 5 mg/kg once every 3 weeks be used for the Phase 2 study. Subjects in the 3rd arm of this study will receive 2 truncated courses of demcizumab at 5 mg/kg once

every 3 weeks (one from Days 0-63 and one from Days 168-231). Only subjects who, on Day 168, meet the original cardiac-related eligibility criteria (Exclusion Criterion 21 in Section 6.2), who did not develop pulmonary hypertension or heart failure while on study, and for whom blood pressure is controlled to ≤140/90 mmHg will receive the 2nd truncated course of demcizumab in this arm of the study. This arm was included in the study to determine if a second truncated course of demcizumab can enhance efficacy compared to a single truncated course of demcizumab. Whereas the demcizumab regimen of the 3rd arm was not directly tested in the supporting Phase 1b program, the risk/benefit ratio for subjects in this arm is deemed acceptable, since the truncated dosing regimen has demonstrated an excellent safety profile, cardiac-related demcizumab toxicity appears reversible, subjects have to meet stringent criteria for the second course of demcizumab, and investigators, in addition, will be able to make an overall risk assessment based on how a subject fared during the first course of demcizumab/placebo. Furthermore, the DSMB for this study (see Section 14.0) will be monitoring the emerging safety data very closely to ensure that this approach is safe for continued use in the trial.

3.6 Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and in accordance with Good Clinical Practice (GCP) standards and all applicable regulatory requirements. No deviation from the protocol will be implemented without the prior review and approval of the IRB/IEC except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB or IEC as soon as possible.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

All objectives apply to the study population of subjects with 1st-line stage IV non-squamous non-small cell lung cancer (NSCLC).

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
- 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 pharamacodynamics (PD) and predictive biomarkers, such as DLL4 tumor expression, in Arm 1 to Arm 2 and Arm 3 *combined*

4.2 Endpoints

All endpoints apply to the study population of subjects with 1st-line stage IV non-squamous non-small cell lung cancer (NSCLC).

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 progression-free survival 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 progression-free survival 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 as outlined in the Schedule of Assessments (see Appendix A) 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

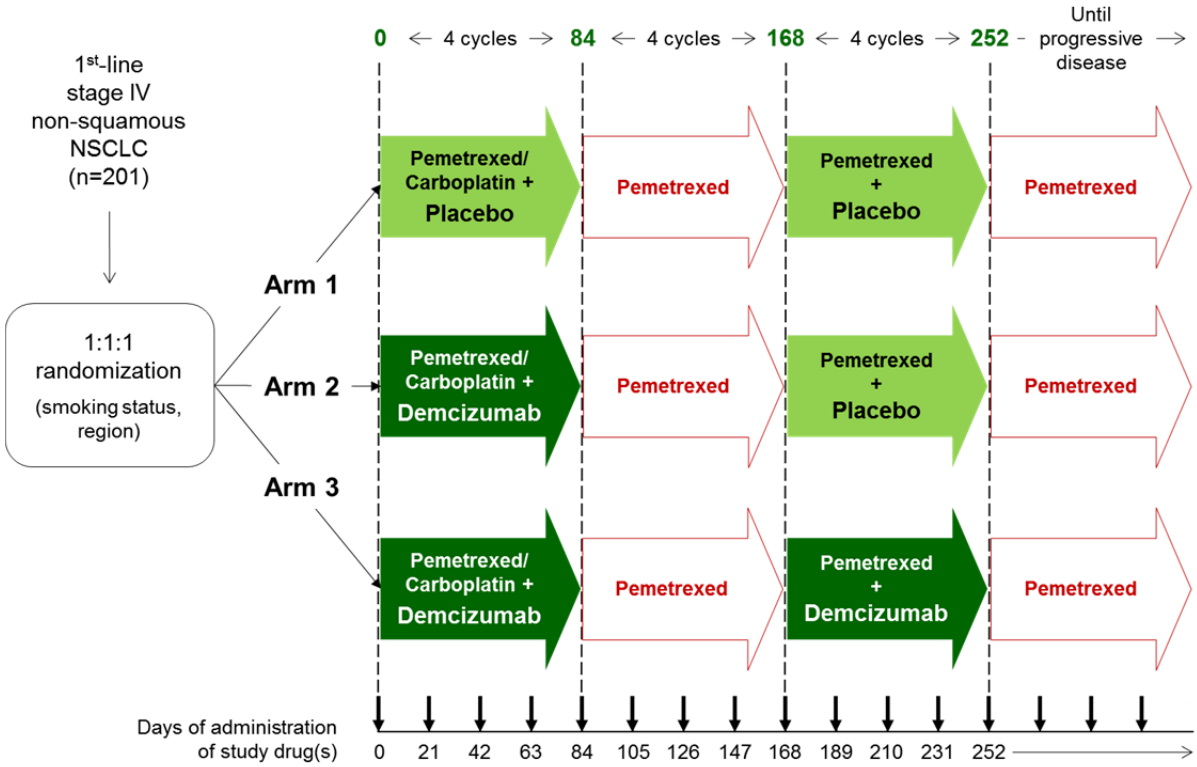
Exploratory Endpoints

- To compare the pharmacodynamics (PD) and predictive biomarkers for demcizumab and determine their correlation with response in Arm 1 to Arm 2 and Arm 3 combined (see Section 11.0).

5.0 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

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 two-hundred and one subjects were to be randomized via an IWRS system to one of three arms (Figure 16). 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.

Figure 16: Three-Arm Design of Study M18-007



Demcizumab (5 mg/kg) or placebo will be administered once every 21 days for a total of 4 cycles (i.e., 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 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* ≥*4*00 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.

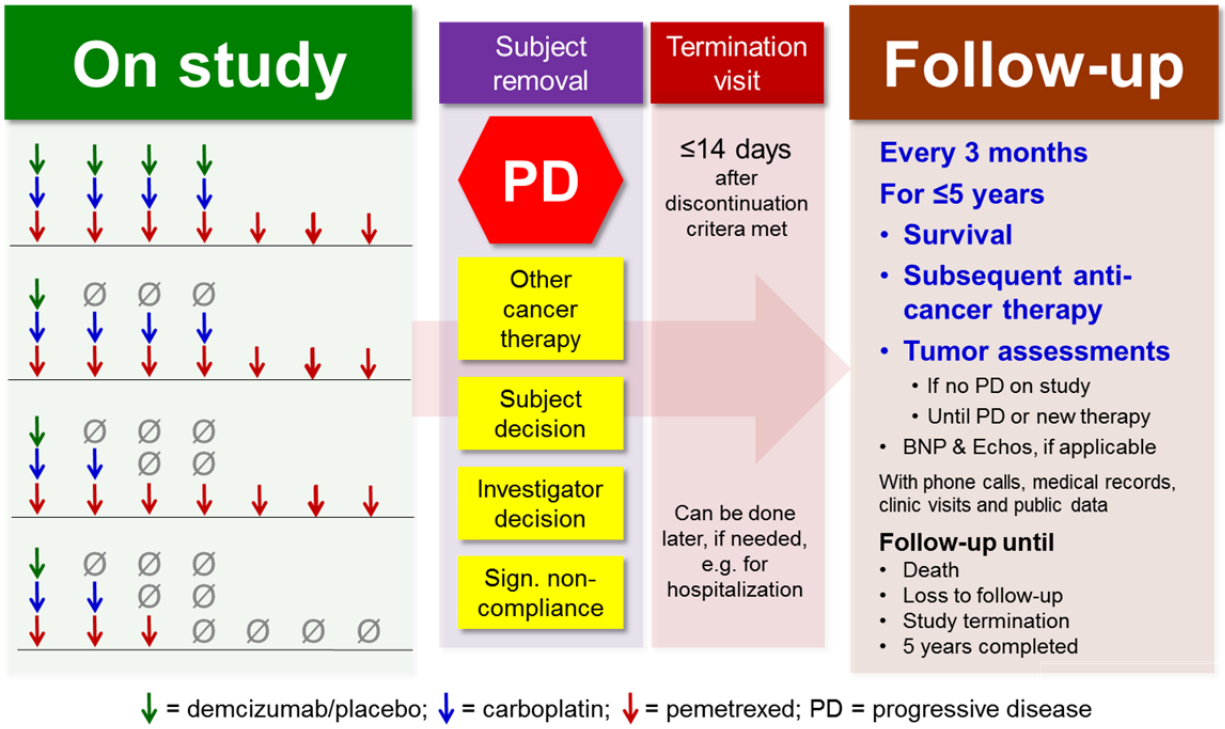
Subjects will be assessed for AEs as outlined in Section 9.1 at every visit and through 30 days following the termination visit. AEs will be graded according to NCI CTCAE, version 4.03 (v4.03).

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 pemetrexed infusion, if applicable) on Days 0, 42, 168 and 210, and at the termination visit. Immunogenicity will be assessed at baseline, every 6 weeks during the study, and at the termination visit. Blood biomarker assessment will be performed at Study Days 0 and 28, and at the termination visit.

Disease status will be assessed using RECIST v1.1, and subjects will undergo tumor assessments during screening, every 6 weeks while on study and at the termination visit (unless performed within 14 days of termination or at a prior response evaluation that documented progressive disease).

In the absence of unacceptable toxicities or disease progression per RECIST v1.1, subjects should continue to receive study treatment. **Regardless of discontinuation of one, two or all three study drugs, subjects should continue on study with assessments as outlined in Section 12 and Appendix A.** Once discontinuation criteria for the study are met (disease progression, use of other anti-cancer therapy, subject or investigator decision or protocol non-compliance, see Section 7.0), a termination visit should occur ≤14 days later. The termination visit may occur later after discussion with the OncoMed Medical Monitor for specific circumstances, such as prolonged hospitalization. After the termination visit, subjects should have regular follow-up for survival, subsequent anti-cancer therapies and other assessments as required per protocol (see Section 12.4). Figure 17 illustrates the two main periods of the study (on study and follow-up), before and after the termination visit.

Figure 17: Two Main Periods (On Study and Follow-up) of Study M18-007



Note: A subject who has discontinued all three study drugs (example at left bottom, discontinued study drugs indicated by 'Ø') should continue with the on-study part of the protocol with assessments as outlined in Section 12.0 and Appendix A.

Study procedures and assessments are further detailed in Appendix A.

6.0 SELECTION OF STUDY POPULATION

6.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study.

1. Signed Informed Consent Form

2. Histologically or cytologically confirmed Stage IV non-squamous NSCLC

    - Stage IV as defined by the International Association for the Study of Lung Cancer International Staging Committee (Ref 29) and adopted by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) in the 7th edition of the lung cancer TMN classification and staging system (Ref 30, Ref 31)

3. If available, agreement to provide archival FFPE tumor tissue (obtained by core biopsy or surgical resection) for exploratory biomarker analyses

    - FFPE tumor tissue may originate from either the primary tumor, locoregional disease or a metastatic site

    - Availability of FFPE tumor tissue is not mandatory for participation in this study

4. Age $\geq$21 years

5. ECOG performance status of 0 or 1 (see Appendix B)

6. Disease that is measurable per RECIST v1.1 (Appendix C)

7. Adequate organ and marrow function as defined below:

    - Absolute neutrophil count $\geq$1.5 x 10^9/L (without granulocyte colony-stimulating factor support within 2 weeks prior to randomization)
    - Hemoglobin $\geq$100 g/L (without transfusion within 2 weeks prior to randomization)
    - Platelets $\geq$125 x 10^9/L (without transfusion within 2 weeks prior to randomization)
    - Total bilirubin $\leq$2 x institutional upper limit of normal (ULN)
    - Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) $\leq$5 x institutional ULN
    - Alkaline phosphatase $\leq$ 5 x institutional ULN
    - International normalized ratio (INR) $\leq$1.5 and activated partial thromboplastin time (aPTT) within 1.5 x institutional ULN
    - Albumin $\geq$ 3 g/dL

- Calculated creatinine clearance ≥60 mL/min using the Cockcroft and Gault formula as follows:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{actual body weight [kg]}}{0.814 \times \text{serum creatinine [µmol/L]}}$$

For women, multiply the value from the equation above by 0.85.

8. For women of childbearing potential and men with partners of childbearing potential, agreement (by subject and/or partner) to use two effective forms of contraception from study entry through at least 6 months after the termination visit.

    - Women of childbearing potential are those women who have not been permanently sterilized or are not postmenopausal. Postmenopausal is defined as 12 months with no menses without an alternative medical cause.

    - Highly effective methods of birth control include those that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, levonorgestrel-releasing intrauterine system, intra-uterine devices (IUDs), vasectomized partner, and true sexual abstinence.

6.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible for participation in the study:

1. Histologically or cytologically documented, advanced, mixed non-small cell and small cell tumors or mixed adenosquamous carcinomas

2. NSCLC with EGFR mutation or anaplastic lymphoma kinase (ALK) gene translocation (such as EML4-ALK)

    - Negative results for these genetic aberrations, as determined by local assessments, must be documented in order for a subject to be eligible.

3. Prior or ongoing therapy (including chemotherapy, antibody therapy, tyrosine kinase inhibitors, radiotherapy, immunotherapy, hormonal therapy, or investigational therapy) for the treatment of Stage IV non-squamous NSCLC

    - Subjects who received prior adjuvant chemotherapy or radiotherapy for non-squamous NSCLC are allowed if the time interval from completion of adjuvant therapy until evidence of metastatic disease is >12 months.
    - Subjects who underwent NSCLC resection with curative intent and were subsequently diagnosed with metastatic disease are allowed regardless of time interval between resection and metastatic disease.
    - Subjects with locally recurrent disease only are not allowed.

- Subjects who received prior palliative radiotherapy for metastatic or lobar lesions (not including target lesions) are not excluded (if >2 weeks prior to randomization).
- Chronic use of bisphosphonate or denosumab therapy is allowed.

4. Evidence of tumor invading major blood vessels on imaging

   - The investigator or the local radiologist must exclude evidence of tumor that is fully contiguous with, surrounding, or extending into the lumen of a major blood vessel (e.g., pulmonary artery or superior vena cava).

5. Evidence of cavitation of one or more pulmonary tumor mass(es)

6. Evidence of a tracheo-esophageal fistula

7. Brain metastases (subjects must have an MRI of the brain, or CT scan with IV contrast, on or after Study Day -28 and prior to randomization, to rule out brain metastases)

8. Uncontrolled seizure disorder or active neurologic disease

9. Leptomeningeal disease

10. Metastases involving the lumen of the gastrointestinal tract

    - Colonoscopy and/or upper gastrointestinal endoscopy must be performed in subjects with symptoms suggestive of possible gastrointestinal involvement to rule out gastrointestinal involvement.

11. Malignancies, other than non-squamous NSCLC, successfully treated within 3 years prior to randomization, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, adequately treated low-stage bladder cancer and ductal carcinoma in situ treated surgically with curative intent

12. Prior radiation to the chest wall or mediastinum if the radiation field involved the heart

13. History of a significant allergic reaction attributed to humanized or human monoclonal antibody therapy

14. Recent (within the last 8 weeks prior to randomization) hemoptysis >2.5 mL or serious bleeding from another site within this timeframe

15. Known bleeding disorder or coagulopathy

16. Therapeutic anti-coagulation with heparin, warfarin, or other anticoagulants

    - Low-dose aspirin and/or non-steroidal anti-inflammatory agents are allowed.

- Use of thrombolytics to establish patency of indwelling venous catheters is allowed.
- Prophylactic anticoagulation for venous access devices is allowed as long as INR is ≤1.5 and aPTT ≤1.5 × institutional ULN.

17. History of cerebral vascular accident (CVA) or transient ischemic attacks (TIAs) within 6 months of randomization

18. Clinically significant arterial aneurysm

19. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of need for major surgical procedure during the course of the study

    - Placement of vascular access device will not be considered major surgery.

20. Blood pressure (BP) of >140/90 mmHg. The BP should be taken using the methods described in Section 9.3. Subjects taking antihypertensive medications must be taking ≤2 medications to obtain this level of BP control.

21. Any of the following cardiac-related criteria:

    - B-type natriuretic peptide (BNP) value of >100 pg/mL
    - Left ventricular ejection fraction (LVEF) <50%
    - Peak tricuspid velocity >3.0 m/s on Doppler echocardiogram
    - Receiving any medications for cardiac ischemia
    - Current evidence of cardiac ischemia
    - History of acute myocardial infarction within 6 months prior to randomization
    - New York Heart Association Classification II, III, or IV (See Appendix D)
        - For subjects to meet class II criteria with mild shortness of breath and/or angina, as defined by the NYHA guidelines, the cardiac etiology of the symptoms should be confirmed by a cardiologist taking 12-lead electrocardiogram, transthoracic Doppler echocardiogram and other studies into consideration, as appropriate.
    - Heart failure within the last 6 months prior to randomization
    - Received a total cumulative dose of ≥400 mg/m^2 doxorubicin
    - Grade ≥2 ventricular arrhythmia

22. History of interstitial lung disease or pneumonitis that required oral or intravenous corticosteroids

23. Active infection requiring antibiotics

24. Known HIV infection

25. Pregnancy or nursing

26. Significant intercurrent illness defined as an illness that may result in the subject's death prior to death from non-squamous NSCLC and/or significantly limit the ability to comply with the requirements of this study

27. Inability to comply with study and follow-up procedures

7.0 REMOVAL OF SUBJECTS FROM ON-STUDY PART OF PROTOCOL

Subjects must be withdrawn from the on-study part of the protocol (see Section 12.2 and Appendix A) for the following reasons:

- Disease progression according to RECIST v1.1
- Use of other anti-cancer therapy
- Subject decision
- Investigator decision based on subject's best interest
- Significant protocol non-compliance by subject

Subjects who meet one of the above criteria will undergo the termination evaluations for the study (see Section 12.3). After the termination visit, subjects will have regular follow-up for survival and other assessments as required per protocol (see Section 12.4).

If a subject has permanently discontinued one, two or all study drugs due to toxicities or any other reasons, the subject should continue with the on-study part of the protocol until one of the above criteria is met. Subjects who have discontinued one, two or all study drugs and continue with the on-study part should have assessments performed as outlined in Section 12.2 and Appendix A.

8.0 STUDY TREATMENTS

8.1 Study Drug (Demcizumab or Placebo)

8.1.1 Administration

Study drug (demcizumab at 5 mg/kg or placebo) will be administered once every 3 weeks for 4 cycles (i.e., last administration on Day 63). A second course of study drug (demcizumab at 5 mg/kg or placebo) will be administered once every 3 weeks for 63 days starting at Day 168 only if the criteria outlined in Section 5.0 are met. No dose reductions of demcizumab/placebo are allowed (see Section 8.1.6 for required modifications of demcizumab/placebo dosing).

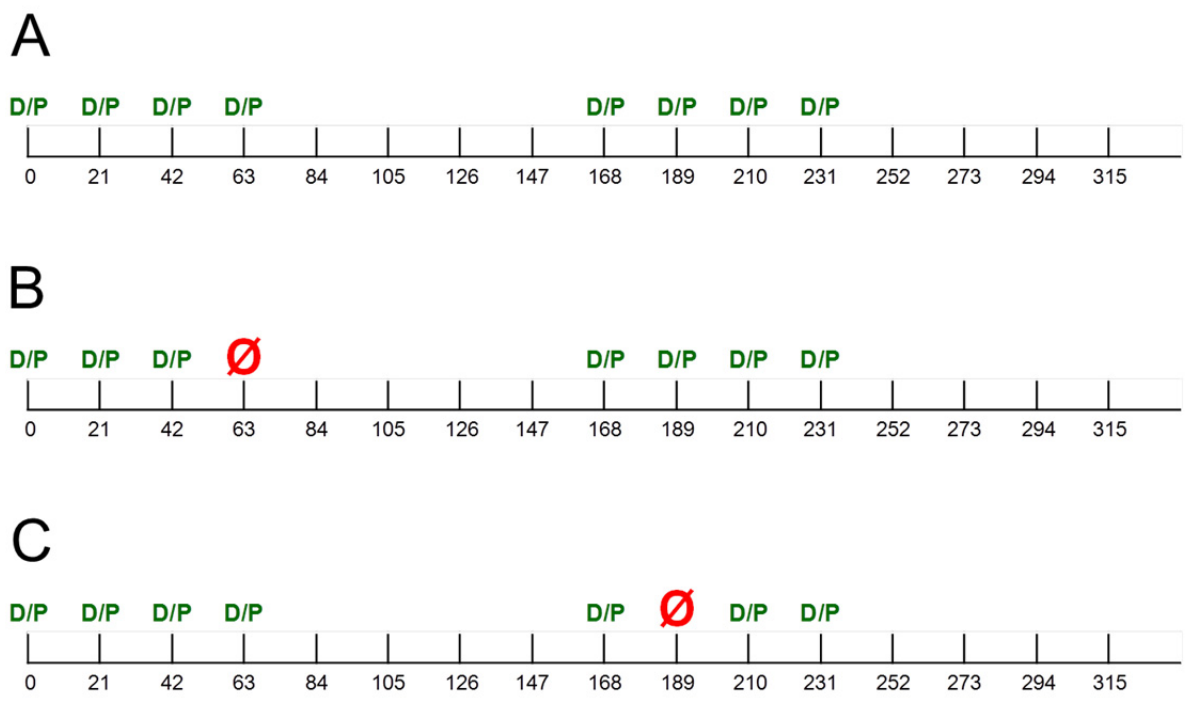
The demcizumab or placebo dose should be based on the Day 0 weight throughout the study, unless the weight changes by >10%. Study drug must be delivered as an intravenous infusion over 30 *(+5)* minutes prior to the administration of pemetrexed and carboplatin, if applicable.

If a semipermanent peripheral or central line is used to administer the drug, the catheter should be flushed per institutional standard procedures prior to and at the end of each infusion.

If an infusion reaction occurs, the infusion must be stopped and any appropriate medical care administered (see Section 8.1.7). Once the infusion reaction has resolved, and at the discretion of the Investigator, the infusion may be resumed at one-half of the initial rate of infusion. All subsequent infusions for that subject should then be administered at the reduced rate of infusion.

Study drug should not be held for chemotherapy-induced toxicity, such as hematologic toxicity. The Investigator should contact the OncoMed Medical Monitor if he/she wishes to hold demcizumab or placebo therapy for what is believed to be chemotherapy-induced toxicity.
If demcizumab/placebo cannot be administered within the specified time window of ±2 days (see Appendix A) for demcizumab/placebo-related (see Section 8.1.6) or other reasons, the missed dose cannot be administered at a later time point. Instead, no demcizumab/placebo is to be administered until the next scheduled dose (Figure 18).

Figure 18: Approach to Demcizumab/Placebo Dosing



D/P = demcizumab/placebo; Ø = demcizumab/placebo dose that was missed for demcizumab/placebo-related or other reasons and that is not to be administered at a later time point.

A) shows the schedule of demcizumab/placebo administrations without any missed doses. The time window for demcizumab/placebo dosing is ±2 days.

B) provides an example for a missed demcizumab/placebo administration during the first course of demcizumab/placebo.

C) illustrates a missed demcizumab/placebo administration during the second course of demcizumab/placebo.

8.1.2 Description

Demcizumab is an IgG2 humanized monoclonal antibody that is directed against the Delta-Like Ligand 4 (DLL4).

Demcizumab is supplied at a concentration of 10 mg/mL in a 25-mL single-use glass vial filled to 20 mL to deliver at total of 200 mg per vial.

Placebo is a clear to slightly opalescent, colorless to slightly yellow liquid formulation of 50 mM Histidine, 100 mM Sodium Chloride, 45 mM Sucrose and 0.01% (v/v) Polysorbate-20, pH 6.0.

All investigational products should be kept in a secure area inaccessible to unauthorized individuals.

8.1.3 Packaging

Labeling of demcizumab or placebo vials and cartons will comply with all applicable regulations.

8.1.4 Drug Ordering, Storage, and Accountability

The instructions for drug ordering via the IWRS are provided in the Pharmacy Binder. Demcizumab or placebo vials must be refrigerated at 2°C–8°C. Demcizumab or placebo must not be shaken or frozen. An accurate demcizumab or placebo accountability log must be maintained and kept up to date at all times. Perforated labels on blinded study drug vials must be retained for review for drug accountability purposes.

8.1.5 Drug Preparation

Demcizumab or placebo should be diluted for infusion using aseptic technique. Withdraw the necessary amount of demcizumab or placebo to obtain the required dose and dilute with 5% dextrose in water, USP to a total volume of 250 mL. For example, if a 70-kg subject is to be dosed at 5 mg/kg, then the subject's dose would be 350 mg. Because the vials contain a concentration of 10 mg/mL, a total of 35 mL containing 350 mg should be withdrawn from the vial and diluted with 5% dextrose in water, USP to a total volume of 250 mL.

Any unused portion left in a vial may not be used for another subject, as the product contains no preservative (i.e., they are single-use vials)

The diluted demcizumab or placebo solutions may be stored at room temperature (19°C–25°C) for up to 4 hours.

8.1.6 Treatment Modification and Termination Criteria for Demcizumab/Placebo

Results for B-type natriuretic peptide (BNP) are one of the important monitoring tools, and they are used to decide on the following:

- Unblind a subject
- Hold demcizumab/placebo
- Discontinue demcizumab/placebo

Results for peak tricuspid velocity (PTV) obtained by Doppler echocardiogram are a second important monitoring tool, and they are used to decide on the following:

- Initiate work-up for clinically significant pulmonary hypertension

Subjects with any of the following findings will have their treatment unblinded by the Investigator through the IWRS system:

- Two BNP values >100 pg/mL at consecutive scheduled BNP assessments (i.e. 21 days apart)
- One BNP value ≥200 pg/mL (e.g. 287, 315 or 459)

The unblinding information should be limited to the smallest number of site team members feasible, ideally to the principal investigator or treating physician only. Assuming criteria for continued demcizumab/placebo dosing are met, dosing for both demicuzmab and placebo should continue as scheduled. Any BNP value >100 pg/ml does not trigger more frequent BNP assessments. BNP assessments should continue to be obtained as scheduled.

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 32). 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.

If the subject is not on demcizumab, the subject should be cared for according to standard medical practice.

For BNP values <300 pg/mL, demcizumab/placebo should be continued as per protocol. Chemotherapy should be continued as well, unless contraindicated.

Subjects with any of the following findings must have their dose of demcizumab or placebo held, regardless of relationship to demcizumab or placebo:

- BNP ≥300 pg/mL
- LVEF decline ≥10% from baseline and LVEF <50% (for example from 55% to 45%)
- 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

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 subject 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.

8.1.7 Infusion Reaction Management

The administration of monoclonal antibodies may result in an infusion reaction that may consist of a symptom complex characterized by symptoms such as fever, chills, nausea, vomiting, headache, dizziness, bronchospasm, dyspnea, hypotension, and/or rash including urticaria. Subjects experiencing a Grade 2 infusion reaction of dyspnea (asymptomatic bronchospasm) or generalized urticaria should be premedicated prior to subsequent demcizumab or placebo infusions. Premedications may include medications such as corticosteroids, diphenhydramine, and/or bronchodialators as indicated. If the Grade 2 allergic reaction recurs during subsequent infusions despite the premedications, the subject should be removed from treatment. In addition, demcizumab or placebo therapy should be permanently discontinued in any subject who experiences a Grade 3 or 4 acute allergic reaction (e.g., symptomatic bronchospasm with or without urticaria, edema, angioedema, or hypotension). Grade 3/4 acute allergic reactions should be medically managed as appropriate and treatment may include the administration of epinephrine, corticosteroids, diphenhydramine, bronchodialators, and/or oxygen as indicated.

8.2 Pemetrexed

Subjects taking NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, subjects should be monitored closely for toxicity, especially myelosuppression and renal and gastrointestinal toxicity.

8.2.1 Administration

Pemetrexed at 500 mg/m^2 should be administered as an intravenous infusion over ≥10 minutes once every 21 days. Adjustments of dosing due to weight changes of the subject should be made according to local standards or guidelines. Pemetrexed must be administered after the administration of demcizumab/placebo, if applicable. Pemetrexed will be administered for the first 4 cycles with carboplatin (or less than 4 full cycles if disease progression or toxicity warrants treatment interruption or termination). Starting with Cycle 5, subjects should continue to receive pemetrexed without carboplatin once every 21 days until disease progression. The administration of pemetrexed should not be held if demcizumab/placebo needs to be held or discontinued.

8.2.2 Description

Pemetrexed is a multitargeted anti-folate agent. Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate.

8.2.3 Storage

Pemetrexed must be stored at controlled room temperature at 25°C.

8.2.4 Packaging

The labeling of pemetrexed will comply with all applicable regulations.

8.2.5 Vitamin Supplementation and Dexamethasone Administration

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 skin rash.

8.2.6 Renally Impaired Subjects

Pemetrexed cannot be administered concurrently with nonsteroidal anti-inflammatory drugs (NSAIDs) to subjects whose calculated creatinine clearance is <80 mL/min. Pemetrexed must be discontinued if a subject's calculated creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula (see below) or GFR measured by Tc99m-DPTA serum clearance method:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{actual body weight [kg]}}{0.814 \times \text{serum creatinine [µmol/L]}}$$

For women, multiply the value from the equation above by 0.85.

8.2.7 Preparation and Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of pemetrexed. The use of gloves is recommended. If a solution of pemetrexed contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed contacts the mucous membranes, flush thoroughly with water. Several published guidelines for the handling and disposal of anticancer agents are available.

Pemetrexed is not a vesicant. There is no specific antidote for extravasation of pemetrexed. To date, there have been few reported cases of pemetrexed extravasation, none of which were assessed as serious by the investigator. Pemetrexed extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

8.2.8 Preparation for Intravenous Infusion Administration

Pemetrexed for injection is a white to either light-yellow or green-yellow lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg pemetrexed.

Reconstitute each 100-mg vial with 4.2 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitute each 500-mg vial with 20 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives a solution containing 25 mg/mL pemetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality.

The appropriate quantity of the reconstituted pemetrexed solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 mL. Pemetrexed is administered as an IV infusion over 10 minutes.

Stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature and lighting. Discard any unused portion.

Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP, and Ringer's Injection, USP, and therefore, these diluents should not be used.

Please refer to the approved prescribing information for additional information on the preparation for pemetrexed.

8.3 Carboplatin

8.3.1 Administration

Carboplatin at 6 mg/mL x min should be administered as an intravenous infusion over 15 to 60 minutes once every 21 days for 4 cycles (or less than 4 full cycles if disease progression or toxicity warrants treatment interruption or termination). Calculation of the carboplatin dose of 6 mg/mL x min may be done according to local standards or guidelines, or as outlined below. Adjustments of dosing due to weight changes of the subject should be made according to local standards or guidelines. The administration of the carboplatin should not be held if demcizumab/placebo needs to be held or discontinued.

Demcizumab or placebo must be administered first, followed by pemetrexed and then immediately afterwards carboplatin. The dose of carboplatin in mg should be calculated by using the following formula:

$$\text{Carboplatin Dose (mg)} = 6 \text{ mg/mL} \times \text{min} \times [\text{CrCl (mL/min)} + 25)$$

Note: carboplatin dose calculated using the formula above is in mg not mg/m^2.

The calculated creatinine clearance (CrCl) should be determined by using the Cockcroft and Gault formula as follows:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{ideal body weight [kg]}}{0.814 \times \text{serum creatinine [µmol/L]}}$$

For women, multiply the value from the equation above by 0.85.

The ideal body weight for use in the Cockcroft and Gault formula should be determined as follows:

- Men: 50 + [(Height [cm] -154) x 0.9]
- Women: 45.5 + [(Height [cm] -154) x 0.9]

Carboplatin is a premixed aqueous solution of 10 mg/mL carboplatin. Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D_5W) or 0.9% Sodium Chloride Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin aqueous solutions be discarded 8 hours after dilution.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Please refer to the approved prescribing information for additional information on the preparation for carboplatin.

8.3.2 Description

Carboplatin produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific.

8.3.3 Storage

Carboplatin must be stored at controlled room temperature at 25°C.

8.3.4 Packaging

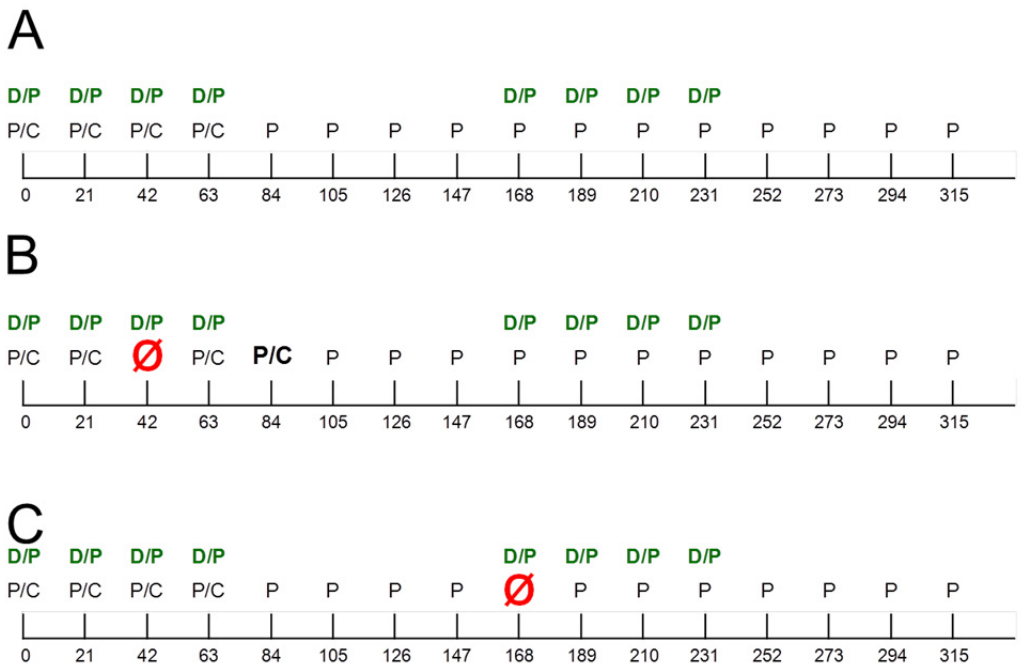
The labeling of carboplatin will comply with all applicable regulations.

8.4 Pemetrexed and Carboplatin Dose Modification/Treatment Delay

As outlined in Section 8.1.6, demcizumab/placebo must be administered on a fixed schedule, and missed doses cannot be made up at a later timepoint. In order to keep chemotherapy administrations synchronized with demcizumab/placebo, a similar approach may therefore be applied to chemotherapy with the difference that all four cycles of pemetrexed with carboplatin

should be administered. Consequently, if pemetrexed and/or carboplatin cannot be administered within the specified time window for demcizumab/placebo of ±2 days (see Appendix A) for chemotherapy-related or other reasons, the missed dose(s) would then not be administered until the next scheduled administration of chemotherapy with or without demcizumab/placebo (Figure 19).

Figure 19: Demcizumab-like Approach to Pemetrexed and Carboplatin Dosing



D/P = demcizumab/placebo; P/C = pemetrexed plus carboplatin; P = pemetrexed; Ø = pemetrexed plus carboplatin or pemetrexed dose that was missed for chemotherapy-related or other reasons.

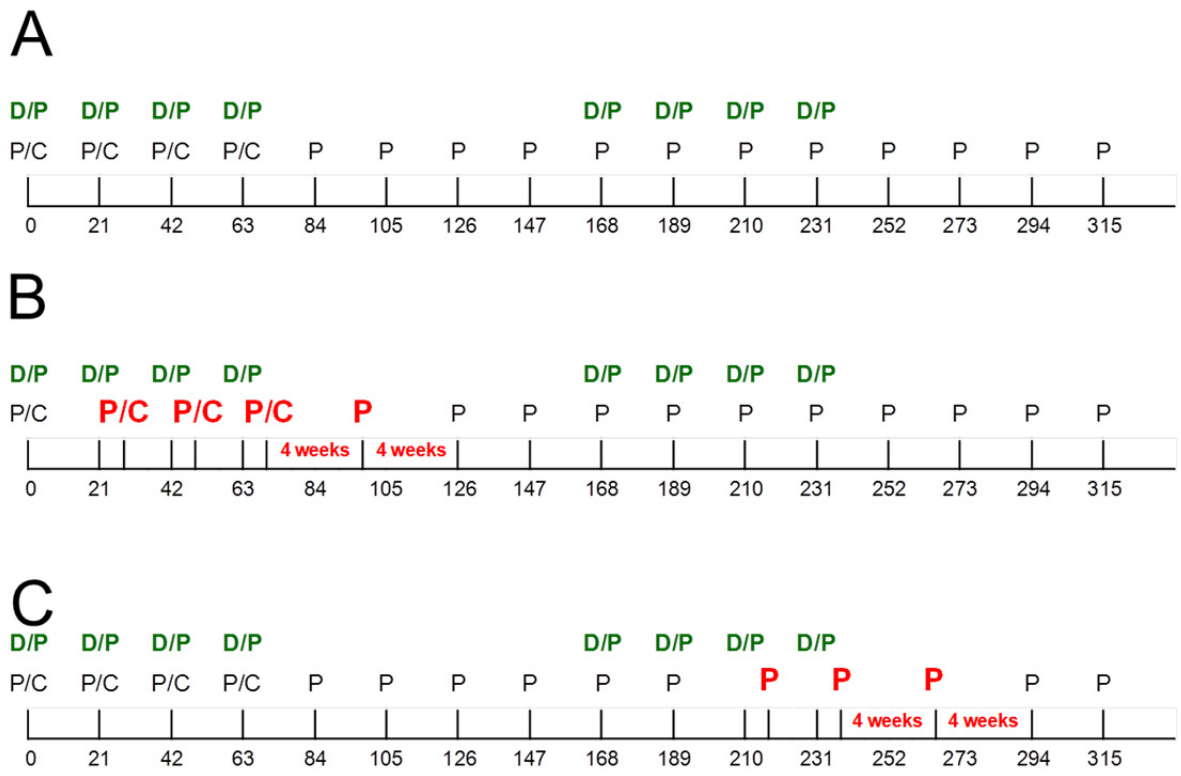
A) shows the schedule of demcizumab/placebo, pemetrexed and carboplatin administrations without any missed doses.

B) provides an example for a missed pemetrexed plus carboplatin administration during the first course of demcizumab/placebo. The missed doses of pemetrexed plus carboplatin should be administered on Day 84 (‘P/C’ in bold) to ensure that the subject receives a total of four cycles of pemetrexed/carboplatin combination therapy.

C) illustrates a missed pemetrexed administration during the second course of demcizumab/placebo. This missed dose is not made up at a later time point because of the general principle that chemotherapy should always be given on the same day as demcizumab/placebo.

Alternatively, the standard approach to chemotherapy administration may be used. If pemetrexed and/or carboplatin cannot be administered within the specified time window for demcizumab/placebo of ±2 days (see Appendix A) for chemotherapy-related or other reasons, the missed dose(s) would then be administered when it is appropriate. As a consequence, any subsequent demcizumab/placebo administrations will continue to be asynchronous with chemotherapy administrations (Figure 20). After completion of demcizumab/placebo dosing on Day 63, pemetrexed cycles may then be extended to up to 4 weeks in order to synchronize pemetrexed administration with assessments with a fixed time window, such as tumor assessments.

Figure 20: Standard Approach to Pemetrexed and Carboplatin Dosing



D/P = demcizumab/placebo; P/C = pemetrexed plus carboplatin; P = pemetrexed

A) shows the schedule of demcizumab/placebo, pemetrexed and carboplatin administrations without any missed doses.

B) provides an example for a missed pemetrexed plus carboplatin administration during the first course of demcizumab/placebo. In the example, all missed doses of pemetrexed plus carboplatin are then administered 7 days after demcizumab/placebo that continues to be administered during the protocol-specified time window.

C) illustrates a missed pemetrexed administration during the second course of demcizumab/placebo.

Examples B and C also show how 4-week chemotherapy cycles can be used to align chemotherapy administrations with other assessments.

The following are suggested guidelines for the management of specific toxicities expected to be related to pemetrexed and/or carboplatin. These general guidelines may be modified at the discretion of the investigator based on local clinical practice and best clinical judgement at that time. Any toxicities related to pemetrexed and/or carboplatin should be managed according to standard medical practice. Dose reductions of carboplatin and pemetrexed are permanent. Dose adjustments at the start of a cycle should be based on nadir hematologic counts (for 2nd and 3rd cycles of pemetrexed with carboplatin) or other nonhematologic toxicity from the preceding cycle of therapy. Additional non-protocol-specified laboratory assessments should be obtained as guided by toxicities observed in prior cycles and per standard of care. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, retreatment should be scheduled as outlined above (Figure 19 and Figure 20) using the criteria in Table 5, Table 6 and Table 7.

Table 5: Dose Reduction for Pemetrexed and Carboplatin - Hematologic Toxicities

Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose (pemetrexed and carboplatin)
Nadir platelets <50,000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose (pemetrexed and carboplatin)
Nadir platelets <50,000/mm^3 with Grade ≥2 bleeding from any site, regardless of nadir ANC	50% of previous dose (pemetrexed and carboplatin)
Nadir ANC <1,000/mm^3 and fever ANC <°C (101°F), regardless of nadir platelets	75% of previous dose (pemetrexed and carboplatin)

If subjects develop Grade 3 or 4 nonhematologic toxicities, treatment should be delayed until resolution to less than or equal to the subject's pre-therapy value. Treatment should be resumed according to criteria in Table 6 and Table 7.

Table 6: Dose Reduction for Pemetrexed and Carboplatin – Nonhematologic Toxicities

	Dose of Pemetrexed (mg/m^2)	**Dose of Carboplatin (mg/m^2)**
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	100% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose
Grade 3 or 4 nausea or vomiting	100% of previous dose	100% of previous dose
Grade 3 transaminase elevation	75% of previous dose	75% of previous dose
Grade 4 transaminase elevation	Discontinue pemetrexed	Discontinue carboplatin
Any other Grade 3 or 4 toxicity (if deemed appropriate by the treating physician)	75% of previous dose	75% of previous dose

In the event of neurotoxicity, the recommended dose adjustments for pemetrexed and carboplatin are described in Table 7.

Table 7: Dose Reduction for Pemetrexed and Carboplatin – Motor or Sensory Neurotoxicity

CTCAE Grade	Dose of Pemetrexed (mg/m^2)	Dose of Carboplatin (mg/m^2)
1 or 2	100% of previous dose	100% of previous dose
3 or 4	75% of previous dose	75% of previous dose

Any subject with 2 prior dose reductions who experiences a toxicity that would cause a third dose reduction should be discontinued from the chemotherapy agent assessed as the cause of the toxicity.

8.5 Anti-Emetics and Hematologic Supportive Care

Antiemetic therapy and/or hematopoietic growth factors and/or red blood cell/platelet transfusions may be administered at the discretion of the Investigator.

8.6 Concomitant and Prohibited Therapy

All concomitant medication administered from randomization through 30 days following the termination visit will be recorded on the Concomitant Medication remote data capture (RDC) screen.

Investigational medicinal products and anticancer agents (e.g., cytotoxic agents, biologics, and hormonal agents with known activity against the subject's specific tumor type) may not be administered from randomization through the termination visit. However, subjects may have radiation or non-invasive surgical resection of a solitary non-target lesion for relief of significant signs or symptoms, such as pain or bleeding, in the absence of disease progression. Such subjects will remain fully evaluable. In addition, subjects who are receiving adjuvant hormonal therapy, such as tamoxifen for a history of breast cancer, may continue to receive this treatment. Previously initiated chronic bisphosphonate or denosumab therapy may be continued during study participation. Initiation of bisphosphonate or denosumab therapy during study treatment is not allowed.

DVT prophylaxis during a hospitalization according to institutional standards is permitted. Should a medical condition require therapeutic anti-coagulation, demcizumab/placebo must be discontinued while therapeutic anti-coagulation is administered (see Section 8.1.6), and the subject should continue on study with continued pemetrexed/carboplatin administrations and regular assessments to ensure close follow-up.

Subjects treated for erectile dysfunction with a daily low dose of a phosphodiesterase type 5 inhibitor may continue to receive this treatment as long as special attention is paid to the possible effects of phosphodiesterase type 5 inhibition on the cardiovascular system.

8.7 Treatment Compliance

Demcizumab, placebo, carboplatin and pemetrexed will be administered IV by study site personnel. Thus, compliance with each infusion will be documented in the subject's medical records and then recorded on the appropriate RDC screen. In addition, drug accountability will be performed.

9.0 SAFETY ASSESSMENTS

Safety will be assessed by adverse event (AE) monitoring (including attribution of AEs and SAEs), physical examination, vital signs, clinical laboratory testing, anti-demcizumab testing, and subject interview on an ongoing basis as outlined in the Schedule of Assessments (see Appendix A).

Samples that test positive for demcizumab antibodies will be assessed for neutralizing capability. The impact of positive samples on safety and biologic activity will be assessed.

9.1 Adverse Events Definitions and Reporting Procedures

All AEs from the time of randomization through 30 days after the termination visit **must** be documented in the medical record and reported on the AE Case Report Form (CRF).

AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). The grading of the AEs will be done using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE), version 4.03 (see Investigator Reference Manual). In addition, for each AE the Investigator must indicate the attribution of AE to demcizumab or placebo (i.e., related or unrelated) and the attribution of the AE to the malignancy.

The principal investigator is responsible for assessing the causality of an AE (related or unrelated) to participation in the research.

In general, AEs are considered **related to participation in the research** if there is not a clear alternative explanation. AEs are considered **unrelated to participation in the research** if they are **solely** caused by the subject's disease or condition or by other circumstances unrelated to either the research or to the subject's condition.

9.1.1 Definition of Adverse Event

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 (e.g., Grade 2 nausea prior to the initial study drug infusion becomes Grade 3 nausea after initial study drug infusion).

Laboratory abnormalities should only be reported as AEs if they are associated with clinical symptoms and/or require treatment.

Pregnancy should not be reported as an AE. Should a subject enrolled in the study become pregnant or suspect she is pregnant while participating in this study or within 6 months after discontinuation of study drug(s), the Medical Monitor should be informed within the same timeframe as required for SAEs (see Section 9.1.4). Monitoring of the subject should continue through outcome of the birth, or longer if any fetal abnormality is present.

9.1.2 Definition of Serious Adverse Event

A **serious adverse event** (SAE) is any event that results in the following:

- Death
- Life-threatening condition (places the subject at immediate risk of death)
- Subject hospitalization or prolongation of existing hospitalization

  The following events involving hospitalization do not require reporting as an SAE as long as there is no occurrence of an AE:

  - Efficacy measurement for the study
  - Diagnostic or elective surgical procedure
  - Administration of scheduled therapy for this study
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Any other AE that, based upon the Investigator's medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse)

9.1.3 Disease Progression and Death

Disease progression (including progression of NSCLC, and death due to disease progression) is generally recorded as part of the efficacy evaluation and should not be reported as an AE or SAE. When an AE resulting from disease progression meets the requirements to be considered serious, the SAE verbatim term should be reported as the sign/symptom that best describes the event rather than as disease progression. For instance, a subject with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The event term may be reported as "pleural effusion" instead of disease progression.

Death should not be reported as an SAE, but as a clinical outcome of a specific SAE. The cause of death, reported on a source document such as the Death Certificate or autopsy report, should be used as the event term for the SAE.

9.1.4 Serious Adverse Event Reporting Procedures

SAEs that occur during the study must be clearly documented in the medical record. An SAE form must be completed for each event and submitted with 24 hours of the Investigator's knowledge of the event. Please see the Investigator Manual for details regarding SAE reporting. The following is the contact information for PPD Drug Safety.

Pharmacovigilance telephone contacts:

- Australia and Europe: [redacted]
- United States: [redacted]

Pharmacovigilance fax contacts:

- Australia and Europe: [redacted]
- United States: [redacted]

All SAEs will continue to be followed until the end of the study or until such events have resolved or the Investigator, in conjunction with the Sponsor, deems them to be chronic or stable.

9.2 Clinical Laboratory Assessments

All clinical laboratory assessments will be performed using the site's local laboratory (*see* Section 9.2.3 for details about BNP assessments).

9.2.1 Hematology

A complete blood count (CBC) with differential and platelet count will be obtained at each protocol-specified visit and an INR and aPTT will be obtained during screening.

9.2.2 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) will be obtained at each protocol-specified visit.

9.2.3 BNP Assessment

BNP will be assessed during screening, then every 21 days, and at the termination visit. After discontinuation of demcizumab or placebo (either as scheduled per protocol or unscheduled for other reasons), BNP assessments are continued every 21 days for another 105 days (5 assessments total). For example, if the last scheduled demcizumab or placebo dose is given on Day 231, a total of 5 more BNP assessments will occur on Days 252, 273, 294, 315 and 336. However, should the BNP result not meet eligibility criteria at the last assessment 105 days after the last demcizumab or placebo dose, BNP assessments have to be continued every 21 days until two consecutive assessments meet eligibility criteria or the termination visit has occurred.

BNP will be measured using any Alere Triage POC device (or the site's laboratory, if approved by OncoMed). BNP must be assessed on the same day prior to each dose of demcizumab/placebo, and elevations will be managed per Section 8.1.6.

9.2.4 Urinalysis

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

9.3 Vital Signs and Other Physical Findings

A full physical examination will be done at screening. Subsequently, an abbreviated physical examination will performed at Day 0, every 3 weeks during the on-study part of the protocol and at the termination visit. The abbreviated physical examination must include respiratory rate, auscultatory examination of the heart and lungs, abdominal examination, and assessment for the presence or absence of edema and/or ascites. A more complete physical examination should be conducted when clinically indicated.

Vitals signs will be done as outlined in Appendix A. On days of demcizumab or placebo dosing, vital signs will be obtained before infusion (-1 hour), 15 (±5) minutes after start of infusion, end of infusion (+5 minutes), and 15 (±5) minutes after end of infusion of demcizumab or placebo. Blood pressure (BP) may be measured with an automated BP monitor or manually. For the measurement, the subject should be in the same position at each study visit. The same cuff method should be used to measure BP throughout the study. For manual measurements, diastolic BP will be measured by the disappearance of Kortokoff sounds, phase V. If possible, measurements will be taken by the same staff member at each visit.

For subjects presenting with hypertension, their BP must be adequately controlled to ≤140/90 mmHg prior to randomization. This may be achieved by adjusting the existing anti-hypertensive medications or adding new ones for a maximum of 2 medications following guidelines for the management of high BP in adults (Ref 33). Any subject with hypertension (i.e., >150/90 mmHg) that is considered to be related to demcizumab or placebo at the time of the termination visit will continue to have BPs monitored once every 2 weeks until the BP is ≤150/90 mmHg over a 4-week period with every-2-week BP measurements.

9.4 Cardiopulmonary Studies

A twelve-lead electrocardiogram (ECG; with assessment of PR interval, QRS duration, and QTc interval) and a transthoracic Doppler echocardiogram (with assessment of left ventricular ejection fraction, right ventricular systolic pressure and peak tricuspid velocity) will be obtained at screening, then every 28 days, and at the termination visit. After discontinuation of demcizumab or placebo (either as scheduled per protocol or unscheduled for other reasons), ECG and Doppler echocardiogram assessments are continued every 28 days for ≥105 days. For example, if the last scheduled demcizumab or placebo dose is given on Day 231, a total of 4 more ECG and Doppler echocardiogram assessments will occur on Days 252, 280, 308 and 336. However, should results of the Doppler echocardiogram not meet eligibility criteria at the last assessment ≥105 days (depending on timing of assessments) after the last demcizumab or placebo dose, assessments have to be continued every 28 days until two consecutive Doppler echocardiograms meet eligibility criteria or the termination visit has occurred. The Doppler echocardiograms may also be sent to an Independent Cardiologist of the Sponsor's choice for central review. Clinically significant ECG abnormalities should be addressed according to standard of care.

A CT pulmonary angiogram (CTPA) should be performed if clinically significant pulmonary hypertension is diagnosed (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) to determine if pulmonary embolism might be the cause of the pulmonary hypertension. An MR angiogram or VQ scan may be performed instead per local or country standards or if the subject has a contrast allergy.

9.5 Immunogenicity Assessments

Serum samples for immunogenicity will be obtained at baseline, every 6 weeks (prior to *the* demcizumab or placebo infusion, if applicable*)* during the study, and at the termination visit. Samples that test positive will be assessed for neutralizing capability. In addition, the impact of positive samples on safety and biologic activity will be assessed. Instructions for sample collection, handling, storage and shipping can be found in the Study Reference Binder.

9.6 Pharmacokinetic Assessments

Plasma samples for PK analysis will be obtained prior to the demcizumab (or placebo) infusion, if applicable, on Days 0, 42, 84, 126, 168, 210, 252, 294 and 336, and at the end of the demcizumab (or placebo) infusion (prior to the chemotherapy infusion, if applicable) on Days 0, 42, 168 and 210, and at the termination visit. The PK samples must be drawn from a location that is different from the site of demcizumab or placebo administration. If demcizumab or placebo is administered via a vein in the arm, the PK samples must be drawn from a vein in the contralateral arm. Instructions for sample collection, handling, storage, and shipping can be found in the Study Reference Binder.

10.0 EFFICACY ASSESSMENTS

Tumor assessments will be performed at screening and then every 6 weeks. The schedule of every 6 weeks is to be maintained throughout the study and will not be shifted if there are dose holds (see Appendix A). Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Progression-free survival, response, and duration of response will be assessed using the RECIST criteria v1.1 (see Appendix C) (Ref 34). The primary response outcomes will be based on the Investigator's assessement. However, the radiographs will be collected centrally (by VirtualScopics), and an optional independent read of the radiographs may be performed. Please refer to the Investigator Manual for instructions of submission of the radiographs to VirtualScopics.

Assessments of the tumor marker CEA (if elevated at baseline) will be performed on the same schedule as imaging studies. Response assessment should be based solely on the radiographic assessment and not based on changes in CEA.

Overall survival will be assessed by collecting survival data including the date and cause of death.

The same imaging method used at screening must be used throughout the study. A documented standard-of-care tumor assessment performed on or after Study Day -28 may be used for the screening assessment provided it meets the below requirements.

At baseline, tumor assessments should include the following:

- Diagnostic-quality, contrast-enhanced CT scans of chest, abdomen, and pelvis

  To be suitable for RECIST v1.1 assessments, CT scans should have a maximum thickness of 5 mm and no gaps.

  CT scan is the preferred imaging modality for tumor assessments of chest, abdomen, and pelvis.

In subjects for whom the preferred CT scans are contraindicated because of, for example, a CT IV contrast allergy, a CT of the chest without contrast and MRI of the abdomen and pelvis with contrast are recommended.

MRI scans may be performed in lieu of CT scans. At screening, tumor assessments should include a diagnostic-quality, contrast-enhanced MRI scan of the chest, abdomen, and pelvis. To be suitable for RECIST v1.1 assessments, MRI scans should ideally have a maximum thickness of 5 mm and minimal gaps.

- MRI of the brain

  MRI is the preferred imaging modality for tumor assessments of the brain.

  In subjects for whom MRI of the brain is not available, a CT scan of the brain with IV contrast may be performed.

- CT scan of the neck or bone scan should be included if clinically indicated.

  MRI scan of the neck may be substituted for CT scan of the neck.

Subsequent tumor assessments should include the following:

- Diagnostic-quality, contrast-enhanced CT scans of chest and abdomen

  If another imaging method was used at baseline, the same imaging method must be used for subsequent tumor assessments.

- Imaging of all other known sites of disease

  The same imaging method as at baseline must be used.

In addition to the scheduled on-protocol tumor assessments, CT scans or other imaging studies may be performed at the investigator's discretion at any time as clinically indicated.

11.0 EXPLORATORY ASSESSMENTS

Instructions for biomarker sample collection, handling, labeling, and shipping are provided in the Study Reference Binder.

FFPE tumor tissue and predictive biomarkers: If available, archival FFPE tumor tissue (from either the primary tumor, locoregional disease or a metastatic site) obtained by core biopsy or surgical resection will be collected for protein and gene expression biomarker analysis. Exploratory predictive biomarkers such as DLL4 will be measured in FFPE tumor specimens. Gene expression biomarker analysis including Notch pathway-related genes may also be measured by RT-PCR and/or microarrays. Tumor-derived DNA may be used to test for mutations in candidate genes relevant to the Notch pathway (e.g., Notch1, DLL4, FBXW7). Exploratory analysis of these tumors may help to identify biomarkers that could be used in the future to predict which subjects are more likely to respond to demcizumab, pemetrexed and carboplatin treatment.

Blood Biomarkers: A sample of *9* mL of blood will be drawn on Study Days 0 and 28, and at *the* termination *visit* to evaluate changes in plasma proteins by immunochemistry (e.g., VEGF, β FGF, SDF1, PLGF, TNFα, MCP1, etc.), and Notch-related gene expression of mRNA using microarrays, e.g., Affymetrix platform. Plasma microRNAs may also be evaluated by microRNA expression profiling. A termination visit sample will not be obtained if one is available from the prior 14 days.

Optional Pharmacogenomics: For subjects who sign the optional Pharmacogenomics Informed Consent (Appendix F), a blood sample (10 mL) will be collected pre-dose at Study Day 0 (where local regulations permit). Pharmacogenomic analysis of candidate genes relevant to demcizumab or placebo may influence safety, tolerability, or pharmacodynamic effects of demcizumab or placebo for the treatment of solid tumors. Analysis of genes relevant to Notch/DLL4 target or pathway genes or disease genes may be performed (e.g., FBW7 and PTEN). Analysis of genes related to carboplatin and pemetrexed metabolism may also be performed (e.g., ABCB1).

12.0 STUDY VISIT SCHEDULE AND ASSESSMENTS

Subjects must sign and date the Informed Consent Form (Appendix E) that has been approved by the IEC/IRB prior to undergoing any study-related procedures. Once the screening process has been completed, the Investigator must complete a randomization request form and submit it for approval. Once OncoMed or its representative has approved randomization in the IWRS system, the investigator/study coordinator will use the IWRS system to randomize the subject. Subjects who are randomized will not be replaced. The IWRS system will then assign a subject number, and the subject will be officially enrolled in the study. This unique subject number will be on all electronic case report form (eCRF) pages. Study drug must be administered within 4 days from the date of randomization. Study Day 0 will be the first day of study drug administration.

12.1 Screening

All screening tests must be performed within 28 days preceding Day 0 (defined as the day of first study drug administration), unless otherwise indicated. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window may be used and do not have to be repeated as long as they meet protocol specifications. Subjects must receive pemetrexed premedication prior to Day 0 as outlined in Section 8.2.5.

Please see the Study Flowchart provided in Appendix A for details of screening assessments.

12.2 Assessments for On-study Part of Protocol (Day 0 up to Termination Visit)

Unless otherwise indicated, all assessments must be performed prior to dosing for all study visits when dosing occurs. **BNP must be assessed on the same day prior to each dose of demcizumab/placebo.**

All on-study evaluations (i.e., from Day 0 up to Termination visit) must be done within the following timeframes:

- Dosing of demcizumab or placebo within ± 2 days of the Study Day listed in Appendix A
- Laboratory evaluations within ± 3 days of the Study Day listed in Appendix A
- Tumor assessment, tumor marker CEA (if applicable), ECG, and transthoracic Doppler echocardiogram within ± 7 days of the Study Day listed in Appendix A

For subjects who only receive pemetrexed maintenance after discontinuation of carboplatin and demcizumab/placebo, every-three-week visits can be rescheduled accordingly if pemetrexed administration and associated assessments (i.e., physical examination, weight, vital signs, ECOG performance status, CBC, and chemistry) were delayed for adverse or other unforeseen events. In addition, if the timing of a protocol-mandated study visit coincides with a holiday or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly. Pemetrexed cycles may be extended from 3 to up to 4 weeks to realign assessments.

Subjects who have discontinued all study drugs and have no clinically significant ongoing related adverse events that require close follow-up have to undergo the following assessments only every 42 days (ideally synchronized with tumor assessments and tumor marker CEA, if applicable): physical examination, weight, vital signs, ECOG performance status, CBC, and chemistry.

However, the schedule for BNP assessments (every 21 days; for more details see Section 9.2.3), for ECG and transthoracic Doppler echocardiogram (every 28 days; for more details see Section 9.4), and for tumor assessment and tumor marker CEA, if applicable (every 42 days), must be maintained.

Please see the Study Flowchart provided in Appendix A for detailed schedule of treatments and assessments.

12.3 Termination Visit

The termination visit should be done as soon as possible, but no later than 14 days, after one of the discontinuation criteria for the study are met (see Section 7.0). The termination visit may occur later after discussion with the OncoMed Medical Monitor for specific circumstances, such as prolonged hospitalization. The visit at which a tumor assessment shows progressive disease may be used as the treatment termination visit provided that all required assessments were performed as outlined in Appendix A.

Tumor assessments do not have to be repeated if they were performed within 14 days of the termination visit or at a prior response evaluation that documented progressive disease. ECG

and Doppler echocardiogram do not have to be repeated if they were performed within 14 days of the termination visit.

12.4 Follow-up after Termination Visit

The subject's treatment assignment will be blinded until the final analysis for overall survival is completed in the study.

If the BP was >150/90 mmHg at the termination visit, the subject needs to be followed as outlined in Section 9.3.

SURVIVAL DATA: Once a subject has completed the termination visit, overall survival follow up will be performed every three months ±1 week for up to 5 years to determine the subject's status and ultimately the date and cause of death. Follow-up may be conducted through telephone calls, review of medical records, and/or clinic visits. In addition, the site may check public data sources to get this information, if needed (e.g., obituaries).

SUBSEQUENT ANTI-CANCER THERAPIES: Subsequent anti-cancer therapies, including systemic therapies, surgery (resection of metastatic disease), and radiation therapy will be collected through telephone calls, review of medical records, and/or clinic visits on the same schedule as for survival data.

RESPONSE ASSESSMENT DATA: Response assessment data (i.e., progressive disease or no progression of disease) will continue to be collected (based on standard-of-care radiographs) on subjects who have not progressed at the time of the termination visit. For these subjects, copies of the standard-of-care radiographs may be provided to the Sponsor in a de-identified manner. These data and radiographs will continue to be collected until the subject starts alternative anti-cancer treatment or develops progressive disease, whichever occurs first.

BNP AND DOPPLER ECHOCARDIOGRAM: If a subject has a BNP of ≥400 pg/mL and/or a diagnosis of pulmonary hypertension or heart failure at the time of the termination visit, all subsequent standard-of-care BNP data until the value is <200 pg/mL and all subsequent standard-of-care LVEF and PTV values until they normalize, if collected or available, will be entered into the database.

13.0 DATA QUALITY ASSURANCE

Accurate, consistent and reliable data will be ensured through the use of standard practices and procedures. Clinical Research Associates (CRAs) from PPD will monitor the study and verify that the data are accurate. OncoMed Pharmaceuticals, Inc. has contracted with PPD to perform the data management of this trial. The data will be captured using a validated remote data capture (RDC) system. The medical monitors, CRAs, and site personnel will be trained in the use of Medidata RAVE. The clinical data and the site-specific laboratory data will be entered by site personal into Medidata. Analysis of samples for antibodies to demcizumab will be performed by ICON. Analysis of biomarker samples and pharmacogenomics samples will be

performed at OncoMed Pharmaceuticals, Inc. Drug Safety Reporting will be the responsibility of PPD. System backups for data stored at OncoMed Pharmaceuticals, Inc. and at all contract research organizations (CROs) and records retention for the study data will be consistent with the standard procedures for these organizations.

14.0 STATISTICAL PLAN

The KEYNOTE-021 Cohort G trial reported a confirmed response rate in the chemotherapy alone arm of 29% (Ref 35). Here, we will assume that the unconfirmed response rate for chemotherapy alone is 40 percent. Table 8 presents the power to detect an increase in the unconfimed tumor response rate in the pooled demcizumab arms (Arm 2 and Arm 3) compared to control. With 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 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.

Table 8: Power to Detect an Increase in Response Rate

Subjects Randomized			Response Rate		Type 1 Error 1-sided	Power
Total	Control	Demcizumab	Control	Demcizumab		
82	27	55	0.4	0.45	0.100	0.20
82	27	55	0.4	0.50	0.100	0.34
82	27	55	0.4	0.55	0.100	0.51
82	27	55	0.4	0.60	0.100	0.68
82	27	55	0.4	0.65	0.100	0.82
82	27	55	0.4	0.70	0.100	0.92
82	27	55	0.4	0.45	0.400	0.57
82	27	55	0.4	0.50	0.400	0.73
82	27	55	0.4	0.55	0.400	0.85
82	27	55	0.4	0.60	0.400	0.93
82	27	55	0.4	0.65	0.400	0.97
82	27	55	0.4	0.70	0.400	0.99
82	27	55	0.4	0.45	0.500	0.67
82	27	55	0.4	0.50	0.500	0.81
82	27	55	0.4	0.55	0.500	0.90
82	27	55	0.4	0.60	0.500	0.96
82	27	55	0.4	0.65	0.500	0.99
82	27	55	0.4	0.70	0.500	1.00

In the Phase 1b trial M18-004, a tail was observed in the OS survival curve suggesting that the hazard of death is greatly reduced beyond 10 months in first-line NSCLC subjects treated with demcizumab. Table 9 presents the power to detect a difference in the hazard between the pooled demcizumab arms and control beyond 10 months. 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.

Table 9: Power to Detect a Difference in the Overall Survial Kaplan Meier Curves Beyond 10 Months

Hazard of Death		End of Study Month	Events		Events >10 months		Power >10 months
0-10 months	>10 months		DEM	Control	DEM	Control	
1	1.00	**25 (Feb 2017)**	31.09	15.55	6.35	3.18	0.1000
1	0.50	25	28.29	15.55	4.11	3.18	0.3616
1	0.25	25	26.58	15.55	2.77	3.18	0.6571
1	0.10	25	25.43	15.55	1.89	3.18	0.8897
1	1.00	**30 (Jul 2017)**	36.31	18.16	10.63	5.32	0.1000
1	0.50	30	31.95	18.16	6.93	5.32	0.4683
1	0.25	30	29.10	18.16	4.56	5.32	0.8135
1	0.10	30	27.12	18.16	2.94	5.32	0.9705
1	1.00	**36 (Jan 2018)**	40.71	20.36	15.59	7.79	0.1000
1	0.50	36	35.03	20.36	10.24	7.79	0.5700
1	0.25	36	30.94	20.36	6.52	7.79	0.9083
1	0.10	36	27.94	20.36	3.85	7.79	0.9920

Cardiac Safety Monitoring

If two or more of the first 10 subjects treated with demcizumab experience Grade 3-5 (per NCI CTCAE v. 4.03) heart failure and/or pulmonary hypertension, that is deemed at least possibly related to demcizumab, the study will be stopped.

If after 10 subjects have been treated with demcizumab, subjects experience greater than or equal to 15% above the rate in the control arm of Grade 3-5 (per NCI CTCAE v4.03) heart failure and/or pulmonary hypertension, that is deemed at least possibly related to demcizumab, the study will be stopped.

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. 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.

Table 10 presents the probability of exceeding the 15-percent threshold at the interim analysis and final analysis in the trial. It is assumed the single course demcizumab arms are combined in Yosemite and Denali and that each study contributes 33-34 subjects to the demcizumab arm and the control arm at the interim analysis (50% enrollment) and 67 subjects at the final analysis (100% enrollment). The actual number of subjects available for the analysis at the interim and final will likely be different from those assumed in the table so the calculation using the appropriate number of subjects will have to be undertaken at the time of the analysis.

Table 10: Probability Heart Failure Rate Will Exceed 15 Percent over Control

Control Rate	Dem Rate	Probabilty of Exceeding 15% at Interim (67 subjects enrolled in demcizumab treated arm, 67 subjects in the control arm)	Probabilty of Exceeding 15% at Final (134 subjects with demcizumab, 134 subjects with control)	Probabilty of Not Exceeding 15% at Final	Total Probability of Exceeding 15%	Total Probability
0.03	0.03	0.00016	0.00000	0.99984	0.00016	1.00000
0.03	0.06	0.00877	0.00016	0.99108	0.00893	1.00001
0.03	0.09	0.05897	0.00502	0.93603	0.06399	1.00002
0.03	0.12	0.17202	0.03042	0.79758	0.20244	1.00002
0.03	0.15	0.33041	0.07915	0.59047	0.40956	1.00003
0.03	0.18	0.50000	0.12501	0.37501	0.62501	1.00002
0.03	0.21	0.65292	0.14233	0.20478	0.79525	1.00003
0.03	0.24	0.77491	0.12838	0.09673	0.90329	1.00002
0.03	0.27	0.86330	0.09702	0.03969	0.96032	1.00001
0.03	0.30	0.92226	0.06359	0.01416	0.98585	1.00001
0.03	0.33	0.95869	0.03694	0.00438	0.99563	1.00001
0.03	0.36	0.97958	0.01926	0.00116	0.99884	1.00000
0.03	0.39	0.99067	0.00907	0.00026	0.99974	1.00000
0.03	0.42	0.99609	0.00386	0.00005	0.99995	1.00000
0.03	0.45	0.99852	0.00147	0.00001	0.99999	1.00000
0.03	0.48	0.99950	0.00050	0.00000	1.00000	1.00000

Note: The sum of the probabilities in columns 3 to 6 adds up to 1.00.

For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum, maximum, and possibly geometric mean and geometric standard error if applicable to biomarker data. For categorical variables, descriptive statistics will include counts and percentages per category. Statistics for time-to-event variables will be estimated by the Kaplan-Meier method.

14.1 Subject Populations for Analysis

Eighty two (82) subjects were randomized in the trial.

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

The Per-Protocol (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 analysed as they were treated. Efficacy, immunogenicity and biomarker data will be analysed using the per-protocol 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. Subjects will be analysed as they were treated. 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 will be analysed as they were treated. 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.

Missing values will not be imputed.

14.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be analyzed using the Intent-to-Treat Population. Quantitative and/or categorical summaries will be presented for demographics, medical history, and other baseline characteristics. For continuous variables, data will be summarized by sample size, mean, standard deviation, median, minimum, and maximum. For categorical variables, data will be summarized as frequency counts and percentages. Medical history will also be displayed by subject in listing formats.

14.3 Treatment Exposure

Treatment exposure will be summarized as duration *of* treatment and extent of exposure to demcizumab/placebo, pemetrexed and carboplatin. Duration of exposure will be summarized

quantitatively in days using sample size, mean, standard deviation, median, minimum, and maximum.

Measures of extent of exposure include the total number of doses per subject, cumulative dose per subject, dose intensity and compliance. Compliance will be summarized as the number of subjects who had dose(s) withheld or delayed. The reasons for dose(s) withheld or delayed will also be summarized.

14.4 Endpoints

14.4.1 Safety Endpoints

Safety endpoints include AEs; SAEs; vital signs; clinical laboratory testing including assessment of BNP every 21 days; electrocardiograms with assessment of PR interval, QRS duration, and QTc interval; transthoracic Doppler echocardiograms with left ventricular ejection fraction and peak tricuspid velocity determination, if measurable; and anti-demcizumab antibody testing. Safety endpoints will be analyzed by treatment arm using the Safety Population.

Adverse Events

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

Clinical Laboratory Assessments and Vital Signs

Clinical laboratory data (hematology, serum chemistry, and urinalysis) and vital signs will be summarized by treatment arm using descriptive statistics of the reported values and change from baseline values at the point of each subject's minimum value/change, maximum value /change and the last value/change. In addition, the frequency counts and percentages of subjects shifting from "low," or "normal," at baseline to "high" post baseline or "high" or "normal" at baseline to "low" post baseline for each treatment group will also be provided at the same time points. The high and low post baseline categories will be further classified by NCI CTC grade if available. All laboratory and vital sign data will be presented in listings and special attention will be given to any unexpected abnormal results.

BNP Assessment

The proportion of subjects with at least two consecutive BNP assessments >100 pg/mL or at least one BNP assessment ≥200 pg/mL, the proportion of subjects who had their treatment held due to a BNP ≥300 pg/mL and the proportion of subjects who have a BNP ≥400 pg/mL will be summarized by treatment group.

Among the subjects in the demcizumab groups with two BNP measurements >100 pg/mL or one ≥200 pg/mL, the use of ACE inhibitors and carvedilol will be described with simple descriptive statistics and the proportion of subjects with an elevation ≥400 pg/mL will also be summarized along with the total amount of follow-up time both preceding and following the initiation of ACE inhibitors or carvedilol.

ECOG and Physical Examination

ECOG performance status at baseline and follow-up and physical examination data at baseline will be listed by subject for each treatment arm. Changes in ECOG performance status scores from baseline will be summarized by treatment group at selected scheduled time points using shift tables.

ECG and Doppler Echocardiogram

An electrocardiogram with assessment of PR interval, QRS duration, and QTc interval will be obtained every 28 days, and a transthoracic Doppler echocardiogram with left ventricular ejection fraction and peak tricuspid velocity determination, if measurable, will be obtained every 28 days. The maximum change in PR interval (increase), QRS duration (increase) and QTc interval (increase) will be summarized by treatment arm.

14.4.2 Immunogenicity Endpoints

Immunogenicity endpoints will be analyzed using the ITT Population. The incidence of anti-demcizumab antibody development in subjects receiving carboplatin, pemetrexed and demcizumab will be summarized by frequency counts and percentages. For subjects with a positive result for an anti-demcizumab antibody, the incidence of neutralizing capability development will be further summarized by standard quantitative methods for each treatment arm. In addition, the impact of positive results on safety and biologic activity will be assessed.

14.4.3 Pharmacokinetic Endpoints

Peak and trough concentrations will be summarized with simple descriptive statistics. Demcizumab concentration data from this study will be also included in a population pharmacokinetic analysis encompasses all studies in which pharmacokinetic sampling was conducted, to estimate the individual PK parameters (i.e., half life, volume of distribution, clearance etc.) and to analyze the inter-subject variability and factors that may contribute to the inter-subject variability of the PK of demcizumab.

14.4.4 Efficacy Endpoints

Efficacy endpoints include best overall response, confirmed response, time to progression, duration of response and survival. Efficacy endpoints will be analyzed using the ITT Population.

Best Overall Response

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 (see detailed definition in Appendix C) in the following order of importance:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Not Evaluable (NE)

The number and proportion of subjects achieving their best overall response will be summarized for each dose group.

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 confimed response rate will be assessed as well and is the number of subjects per treatment arm who have either a confirmed CR or a confirmed PR (according to RECIST v1.1 criteria) divided by the number of subjects randomized to the respective arms. These proportions and their 95% confidence intervals will be displayed. The p-value for equality between a demcizumab treatment arm and control will be calculated for the two groups using a logistic regression model with treatment, performance status and region as factors in the model.

Progression-Free Survival and Duration of Response

The secondary endpoint of PFS based on the Investigator assessment of tumor response, is defined as the number of days from randomization until death or disease progression as defined by the RECIST v1.1 criteria for the ITT Population. Deaths that occur more than 49 days (1 tumor assessment + 7 days) after the last tumor assessment will not be accounted as PFS events. 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. The 95% confidence intervals for median progression-free survival time will also be calculated for each treatment arm. 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. The stratification factors will be smoking status (current versus former or never) and region (Australia/Europe versus North America). Subjects who have not experienced death or progression by their last contact will be censored at the time of their last radiographic response assessment and the number and percentage of these subjects will be displayed. In addition subjects who receive non-protocol therapy will be censored at the point they start this treatment. Radiotherapy and surgery directed at a disease site will be considered non-protocol

therapy. Bisphosphonates and hormones will not be considered non-protocol therapy. If there is a disparity in discontinuation rates between treatment arms or in the types of censoring or in the use of non-protocol therapy, sensitivity analyses will be performed to assess the impact.

In addition, for subjects who died or progressed after an extended lost-to-follow-up period (greater than 17 weeks from the previous assessment), PFS will be right censored at the date of the last adequate assessment prior to the lost to follow-up period. Subjects who do not have any tumor assessments will be treated as censored at Day 0.

PFS based on the IRF (optional) assessment of tumor response will be similarly defined with performance status and prior history of smoking being the stratification factors. The optional IRF assessment will be performed if the Investigator-assessed efficacy data show a sufficiently positive trend in favor of the combined demcizumab arms.

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 progression free survival.

To evaluate the impact of the second course of demcizumab therapy, a cox regression analysis will be used with a time dependnent covariate to capture the affect of the second course of demcizumab. The two demcizumab arms will be pooled and compared with control. A time-dependent variable to capture the effect of the second course of demziumab will be used. The variabe will be zero unless a subject has started a second course of demcizumab which case the variable will assume the value of 1. A standard variable will also be included in the model to capture the randomized assignment of subjects to control or demcizumab (pooled).

14.4.5 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 both the Investigator and the IRF [optional]). 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, as well as 6, 12 and 18 weeks post baseline. These summary statistics will also be presented for differences 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 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 the event that the parametric assumptions are not met, the p-value will be generated using a nonparametric test utilizing ranks. This nonparametric test will be performed at scheduled tumor assessments, using the log of (tumor length at week X divided by tumor length at baseline) as the endpoint. In the case of complete response when the outcome variable is undefined, the best

possible rank will be assigned. In the case of death or withdrawal due to AE, the worst possible rank will be assigned.

In addition, the rate of change in tumor volume at progression (sum of the longest diameters (SLD) at progression – SLD at nadir)/SLD at nadir as determined by both the Investigator and the IRF (optional) will be compared between the two arms of the study. The rate of change in tumor burden at progression has been associated with survival (references)

14.4.6 Duration of Response

The Investigator-assessed and IRF-assessed (optional) duration of response are defined as the time from the first partial or complete response to the time of death or disease progression for subjects with a confirmed response. Subjects who have not experienced death or progression by their last contact will be censored at the time of their last radiographic response assessment. 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 each treatment arm. The p-value for treatment effect will be generated using a Cox proportional hazards model.

Sites of Progression

The sites of progression as determined by the Investigator and by the IRF (optional) will be classified according to organ type and compared between the two arms of the study using a chi-square test. If a subject has a new site of disease, that site will be used as the organ site. If a subject has no new site of disease then the organ site will be classified as existing tumor. Two chi-square tests will be performed, one using the classification existing organ site versus other and the second using the full classification described above.

14.4.7 Overall Survival

A comparison of the overall survival for the combined demcizumab arms with control will be performed. Overall survival is defined as the number of days from randomization until death occurs. Subjects who have not experienced death by their last contact date will be censored at that time. No treatment cross-over is permitted in the study. 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 36). 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 37) to the following list of baseline covariates: baseline albumin, LDH, alkaline phosphatase, ECOG PS, and smoking status (others may be added).

14.4.8 Landmark Survival

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

14.4.9 Exploratory Endpoints

Exploratory endpoints include blood markers (see Section 11.0). These endpoints will be analyzed using the Intent-to-Treat Population. The correlation of changes in these endpoints with tumor response (best response and PFS) and extended survival past 10 months will be explored.

14.5 Termination Criteria

Randomization was terminated after 82 subjects had been randomized. All ongoing subjects will continue to be dosed until disease progression, subject withdrawal, or the Investigator withdraws subjects from the study.

14.6 Deviation Reporting

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.

15.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

By participating in this trial, the investigator(s)/institution(s) agree to permit trial-related monitoring, audits, IRB/IEC(s) review by OncoMed and its representative and regulatory inspection(s) by providing direct access to all primary source documents, such as medical records, CT scans, etc.

16.0 ETHICAL CONSIDERATIONS

This study will be conducted according to international standards of Good Clinical Practice (ICH guidance E6).

17.0 INVESTIGATOR REQUIREMENTS

17.1 Informed Consent

A sample informed consent form will be provided. OncoMed or PPD must review any proposed deviations from the sample informed consent form prior to submission to the IRB/IEC. The final IRB/IEC-approved document must be provided to OncoMed for regulatory purposes.

The informed consent document must be signed and dated by the subject or the subject's legally authorized representative before his/her participation in the study. Documentation is required in each subject's record that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative.

Signed consent forms must be kept in each subject's study file and must be available for review/verification by study monitors at any time.

17.2 Institutional Review Board/Ethics Committee Approval

This protocol, the informed consent documents, and relevant supporting information must be submitted to the IRB or IEC for review and must be approved before the study is initiated. The study will be conducted in accordance with regulatory requirements and IRB or IEC requirements.

The Principal Investigator is responsible for keeping the IRB or IEC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate. The IRB or IEC must

be updated at least once a year or in accordance with local requirements. The Principal Investigator must also inform the IRB or IEC of any significant AEs.

Investigators are required to follow their respective IRB or IEC requirements for the reporting of SAEs and written safety reports to the IRB or IEC. Investigators must immediately forward to their IRBs or IECs any written safety report or update provided by OncoMed (e.g., Investigator Brochure, safety amendment, etc.)

17.3 Study Monitoring

Site visits will be conducted on a regular basis by an authorized OncoMed representative (e.g., CRA) to inspect study data, subjects' medical records, and remote data capture (RDC) fields in accordance with current U.S. GCPs. During the site visit, the OncoMed CRA or representative will review the following:

- Completeness of subject records
- Accuracy of entries in the RDC fields
- Adherence to the protocol and to GCP
- Adherence to specifications for demcizumab storage, dispensing, and accountability

The OncoMed CRA or representative will be responsible for reviewing completed RDC fields and clarifying and resolving any data queries.

The CRA will also review regulatory study documents during site visits. The investigator and key study personnel must be available to assist the OncoMed monitor or representative during these visits.

The Principal Investigator will permit authorized representatives of OncoMed and any regulatory authority to inspect facilities and records relevant to this study.

17.4 Auditing Procedures

A representative of OncoMed may conduct an audit of the clinical research activities to ensure accordance with internal standard operating procedures (SOPs) and to evaluate compliance with the principles of GCP. Any regulatory authority may also conduct an inspection during the study or after its completion. If an inspection is requested by a regulatory authority, the investigator must inform OncoMed of this immediately.

17.5 Data Collection

The data will be reported by the site via an internet-based remote data entry capture (RDC). The RDC screens should be completed in accordance with instructions from OncoMed.

The RDC screens should be completed by examining personnel, the study coordinator, or designee. The RDC screens must be reviewed by the investigator. The investigator will ensure that all data is completely and accurately recorded on the RDC screens.

17.6 Investigational Medicinal Product Accountability

All IMP required for completion of this study will be provided by OncoMed or its agent. The recipient will acknowledge receipt of this IMP by *confirming receipt in the IWRS system*. Damaged supplies will be replaced.

Accurate records of all IMP dispensed from and returned to the pharmacy should be documented by completing the Drug Accountability Log.

Sites will destroy and document destruction on the Investigational Medicinal Product Return or Destruction Form, or return all unopened, unused, and expired vials to the drug distribution center along with a completed Investigational Drug Product Return or Destruction Form. Sites must have appropriate processes or SOPs and capabilities, in order to destroy study drug.

All IMP Accountability Forms will be provided by OncoMed. Upon agreement by OncoMed, the site may use its own IMP Accountability Log if it contains all of the information required on OncoMed's log.

17.7 Disclosure of Data and Publication

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his/her welfare.

Data generated by this study must be available for inspection upon request by representatives of any regulatory authority, auditors, OncoMed representatives, and the local IRB or IEC for each study site.

OncoMed commits to publish the study results. The manuscript will include all subjects from all sites. The Investigators will participate in writing and reviewing the manuscript. OncoMed will make the final decision on all presentations of study results and submissions of abstracts and manuscripts working in good faith with the Investigators.

17.8 Retention of Records

Regulations require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including consent forms, laboratory test results, study medication inventory records, and regulatory documents, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept for 2 years after the study is discontinued and the applicable regulatory authorities are notified. OncoMed will notify the Principal Investigator of these events.

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APPENDIX A: SCHEDULE OF ASSESSMENTS

	Screening[a]	On Study (pemetrexed, carboplatin + demcizumab/placebo)									On Study (pemetrexed maintenance)							Termination Visit	Follow-up Period
Day(s)	**-28 to -1**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**63**	**84**	**105**	**112**	**126**	**140**	**147**	**168[b]**		
Informed consent[a]	X																		
Folic acid[c]	X……..……X[c]																		
Vitamin B12[d]	X									X				X[d]					
Dexa-methasone[e]	X	X			X			X		X	X	X		X		X	X		
Pemetrexed[f,g]		X			X			X		X	X	X		X		X	X		
Demcizumab or placebo[f,g]		X			X			X		X							X[f]		
Carboplatin[f,g]		X			X			X		X									
Past medical history	X																		
Height	X																		

APPENDIX A: SCHEDULE OF ASSESSMENTS (CONT'D)

	Screening[a]	On Study (pemetrexed, carboplatin + demcizumab/placebo)									On Study (pemetrexed maintenance)							Termination Visit	Follow-up Period
Day(s)	**-28 to -1**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**63**	**84**	**105**	**112**	**126**	**140**	**147**	**168[b]**		
Physical examination[h]	X	X			X			X		X	X	X		X		X	X	X	
Weight	X	X	X	X	X	X	X	X		X	X	X		X		X	X	X	
Vital signs[i]	X	X	X	X	X	X	X	X		X	X	X		X		X	X	X[j]	
ECOG performance status	X	X	X	X	X	X	X	X		X	X	X		X		X	X	X	
CBC with differential and platelet count	X	X	X	X	X	X	X	X		X	X	X		X		X	X	X	
Chemistry[k]	X	X			X			X		X	X	X		X		X	X	X	

APPENDIX A: SCHEDULE OF ASSESSMENTS (CONT'D)

	Screening[a]	On Study (pemetrexed, carboplatin + demcizumab/placebo)									On Study (pemetrexed maintenance)							Termination Visit	Follow-up Period
Day(s)	**-28 to -1**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**63**	**84**	**105**	**112**	**126**	**140**	**147**	**168[b]**		
INR/aPTT	X																		
Serum pregnancy test[l]	X																		
Urinalysis with micro	X																	X	
MRI or CT of brain[m]	X																		
Tumor assessment[m]	X							X			X			X			X	X	
Tumor marker CEA	X							X[n]			X[n]			X[n]			X[n]	X[n]	
BNP[o]	X				X			X		X	X	X		X		X	X[b]	X	

APPENDIX A: SCHEDULE OF ASSESSMENTS (CONT'D)

	Screening[a]	On Study (pemetrexed, carboplatin + demcizumab/placebo)									On Study (pemetrexed maintenance)							Termination Visit	Follow-up Period
Day(s)	**-28 to -1**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**63**	**84**	**105**	**112**	**126**	**140**	**147**	**168[b]**		
ECG[p]	X					X			X		X		X		X		X[b]	X	
Transthoracic Doppler echocardiogram[q]	X					X			X		X		X		X		X[b]	X	
CT pulmonary angiogram (if applicable)[r]		If clinically significant pulmonary hypertension is diagnosed, perform CT pulmonary angiogram (or other appropriate study) to rule out pulmonary embolism																	
Concomitant medications		X……X																	
Adverse event evaluation[s]		X……X[s]																	

APPENDIX A: SCHEDULE OF ASSESSMENTS (CONT'D)

	Screening[a]	On Study (pemetrexed, carboplatin + demcizumab/placebo)									On Study (pemetrexed maintenance)							Termination Visit	Follow-up Period
Day(s)	**-28 to -1**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**56**	**63**	**84**	**105**	**112**	**126**	**140**	**147**	**168[b]**		
Pharmaco-kinetics[t]		X						X			X			X			X[t]	X	
Anti-demcizumab antibody[u]		X						X			X			X			X[u]	X	
Blood for biomarkers[v]		X				X												X	
Optional Pharmaco-Genomics[w]		X																	
Colonoscopy and/or upper GI endoscopy (if applicable)[x]	X																		
FFPE[y]	X																		
Survival data (with date and cause of death)[z]																			X[z]
Subsequent anti-cancer therapies[aa]																			X[aa]
Response assessment data[bb]																			X[bb]
BNP and Doppler echocardio-gram[cc]																			X[cc]

NOTES TO APPENDIX A

Unless otherwise indicated, all assessments must be performed prior to dosing for all study visits when dosing occurs.

All on-study evaluations (i.e., from Day 0 up to Termination visit) must be done within the following timeframes:

- Dosing of demcizumab or placebo within ± 2 days of the Study Day
- Laboratory evaluations within ± 3 days of the Study Day
- Tumor assessment, tumor marker CEA (if applicable), ECG, and transthoracic Doppler echocardiogram within ± 7 days of the Study Day

For subjects who only receive pemetrexed maintenance after discontinuation of carboplatin and demcizumab/placebo, every-three-week visits can be rescheduled accordingly if pemetrexed administration and associated assessments (i.e. physical examination, weight, vital signs, ECOG performance status, CBC, and chemistry) were delayed for adverse or other unforeseen events. In addition, if the timing of a protocol-mandated study visit coincides with a holiday or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly. Pemetrexed cycles may be extended from 3 to up to 4 weeks to realign assessments.

Subjects who have discontinued all study drugs and have no clinically significant ongoing related adverse events that require close follow-up have to undergo the following assessments only every 42 days (ideally synchronized with tumor assessments and tumor marker CEA, if applicable): physical examination, weight, vital signs, ECOG performance status, CBC, and chemistry.

However, the schedule for BNP assessments (every 21 days; see footnote o. for more details), for ECG and transthoracic Doppler echocardiogram (every 28 days; see footnotes p. and q. for more details), and for tumor assessment and tumor marker CEA, if applicable (every 42 days), is to be maintained.

a. Subjects must sign and date the Informed Consent Form (Appendix E) that has been approved by the IEC/IRB prior to undergoing any study-related procedures. Once the screening process has been completed, the Investigator must complete a randomization request form and submit it for approval. Once OncoMed or its representative has approved randomization, the investigator/study coordinator will use the IWRS system to randomize the subject. Subjects who are randomized will not be replaced. The IWRS system will then assign a subject number, and the subject will be officially enrolled in the study. This unique subject number will be on all electronic case report form (eCRF) pages. Study drug must be administered within 4 days from the date of randomization. Study Day 0 will be the first day of study drug administration.

b. **The frequency of assessments from Days 168 to 252 (then Days 252 to 336, and so on) is the same as shown for the 84-day time window from Days 84 to 168. Four types of assessments are exceptions to this general rule as they are eventually discontinued.**
   - **BNP: see footnote o.**
   - **ECG: see footnote p.**
   - **Doppler echocardiogram: see footnote q.**
   - **Pharmacokinetics: see footnote t.**

c. Subjects must receive oral folic acid ≥400 µg daily for at least 5 days of the 7 days preceding the first dose of pemetrexed and continue folic acid at this dose level during the full course of therapy and for 21 days after the last dose of pemetrexed.

d. Subjects must receive an IM injection of vitamin B12 1000 µg during the week preceding the first dose of pemetrexed and then every 63 days while receiving pemetrexed.

e. 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.

f. Arm 1 - carboplatin, pemetrexed plus placebo every 3 weeks for 4 cycles (i.e., last administration on Day 63), then maintenance pemetrexed once every 3 weeks beginning on Day 84 and a second course of placebo once every 3 weeks for 63 days beginning at Study Day 168
   Arm 2 - carboplatin, pemetrexed plus demcizumab every 3 weeks for 4 cycles (i.e., last administration on Day 63), then maintenance pemetrexed once every 3 weeks beginning on Day 84 and a course of placebo once every 3 weeks for 63 days beginning at Study Day 168
   Arm 3 - carboplatin, pemetrexed plus demcizumab every 3 weeks for 4 cycles (i.e., last administration on Day 63), then maintenance pemetrexed once every 3 weeks beginning on Day 84 and a second course of demcizumab once every 3 weeks for 63 days beginning at Study Day 168
   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 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.

NOTES TO APPENDIX A: CONT'D

g. Demcizumab or placebo, pemetrexed and carboplatin must be dosed as described in Section 8.0. Demcizumab or placebo is to be administered first, followed by pemetrexed and then carboplatin.

h. A full physical examination will be done at screening. Subsequently, an abbreviated physical examination will be performed at Day 0, every 3 weeks during the on-study part of the protocol and at the termination visit. The abbreviated physical examination must include respiratory rate, auscultatory examination of the heart and lungs, abdominal examination, and assessment for the presence or absence of edema and/or ascites. A more complete physical examination should be conducted when clinically indicated.

i. On days of demcizumab or placebo dosing, vital signs will be obtained before infusion (- 1 hour), 15 (±5) minutes after start of infusion, end of infusion (+ 5 minutes), and 15 (±5) minutes after end of infusion of demcizumab or placebo.
Vitals will be obtained once at the visits where demcizumab or placebo is not administered, prior to pemetrexed (and/or carboplatin) infusion, if applicable.

j. Any subject with hypertension (i.e., >150/90 mmHg) that is considered to be related to demcizumab or placebo at the time of the termination visit will continue to have BPs monitored once every 2 weeks until the BP is ≤150/90 mmHg over a 4-week period with every-2-week BP measurements.

k. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST (SGOT), ALT (SGPT), sodium

l. Serum pregnancy test (women of childbearing potential only) must be obtained within 7 days prior to randomization.

m. Perform tumor assessment at screening (Study Days -28 to -1), every 6 weeks thereafter until disease progression, and at the termination visit (unless performed within 14 days of termination or at a prior response evaluation that documented progressive disease). The schedule of every 6 weeks is to be maintained throughout the study and will not be shifted if there are dose holds.
Screening assessments should include CT scans of the chest, abdomen, and pelvis, as well as MRI of the brain. CT scan of the neck or bone scan should be performed if clinically indicated. A documented standard-of-care tumor assessment performed on or after Study Day -28 may be used for the screening assessment provided it meets protocol requirements. Alternative imaging modalities may be used as outlined in Section 10.0. Subsequent tumor assessments must include imaging of chest and abdomen, as well as all other known sites of disease. The same imaging methods used at screening must be used throughout the study. Response assessments will be performed by the investigator according to RECIST v1.1 (Appendix C).

n. If elevated at baseline

o. **BNP must be assessed on the same day prior to each dose of demcizumab/placebo**, and elevations will be managed per Section 8.1.6. After discontinuation of demcizumab or placebo (either as scheduled per protocol or unscheduled for other reasons), BNP assessments are continued every 21 days for another 105 days (5 assessments total). For example, if the last scheduled demcizumab or placebo dose is given on Day 231, a total of 5 more BNP assessments will occur on Days 252, 273, 294, 315 and 336. However, should the BNP result not meet eligibility criteria at the last assessment 105 days after the last demcizumab or placebo dose, BNP assessments have to be continued every 21 days until two consecutive assessments meet eligibility criteria or the termination visit has occurred.

p. A 12-lead ECG must include assessment of the PR interval, QRS duration, and QTc interval and must be done every 28 days. After discontinuation of demcizumab or placebo (either as scheduled per protocol or unscheduled for other reasons), ECG assessments are continued every 28 days for ≥105 days. For example, if the last scheduled demcizumab or placebo dose is given on Day 231, a total of 4 more ECG assessments will occur on Days 252, 280, 308 and 336. Clinically significant ECG abnormalities at the last assessment ≥105 days (depending on timing of assessments) after the last demcizumab or placebo dose should be addressed according to standard of care. ECG does not have to be repeated at the termination visit if it was performed within 14 days of the termination visit.

q. A Doppler echocardiogram with left ventricular ejection fraction and peak tricuspid velocity determination, if measurable, must be done every 28 days. After discontinuation of demcizumab or placebo (either as scheduled per protocol or unscheduled for other reasons), Doppler echocardiogram assessments are continued every 28 days for ≥105 days. For example, if the last scheduled demcizumab or placebo dose is given on Day 231, a total of 4 more ECG and Doppler echocardiogram assessments will occur on Days 252, 280, 308 and 336. However, should results of the Doppler echocardiogram not meet eligibility criteria at the last assessment ≥105 days (depending on timing of assessments) after the last demcizumab or placebo dose, assessments have to be continued every 28 days until two consecutive Doppler echocardiograms meet eligibility criteria or the termination visit has occurred. Doppler echocardiogram does not have to be repeated at the termination visit if it was performed within 14 days of the termination visit.

r. A CT pulmonary angiogram (CTPA) should be performed if clinically significant pulmonary hypertension is diagnosed (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) to determine if pulmonary embolism might be the cause of the pulmonary hypertension. An MR angiogram or VQ scan may be performed instead per local or country standards or if the subject has a contrast allergy.

NOTES TO APPENDIX A: CONT'D

s. To be collected from randomization until 30 days after the termination visit.

t. Plasma samples for PK analysis will be obtained prior to the demcizumab/placebo infusion, if applicable, on Days 0, 42, 84, 126, 168, 210, 252, 294 and 336, and at the end of the demcizumab/placebo infusion (prior to the chemotherapy infusion, if applicable) on Days 0, 42, 168 and 210, and at the termination visit. Instructions for the collection handling, storage, and shipment of these samples are provided in the Study Reference Binder.

u. Serum samples for immunogenicity will be obtained at baseline, every 6 weeks (prior to the demcizumab or placebo infusion, if applicable) during the study, and at the termination visit. Instructions for the collection, handling, storage, and shipment are provided in the Study Reference Binder.

v. A total of 9 mL of blood will be drawn for biomarkers on Days 0 and 28, and at the termination visit, unless one has been obtained during the prior 14 days for subjects continuing on demcizumab/placebo to evaluate changes in plasma proteins (4 mL; e.g., VEGF, βFGF, SDF1, PLGF, TNFα, MCP1, etc.), and Notch-related gene expression of mRNA (5 mL) as described in Section 11.0. Instructions for the collection, handling, storage, and shipment are provided in the Study Reference Binder.

w. For subjects who sign the optional Pharmacogenomics Informed Consent only, a blood sample (10 mL) will be collected at Day 0 (where local regulations permit). Analysis of genes relevant to Notch/DLL4 target or pathway genes may be performed (e.g., FBW7 and PTEN). Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder

x. Colonoscopy and/or upper gastrointestinal endoscopy must be performed in subjects with symptoms suggestive of possible gastrointestinal involvement to rule out gastrointestinal involvement.

y. If available, archival FFPE tumor tissue (from either the primary tumor, locoregional disease or a metastatic site) obtained by core biopsy or surgical resection will be collected. Analysis of candidate genes and/or proteins relevant to the Notch pathway may be performed (e.g., DLL4, Notch1, Hey 1, FBW7, etc.). Archived FFPE specimens may be obtained during screening or post-screening, as long as the trial is active. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder.

z. Once a subject has completed the termination visit, overall survival follow-up will be performed every three months ± 1 week for up to 5 years to determine the subject's status and ultimately the date and cause of death. Follow-up may be conducted through telephone calls, review of medical records, and/or clinic visits. In addition, the site may check public data sources to get this information, if needed (e.g., obituaries).

aa. Subsequent anti-cancer therapies, including systemic therapies, surgery (resection of metastatic disease), and radiation therapy will be collected through telephone calls, review of medical records, and/or clinic visits on the same schedule as for survival data (see note z.).

bb. Response assessment data (i.e., progressive disease or no progression of disease) will continue to be collected (based on standard-of-care radiographs) on subjects who have not progressed at the time of the termination visit. For these subjects, copies of the standard-of-care radiographs may be provided to the Sponsor in a de-identified manner. These data and radiographs will continue to be collected until the subject starts new anti-cancer treatment or develops progressive disease, whichever occurs first.

cc. If a subject has a BNP of ≥400 pg/mL and/or a diagnosis of pulmonary hypertension or heart failure at the time of the termination visit, all subsequent standard-of-care BNP data until the value is <200 pg/mL and all subsequent standard-of-care LVEF and PTV values until they normalize will be collected and entered into the database.

APPENDIX B: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX C: RECIST CRITERIA VERSION 1.1

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

ELIGIBILITY

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

Measurable Disease – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable Lesions – lesions that can be accurately measured in at least one dimension with the minimum size of:

- 10 mm by CT scan or MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
- 15 mm for nodal disease in short axis
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)
- Malignant lymph node: 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up only the short axis is to be followed.

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

Special Considerations Regarding Lesion Measurability: Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

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

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Measurement of Lesions

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and at each subsequent response assessment. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

CT is currently the best currently available and reproducible method to measure target lesions selected for response assessment. The CT scan slice thickness should be 5 mm or less. When the CT scans have a slice thickness that is greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. Please see Appendix II (Ref 34) for more details concerning the use of CT scan and MRI.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Ultrasound (US) should not be used to measure tumor lesions. The utilization of endoscopy and laparoscopy for objective tumor evaluations not advised.

FDG-PET can be used to determine a new lesion if the lesion was absent at baseline on FDG PET

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete response when all lesions have disappeared.

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

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

All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline.

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

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added to the sum.

If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded at 0 mm.

If extranodal target lesions fragment, the LDs of the fragmented portions are added in the sum. If targets lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.

For a subjectwith SD or PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a subjectwith CR, reappearance of a lesion is considered PD.

New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor. If a new lesion is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed from the date of the first scan.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each or in rare case unequivocal progression should be noted at each subsequent response assessment.

RESPONSE CRITERIA

Evaluation of Target Lesions

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

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (i.e., <10 mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Unequivocal progression of the existing non-target lesions. The appearance of one or more new lesions is also considered progressive disease.

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the Investigator should prevail.

Evaluation of Overall Response

The overall response is assessed according to the following table.

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

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease

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

Confirmation

Confirmation of response is not required in this randomized study since the control arm serves as an appropriate means to interpret the data.

REPORTING OF RESULTS

- All subjects included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each subject will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) inevaluable for response: specify reason such as early death from malignant disease, early death from toxicity, tumor assessments not repeated/incomplete, or other (specify).

APPENDIX D: NEW YORK HEART ASSOCIATION CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound subjects.

APPENDIX E: SAMPLE INFORMED CONSENT

PROTOCOL 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

Principal Investigator: _____

Before you decide whether or not to take part in this research study, it is important for you to understand the purpose of the study, what risks may be involved, and what is expected of you during the study. If you have any questions that are not answered or if there are words that you do not understand in this consent form, a member of the research team will give you further information. Once you understand the purpose of this study, and if you decide to volunteer to participate in the study, you will be asked to sign this consent form.

You are being asked to participate in this research study because you have been diagnosed with advanced non-squamous non-small cell lung cancer that is no longer operable.

PURPOSE AND BACKGROUND

Current cancer therapies often produce an initial reduction in tumor size but may not have long-term benefits. One possible explanation for this is the presence of a specific type of cancer cell known as a cancer stem cell. Cancer stem cells represent a small part of the tumor but are believed to be responsible for much of the growth and spread of the cancer. Cancer stem cells may also be more resistant to traditional types of therapy, such as chemotherapy and radiation therapy.

The purpose of this study is to test the efficacy and safety of a new experimental drug, demcizumab, when given in combination with carboplatin and pemetrexed. To evaluate the efficacy of demcizumab, demcizumab will be compared to placebo (looks like demcizumab, but does not contain any medication). The administration of carboplatin and pemetrexed is a standard treatment for patients with non-squamous non-small cell lung cancer. You will also be given 2 vitamins (folic acid and vitamin B12) and 1 corticosteroid (dexamethasone) to reduce the adverse effects of pemetrexed.

Demcizumab is a humanized monoclonal antibody and was developed to target cancer stem cells. Demcizumab may block the growth of cancer stem cells and the remaining cancer cells, and it may also prevent the growth of new blood vessels that tumors need to grow and spread. Demcizumab, used in this study, is experimental. That means that the United States Food and Drug Admininstration (FDA) has not approved it for use by the general public. This study is sponsored by OncoMed Pharmaceuticals, which is referred to as OncoMed or the Sponsor in this consent form.

WHAT IS EXPECTED FROM YOU?

When deciding whether to participate, consider whether you are able and willing:

- To follow the study rules
- To commit the time required to keep appointments
- To tell the study doctor truthfully about your complete medical history
- To report any new problems, illnesses, or changes in medication during the study

PROCEDURES

At least 201 patients will be enrolled at up to approximately 60 to 90 centers in North America, Western Europe and Australia. Up to 28 days (4 weeks) prior to treatment you will undergo testing to determine your eligibility to take part in this study, and then, if enrolled in the study, you will receive intravenous (in the vein) infusions of demcizumab (or placebo), carboplatin, and pemetrexed administered on the same day, every 21 days for 4 cycles, or until it has been shown that your cancer has gotten worse. If your physician decides to delay treatment with one of the agents due to side effects, the other agents may still be administered as scheduled. After 4 cycles, if you have stable or improved disease, you will continue to receive pemetrexed once every 21 days as maintenance therapy. After 8 cycles, if you have stable or improved disease, you will receive demcizumab (or placebo), every 21 days for 4 more cycles. You will undergo assessments every 6 weeks to determine the status of your disease.

In addition to routine testing of blood and urine (for complete blood counts with differential and platelets; coagulation studies to determine how quickly your blood is clotting; serum chemistries; B-type natriuretic peptide [BNP], which indicate how well your heart is working; creatinine clearance to measure your kidney function; and urinalysis), special tests will be performed during the study at specific time points listed below. The special tests include the following:

- Tumor markers: These are substances that can be detected in higher than normal amounts in blood, urine, or body tissues for certain types of cancer. The tumor marker level may indicate the extent of the cancer in your body and may show how you are responding to treatment. For this study, only blood samples will be taken to check for tumor markers. The tumor marker for non-small cell lung cancer is CEA. If your baseline CEA tumor marker is not elevated, the test will not be repeated during the study. If your baseline CEA is elevated at baseline, the test will be repeated every 6 weeks.

- Antibodies to demcizumab: Antibodies are proteins produced by your body's immune system in response to a foreign substance. In some cases, the development of antibodies to a treatment will not have any impact on the effectiveness of the treatment. In other cases, the development of antibodies to a treatment can cause the treatment to be ineffective. Blood will be drawn every 6 weeks while you are receiving study drugs (demcizumab or placebo, or carboplatin or pemetrexed) and at the termination visit to determine if you are developing antibodies to demcizumab. Additional testing may also

be done to provide information on the response seen in the demcizumab test. Various experiments would be performed on the samples taken from you for antibodies to demcizumab testing. These experiments will determine the identity and obtain more detailed information on the anti-drug antibody response.

- Pharmacokinetic Analysis: Blood samples will be obtained prior to your demcizumab (or placebo) infusion on Study Days 0, 42, 84, 126, 168, 210, 252, 294 and 336, and at the end of infusion on Study Days 0, 42, 168 and 210, and at your termination visit, to determine how the demcizumab is distributed and eliminated from your body.

- Biomarkers: On Study Days 0 and 28, and at your termination visit, blood samples will be obtained to assess whether the demcizumab is producing desired changes to the genes and proteins related to your cancer. In addition, archival tumor tissue sections (formalin-fixed paraffin-embedded, FFPE) will be collected any time after enrollment, if available, for gene and protein testing of biomarkers related to your cancer. No additional procedures or surgery will be performed to obtain these archival tumor tissue sections. If you agree to have DNA testing on your FFPE tissue, you will sign a separate consent. DNA testing of your tumor may help to identify biomarkers that could be used in the future to predict which patients are more likely to respond to demcizumab, carboplatin and pemetrexed treatment.

In addition, you will have an electrocardiogram (ECG) and Doppler echocardiogram performed during screening, then every 28 days on study (up to Study Day 336, assuming you receive all doses of demcizumab/placebo) and at your termination visit. Your Doppler echocardiograms may be sent to a cardiologist at another hospital who may perform a central read on some of the Doppler echocardiograms in this study. Finally, you will have imaging of your brain (magnetic resonance imaging [MRI] or computerized tomography [CT]) at baseline, and CT scans and/or other radiographs performed at baseline, then every 6 weeks, and at your termination visit, to assess the status of your tumor. A CT pulmonary angiogram (CTPA; or MR angiogram or VQ scan) may be performed if you are diagnosed with pulmonary hypertension to see if you have a pulmonary embolism.

SCREENING

If you volunteer to be in this study and you sign this informed consent form, you will be screened within 28 days before study entry to make sure that you are a suitable candidate. No study-related tests will be performed prior to signing this informed consent form. Your doctor will conduct a review of your physical health and medical history, including other cancer treatments that you have had and a review of any medications you are or have been taking. In addition, a physical examination including height and weight will be performed, and vital signs including your pulse, blood pressure, breathing rate and temperature will be measured. Blood and urine samples will be collected for routine testing, including BNP. Blood will also be drawn for testing of the tumor marker CEA. Approximately 3 tablespoons of blood will be taken at this

visit. You will also have an ECG, Doppler echocardiogram, and either a CT scan or MRI of your chest, abdomen, pelvis, and head. Finally, if your tumor involves your esophagus, stomach, or intestinal tract or if you have symptoms that suggest that your tumor may involve these areas, you will also have a colonoscopy and/or upper gastrointestinal endoscopy to ensure that your tumor does not currently involve your gastrointestinal tract. If you are a female of childbearing potential, you will have a serum pregnancy test within 7 days prior to randomization (time when you are assigned a treatment arm), to ensure that you are not pregnant at the start of the study.

TREATMENT PHASE

Demcizumab (or Placebo)

Once your doctor has evaluated the results of your screening tests to ensure that you meet the criteria for the study and are eligible to participate, you will be randomized in the study and assigned to a treatment arm.

You will receive 5 mg/kg demcizumab or placebo as shown in the treatment arms, below. A placebo looks like the demcizumab, but does not contain any medication. The demcizumab or placebo will be administered intravenously (in the vein) over 30 minutes, every 3 weeks for 63 days, starting on Day 0 and again starting on Day 168. With each infusion, your vital signs will be obtained at least four times: before the infusion; 15 minutes after the start of the infusion, at the end of the infusion, and 15 minutes after the end of the infusion.

You will be randomly (by chance) assigned to one of the three treatment arms:

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

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

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

You will have an equal chance of being assigned to Arm 1, Arm 2 or Arm 3. Neither you nor your doctor will know which treatment arm you have been assigned to or whether you are receiving demcizumab or placebo.

Pemetrexed

Pemetrexed will be administered at a dose of 500 mg/m^2 as an intravenous infusion over ≥10 minutes on the first day of every 21-day cycle for 4 cycles, after the administration of demcizumab or placebo. Pemetrexed may be given for 4 cycles unless you have side effects or disease progression that necessitates stopping the drug. After 4 cycles, if you have stable or improved disease, you will continue to receive pemetrexed once every 21 days as maintenance therapy until your tumor progresses.

In order to reduce gastrointestinal and hematologic side effects, you will take folic acid of ≥400 µg daily for at least 5 of the 7 days before the first dose of pemetrexed is administered and you will continue to take ≥400 µg of daily folic acid throughout the treatment period and for the first 21 days after the last dose of pemetrexed. You will also receive an intramuscular injection of vitamin B12 at a dose of 1000 µg during the week before the first dose of pemetrexed and every 63 days while you are being treated with pemetrexed (on Days 63, 126, 189, etc.).

In order to reduce the occurrence of skin rashes, you will receive dexamethasone, 4 mg orally twice a day on the day before, the day of, and the day after pemetrexed administration, unless your physician determines that this is not right for you.

Carboplatin

Carboplatin will be administered as an intravenous infusion over 15–60 minutes on Day 1 of every 21-day cycle for 4 cycles, after the administration of demcizumab and pemetrexed. The dose will depend on several factors including your kidney function as determined by the creatinine clearance test and your serum creatinine level. Carboplatin may be given for 4 cycles unless you have side effects or disease progression that necessitates stopping the drug. Your physician may prescribe medication to prevent nausea and vomiting from the administration of pemetrexed and carboplatin therapy.

If you develop side effects during this time period, your physician may decide to hold or reduce the carboplatin and/or pemetrexed. If this occurs, the demcizumab or placebo may still be administered as scheduled.

Study Day 0: The following assessments will be done prior to the infusion of demcizumab or placebo, carboplatin, and pemetrexed: abbreviated physical examination including weight; review of medications you are taking, including any changes in medication since the screening visit; changes in your medical status; and vital signs. Approximately 4 tablespoons of blood will be drawn for routine tests, antibody testing, pharmacokinetic testing (before and after your infusion) and biomarkers.

If you agree to the optional pharmacogenomics testing, you will sign the optional Pharmacogenomics Informed Consent, and a blood sample will be collected.

Study drug will be administered and you will be monitored for at least 15 minutes after the demcizumab (or placebo) has been stopped. Pemetrexed will then be administered, followed by carboplatin.

Study Days 7, 14, 21, 28, 35, and 42: Demcizumab or placebo, carboplatin, and pemetrexed will be given on Study Days 21and 42 only. The following assessments will be obtained weekly: weight; review of the medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs. An abbreviated physical examination will be performed on the days that you receive demcizumab or placebo.

Blood will be taken weekly for routine testing (including BNP on Day 21 and Day 42). At Day 42 only, blood will also be obtained to test for pharmacokinetic testing and antibodies to demcizumab, and blood will be taken for testing tumor markers (if your CEA was elevated at your screening visit). On Day 28, blood will also be obtained for biomarkers. Approximately 3 tablespoons of blood will be drawn on Study Days 7, 14, 21, 28, 35, and 42.

On Day 28, an ECG and Doppler echocardiogram will be done.

In addition, on Day 42, you will undergo a CT scan or MRI of the chest, abdomen, and other parts of your body, if your cancer has spread there, to assess whether your cancer has improved, progressed, or is stable. If the CT scan or MRI shows that you have stable or improved disease, you may continue to receive demcizumab/placebo, carboplatin and pemetrexed.

If the CT scan or MRI shows disease progression, you will be taken off the study and will undergo assessments listed under **Termination Visit**.

Study Day 56: The following assessments will be obtained: changes in your medical status or new health problems since the previous study visit.

An ECG and Doppler echocardiogram will be done.

Study Day 63: Demcizumab or placebo, carboplatin, and pemetrexed will be given. The following assessments will be obtained prior to the infusion of drug: weight; review of the medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs. An abbreviated physical examination will be performed.

Blood, approximately 3 tablespoons, will be taken for routine testing (including BNP).

Study Day 84: Pemetrexed will be given. The following assessments will be obtained: weight; review of the medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs. An abbreviated physical examination will be performed on the day that you receive pemetrexed.

Blood will be taken for routine testing (including BNP). Blood will also be obtained for testing for antibody formation to demcizumab and for pharmacokinetic testing, and blood will be taken for testing tumor markers (if your CEA was elevated at your screening visit). Approximately 3 tablespoons of blood will be drawn.

An ECG and Doppler echocardiogram will be done.

You will undergo a CT scan or MRI of the chest, abdomen, and other parts of your body, if your cancer has spread there, to assess whether your cancer has improved, progressed, or is stable. If the CT scan or MRI shows that you have stable or improved disease, you may continue to receive demcizumab/placebo, carboplatin and pemetrexed.

If the CT scan or MRI shows disease progression, you will be taken off the study and will undergo assessments listed under **Termination Visit**.

Study Day 105: The following assessments will be obtained prior to the infusion of pemetrexed: abbreviated physical examination including weight; review of the medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs.

Approximately 3 tablespoons of blood will be taken for routine testing, including BNP.

As long as your disease is stable or shows a response, you may continue to receive pemetrexed every 3 weeks. You will undergo the tests listed for Study Day 105 during each of these 3-week cycles. You will receive intramuscular injection of vitamin B12 at a dose of 1000 μg every 63 days while receiving pemetrexed. In addition, every 6 weeks you will undergo a CT scan or MRI of the chest, abdomen and other parts of your body, if your cancer has spread there, to assess whether your cancer has improved, progressed, or is stable.

Every 6 weeks blood will be taken for antibodies to demcizumab, and blood will be obtained for tumor markers, if applicable. You will also have an ECG and a Doppler echocardiogram every 4 weeks.

Starting on Day 168, you will receive demcizumab or placebo every 3 weeks for four 21-day cycles. On Day 168 (before and after your infusion), Day 210 (before and after your infusion) and Days 252, 294 and 336 (before infusion) only, blood samples will be taken for pharmacokinetic testing.

TERMINATION VISIT

When you have discontinued receiving study drugs (demcizumab or placebo, carboplatin, and pemetrexed, or pemetrexed alone), and you are no longer being followed with study assessments, including CT scans or MRIs every 6 weeks to assess whether your cancer has improved, progressed, or is stable, the following assessments will be performed: abbreviated physical exam with weight; review of medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs.

Blood samples will be obtained for routine testing (including BNP), antibody formation to demcizumab, and pharmacokinetic testing. Blood will also be obtained for biomarkers unless obtained within the previous 14 days. Blood will also be obtained for tumor marker testing if applicable and for BNP unless obtained within the previous 28 days. A urine specimen will be obtained. An ECG and a Doppler echocardiogram will be performed. A repeat CT scan or MRI of the chest, abdomen, and other parts of your body, if your cancer has spread there, will be obtained unless performed within 14 days of Termination visit.

Approximately 3 tablespoons of blood will be drawn during this visit.

FOLLOW-UP AFTER TERMINATION VISIT

If your blood pressure was too high at the Terminiation visit (greater than 150/90 mmHg), your blood pressure will be determined every 2 weeks until your blood pressure is less or equal to 150/90 mmHg for a 4-week period.

You will be contacted every 3 months for up to 5 years by the clinic study staff to check on your condition. This contact may be by telephone or medical record review. Information regarding any anti-cancer therapies that you receive will also be collected through telephone calls, review of medical records, and/or clinic visits.

In addition, if your tumor has not progressed at the time of your Termination visit, your tumor response outcome will continue to be followed until you begin receiving alternative anti-cancer treatment or your tumor progresses, whichever occurs first, and a copy of the corresponding radiographs (e.g., CT scans and/or MRIs) may be provided to OncoMed, the Sponsor of the trial. If you have a BNP ≥400 pg/mL and/or a diagnosis of pulmonary hypertension or heart failure at

the time of termination, all subsequent standard of care BNP data will be collected until the value is <200 pg/mL and all subsequent standard of care left ventricular ejection fraction (LVEF) and peak tricuspid velocity (PTV) values will be collected until they normalize. LVEF and PTV are tests that provide information on how your heart is functioning.

POSSIBLE RISKS AND DISCOMFORTS

Demcizumab

The following are the side effects that were observed in >10% (common) and 5-10% (less common) of the 55 patients treated in the initial **single-agent study** of demcizumab and were considered to be possibly related to demcizumab.

Common (occurred in >10% of patients who received demcizumab)

Hypertension, fatigue, anemia, diarrhea, headache, nausea, decreased protein in the blood and shortness of breath

Less Common (occurred in 5-10% of patients who received demcizumab)

Low sodium in blood, dizziness, weight loss, heart failure, shortness of breath with activity, laboratory values indicating a decrease in liver or kidney function, decreased white blood count in the blood, abdominal pain, chills, fever, insomnia and cough

The following are the side effects that were observed in >10% (common) and 5-10% (less common) of the 99 patients treated in the 4 studies of **demcizumab plus chemotherapy** and were considered to be possibly related to demcizumab.

Common (occurred in >10% of patients who received demcizumab and chemotherapy)

Fatigue, nausea, hypertension, swelling of tissue due to increased fluid, diarrhea, appetite decreased, increased BNP (suggesting possible early damage to the heart), anemia, decreased platelet count in the blood, decreased white blood count in the blood, shortness of breath, headache, increased pressure in the lungs, constipation and rash.

Less Common (occurred in 5-10% of patients who received demcizumab and chemotherapy)

Change in taste, hair loss and laboratory values indicating a decrease in liver function

The majority of the side effects observed in these studies were mild to moderate. The most common adverse event across these studies that was clearly related to demcizumab was hypertension which occurred in 14-60% of the patients. Thus, if you participate in this study, your blood pressure will be checked frequently and, if necessary, you will be treated with medication(s) to lower your blood pressure. If your increased blood pressure is not controlled by medications, administration of demcizumab will be discontinued.

In addition, in these studies, 7 patients developed serious bleeding in the gastrointestinal tract. Two patients died as a result of this bleeding. Because of that, you will not be treated in this study if you have tumor in one or more locations that carries an increased risk for bleeding. If you participate in the study, your hemoglobin (a measurement of the amount of red blood cells) will be tested regularly. If your hemoglobin decreases, your physician will look carefully for the reason. If you develop active significant bleeding, administration of demcizumab will be discontinued.

One patient in the single-agent study died as a result of complications relating to a tumor within the brain. As a result, if you choose to participate in this study, prior to treatment you will have a scan of the brain to ensure that there is no tumor within the brain. Patients who have a tumor within the brain will not be able to participate in the study.

Finally, approximately 40% of patients treated in these trials developed rises in a laboratory test (BNP) suggesting possible early damage to their heart. In addition, approximately 5-10% of the patients had symptoms of heart failure (such as shortness of breath and/or extra fluid in their legs). These patients typically improved after discontinuation of demcizumab and treatment with medications to reduce their symptoms. In addtition, the heart failure typically developed in patients who received demcizumab for at least 3 months. Also, an increase in the blood pressure in the lungs which can also result in heart failure has been observed in some patients that were typically treated for more than than 3 months. As a result, demcizumab will not be given on an ongoing basis in this study. Instead, a shortened regimen of 4 doses over 63 days will be administered either once or twice during your time on study. Approximately 50 patients have received this type of shortened treatment schedule, and none have developed serious heart failure or increased blood pressure in the lungs. However, it is anticipated that heart failure and /or increased blood pressure in the lungs will likely still occur in some patients receiving this shortened duration of treatment with demcizumab. Finally, no patients have been previously treated with a 2nd 63-day course of demcizumab that some patients will be receiving in this study, so the risks of this approach are unknown.

You will not be treated in this study if you have an elevated BNP value, evidence of heart failure or evidence of disease in the vessels in your heart, or have a significant decrease in the amount of blood your heart is pumping on Doppler echocardiogram. Your heart and lung function will be watched closely while you are on study using blood tests and echocardiograms. If these side effects are noted, you will be referred to a heart specialist who may be able to treat the side effects with drugs. If further increases in your BNP occur or the amount of blood your heart is pumping declines further, your demcizumab therapy will be discontinued.

As with all antibody treatments, there is the possibility of an allergic reaction, such as fever, chills, rash, and/or hives associated with the infusion of demcizumab. Rarely, a severe or serious allergic reaction can occur during or following the administration of an antibody.

Not enough patients have yet been treated with demcizumab to fully understand the side effects that may be associated with this antibody.

The following side effects have been observed in other drugs that have an anti-angiogenic effect (drugs that prevent the growth of new blood vessels that tumors need to grow and spread) and in other drugs that may inhibit the growth of cancer stem cells. It is not known if the administration of demcizumab will result in any of these findings:

- Gastrointestinal perforation sometimes associated with intra-abdominal abscess
- Diarrhea, weight loss, constipation, vomiting, abdominal pain, nausea, and fever
- Wound healing complications
- Hemorrhage including minor bleeding events such as nose bleeds or more serious, sometimes fatal bleeding events
- Arterial or venous thromboembolic events, including cerebral (brain) infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), angina, and other sometimes fatal events
- Hypertension including episodes of severe increased blood pressure
- Neutropenia and/or infection
- Proteinuria (loss of protein through your kidneys)
- Congestive heart failure
- Diarrhea
- Rashes
- Somnolence (sleepiness)
- Fatigue
- Prolonged QT interval (irregular heart rhythm)

Pemetrexed: The following side effects have been reported in >10% of patients receiving pemetrexed:

- Low blood counts. Your white and red blood cells, neutrophils and platelets may decrease. This may put you at an increased risk for infection, anemia, and/or bleeding
- Decreased kidney function
- Fatigue
- Nausea
- Sensory neuropathy. Neuropathy (nerve damage). You may feel weakness, pain, numbness, and/or a tingling sensation especially in your fingers and toes
- Taste disturbance
- Rash, peeling of the skin, hives
- Increases in liver enzymes

Carboplatin: The following side effects have been reported in >10% of patients receiving carboplatin:

- Low blood counts. Your white and red blood cells, neutrophils, and platelets may decrease. This may put you at an increased risk for infection, anemia, and/or bleeding.
- Infection
- Bleeding
- Nausea
- Vomiting
- Peripheral neuropathy
- Hearing loss
- Central neurologic toxicity
- Decreased kidney function
- Elevation of liver function tests
- Electrolyte imbalances
- Pain
- Weakness
- Cardiovascular abnormalities
- Respiratory problems
- Mouth and lip sores and sore throat
- Allergic reaction such as hives, redness and itching
- Serious allergic reactions such as anaphylaxis
- Hair loss

Other less frequent adverse events occur following the administration of carboplatin and pemetrexed.

Infusions

Demcizumab or placebo, carboplatin and pemetrexed will be given as intravenous infusions. There may be minor discomfort from the needle in your arm. Bruising, swelling and, in rare instances, infection and blood clot may occur at the infusion site.

Blood Draws

During the course of this study, your blood will be drawn for laboratory tests (3-4 tablespoons will be collected at each blood draw). The risks of drawing blood include some discomfort from

the needle in your arm, bruising, swelling at the needle site and, in rare instances, infection or fainting.

You will also be informed of any new significant side effects that develop during the course of this research study, or others regarding the use of demcizumab.

Radiation exposure

Risk relevant to the radiation exposure due to the following procedures: Radiographic evaluation: Conventional CT, Spiral CT, or MRI of the chest, abdomen, and pelvis performed in screening, the same radiographic technique of each region must be used consistently throughout the study. Radiographic evaluation: Conventional CT, Spiral CT, or MRI of the head performed in screening.

PREGNANCY

There is a very high risk that demcizumab may be harmful to an unborn baby (embryo or fetus) or newborn child.

Therefore, women who are pregnant or breastfeeding may not participate in this study. Women must have a negative pregnancy test before beginning the study. It is important that both men and women take steps to prevent pregnancy during this study through the use of adequate contraception (for example, a barrier or hormone method or abstinence) prior to study entry and for the duration of the study until 6 months after the last dose of demcizumab.

If you become pregnant or suspect that you are pregnant, or if your partner becomes pregnant or suspects that she is pregnant during the study or within 6 months after the last dose of demcizumab, you must notify the study investigator immediately. If you become pregnant, you will be taken off of treatment and will undergo assessments listed under the Termination Visit section of this document, except for the radiographic studies, which will not be performed. If your partner becomes pregnant, you will remain on the study. If either you or your partner becomes pregnant during the study or within 3 months after the last dose of demcizumab, you and/or your partner will be followed through the first well-baby visit or longer if any abnormality is present.

POTENTIAL BENEFITS

There is no guarantee that there will be any direct benefit to you if you take part in this research study. The treatments you receive may be harmful. It is possible that the information learned from this study may be helpful in the future to other people with cancer.

SIGNIFICANT NEW FINDINGS

Any significant new findings regarding demcizumab that become known during the course of this research study that might reasonably affect your willingness to participate in this study, will be provided to you in a timely manner.

ALTERNATIVE TREATMENTS AND PROCEDURES

If you decide not to participate in this study, you will continue to receive medical care to which you were entitled prior to your participation in this study. Your doctor will discuss other options available to you. Your choice not to participate in this study will not affect your medical care in any way.

TERMINATION OF PATIENT PARTICIPATION

Your participation in this research study may be terminated at any time for medical reasons or because the sponsor finds it necessary to limit or terminate this clinical trial. Some reasons for termination include progression of your disease, any other illness that prevents further administration of demcizumab, unacceptable adverse events, unacceptable BNP and/or LVEF values, general or specific changes in your condition that make further treatment unacceptable in the opinion of your doctor, and protocol non-compliance.

Your doctor may decide to hold or stop the demcizumab or placebo injections at any time during the study for safety reasons.

If your doctor or the sponsor decides to withdraw you from the study, you will undergo the same assessments listed under **Termination Visit**. In addition, your doctor will discuss with you alternate therapies for your disease.

COSTS AND COMPENSATION

The cost of all "standard of care" assessments related to your participation in this study and your medical care will be billed to you and/or your insurance company. These are tests that would normally be performed in patients to evaluate their cancer. Due to the investigational nature of this research study, insurance companies or government health care programs may limit their obligation to pay for experimental treatments and their consequences. You may want to discuss this with your insurance company before agreeing to participate. The cost of all non-standard of care assessments will be paid for by OncoMed.

You will not be paid for participation in this study.

You may be reimbursed for any reasonable travel expenses (bus/train/taxi fares) incurred as a result of taking part in this study on production of a receipt.

COMPENSATION FOR RESEARCH-RELATED INJURY

If you are physically injured as a direct result of demcizumab or a study procedure properly performed under the plan for this study and it is not due to a pre-existing medical condition or underlying disease, or your failure to follow the instructions provided by your doctor or another member of the study team, OncoMed will reimburse you for the reasonable medical expenses for medically necessary treatment of that injury which are not covered by another payor, your own insurance or health care program. No other compensation is available from OncoMed if any injury occurs.

CONFIDENTIALITY

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at anytime.

HOW WILL YOUR CONFIDENTIALITY BE RESPECTED AND THE PRIVACY OF YOUR PERSONAL INFORMATION MAINTAINED?

You have the right to control the use and disclosure of your personal information. Basic personal information will be recorded including your name, contact details, gender, height, weight and racial origin, as well as information on your medical history, and clinical data collected about your participation in the study. All this information will be used for research and clinical purposes only, including without limitation the pharmacokinetic and optional DNA research described in this consent form.

The following people may also have access to these records: representatives of the FDA, other regulatory authorities, the Institutional Review Board/Independent Ethics Committee, OncoMed representatives and monitors, and OncoMed collaborators and licensees. All personnel accessing your records are required to respect your confidentiality at all times.

To ensure privacy, your name and other identifying information will not be attached to records or samples released for research purposes. Instead, you will only be identified by a code. Only the study doctor and authorized personnel will be able to connect this code to your name, by a list that will be kept securely by the study site for "[insert retention period]" years. Your date of birth (Amend the sentence to account for any country-specific rules) may also be recorded to help identify your study record. Your coded data will be forwarded to OncoMed and its service providers for activities related to the study e.g., laboratory analysis. It will be transferred into a computer database and processed to allow the results of this study to be analyzed and reported or published. If the results of the study are published, your identity will remain confidential, you will not be identified by name, picture, or by any other personally identifying information. A list of companies to whom your coded information is transferred is available from OncoMed via your study doctor.

EMEA: Under data protection law [identification of national law] your study site and OncoMed Pharmaceuticals shall be jointly responsible as 'controllers' for ensuring that your information is safeguarded. OncoMed has appointed [PPD local company name] as its 'representative' in your country to fulfill its obligations under this law.

The information that we collect from you may be transferred to, and stored at, a destination outside the European Economic Area ("EEA"). It may also be processed by staff operating outside the EEA who work for us or for our representative. By participating in the research study, you agree to this transfer, storing or processing outside of the EEA. When transferring such information to destinations outside of the EEA, we will also make sure that your information will be treated with an adequate level of protection as required under your local data protection laws.

APAC: Under data protection law [identification of national law] your study site shall be responsible for ensuring that your named personal information is safeguarded.

USA: Because of the research goals of this study, however, your study records cannot be kept completely confidential. The sponsor of this study is OncoMed Pharmaceuticals.

The study data may be transferred to other countries for processing, including countries not covered by data protection legislation similar in scope to the data protection legislation of your country, or at all. The laws of your state may provide further protection.

CANADA: Under federal data protection law, The Personal Information Protection and Electronic Documents Act (PIPEDA) and regional specific regulations, your study site shall be responsible for ensuring that your information is safeguarded.

You have the right to access, through your study doctor, all the information collected about you and, if applicable, ask for corrections. But, in order to protect the scientific integrity of the study, the treatment you received in this study needs to remain unknown (i.e., blinded) until the study data is analyzed. Recipients of your information may be in countries that do not have data protection safeguards and rights. In such case, OncoMed and its authorized representatives, and regulatory authorities, shall anyway seek to maintain confidentiality within the limits of local laws in these countries and comply with the data export requirements of your country, including any requirements to ensure an adequate level of protection.

If you should withdraw from the study, data collected prior to your withdrawal may still be processed along with other data collected as part of the study. Normally no new information will be collected for the study database unless you specifically consent to such collection. However, the law does require that any side effects you may suffer are documented and reported. To complete the study findings, your long term health status may also be recorded (unless you object). You have the right to require that any previously retained samples are destroyed.

WHAT WILL HAPPEN TO YOUR DATA?

This clinical study may only be performed by collecting and using your medical information. Data protection laws give you the right to control the use of your personal information. Therefore, by signing this form you specifically authorize your information to be checked, transferred and processed as follows:

- The authorized representatives of Oncomed, the Ethics Committee and regulatory authorities' inspectors may review your medical information by direct access to your medical records.
- Study data, including your coded medical information, may be used and shared for legitimate study and scientific purposes, including if you do not object, for future use in medical or pharmaceutical research.

☐ I agree to the use of my coded medical information for future research purposes.

Signature: _____

☐ I don´t agree to the use of my coded medical information for future research purposes.

Signature: _____

- Study data may be transferred to other countries for processing, including countries not covered by data protection legislation similar in scope to the data protection legislation of your country, or at all.

HAS THE STUDY RECEIVED MEDICAL OR ETHICAL APPROVAL?

The Ethics Committee has given this study a positive opinion.

You will be asked to review and sign a HIPAA (Health Insurance Portability and Accountability Act) Research Authorization Form requesting your authorization to collect, use, and disclose your medical information.

OR IF SITE DOES NOT HAVE OWN HIPAA FORM:

AUTHORIZATION TO USE AND DISCLOSE MY HEALTH INFORMATION

I authorize (give permission to) insert name of study site to use and disclose (share) my health information solely for the purposes of this research study and research directly related to the use of demcizumab. I understand that my health information that I am authorizing to be used and disclosed (Authorized Health Information) includes all health information about me that has been

and will be created or received by (SITE) and that is in my medical records maintained by (SITE).

I understand that I am free at any time to restrict the (SITE's) use and disclosure of my Authorized Health Information, without penalty or other consequences. However, I also understand that I may be denied participation in, or continued participation in, this research study if at any time I choose to restrict the (SITE's) use and disclosure of Authorized Health Information that is necessary for the completion of this research study.

AUTHORIZED PERSONS AND RECIPIENTS

I authorize the following person(s) and groups of persons to request, receive, and use my Authorized Health Information: representatives of the FDA, other regulatory authorities, the Institutional Review Board/Independent Ethics Committee, OncoMed representatives and monitors, and OncoMed collaborators and licensees. I authorize (SITE) to disclose my Authorized Health Information to these persons and groups of persons.

RE-DISCLOSURES TO THIRD PARTIES

I understand that once (SITE) discloses my Authorized Health Information to the recipient(s) identified in the previous section Authorized Persons and Recipients, (SITE) cannot guarantee that the recipient(s) will not re-disclose my Authorized Health Information to other persons who may not be bound by this informed consent form.

EXPIRATION DATE

My authorization (permission) to use and disclose my Authorized Health Information will continue indefinitely, but that use and sharing will only be for the purposes described in this informed consent form.

EFFECT OF MY REVOCATION OF AUTHORIZATION TO USE AND DISCLOSE AUTHORIZED HEALTH INFORMATION

I understand that my authorization for (SITE) to use and disclose my Authorized Health Information will remain in effect until I withdraw my permission by sending my written notice of revocation (withdrawal of permission) to the Privacy Office listed in the Questions section. My written revocation will be effective immediately upon (SITE's) receipt of my written notice, except that the revocation will not have any effect on any actions take by (SITE) in relying on this authorization before it received my written notice of withdrawal of permission.

QUESTIONS

If you have any question about the study and/or its procedure or safety, you may contact Dr. (Name of Investigator) at (telephone number). In the event of any injury, you may contact Dr. (name) at (telephone number). You may also call (Name) at (telephone number) for information on experimental patients' rights.

If at any time during this research study you feel that you have not been adequately informed of your rights with respect to the privacy of your health information, or you feel that the privacy of your health information has not been adequately protected, you may contact or visit (Site's) privacy office during normal working hours at (Privacy Office name) at (telephone number and address).

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

PROTOCOL M18-007: A Three 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

Your decision to participate in this study is entirely voluntary. You may refuse to participate in or withdraw from the study at any time without prejudice or loss of benefits to which you are otherwise entitled. A signed copy of this consent form will be given to you for your records and a copy will be retained by the investigator for his or her files

By signing the form below, you acknowledge that you have read the above information about this research study, and have had a chance to ask questions to help you understand your participation in this study and how your information will be used.

_____ _____

Signature of Patient or Patient's Authorized Representative **Date**

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent **Date**

_____

Printed Name of Witness*

_____ _____ _____

Signature of Witness* **Date**

*If the Principal Investigator or Institutional Review Board deems a witness signature is necessary.

APPENDIX F: PHARMACOGENOMICS INFORMED CONSENT

PROTOCOL M18-007: A Three 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

This Informed Consent Form is linked to the main ICF for the trial Master ICF version 1.0. This Informed Consent Form is only valid in addition to the main ICF described above.

WHAT IS THE PURPOSE OF THIS PART OF THE STUDY?

The cells of your body contain deoxyribonucleic acid, or DNA for short. DNA is passed down from your parents. Genes carry the DNA that determine your physical appearance such as the color of your eyes and hair. Differences in our genes help explain why we all look different. Differences in our genes may also help explain why some drugs work and are safe in some people, but not in others. Differences in our genes also help explain why some people get certain diseases, but others do not.

The sponsor would like to study the differences in people's DNA to learn more about diseases and response to drugs. This information will be used to try to develop safer and better drugs. To do this, the Sponsor would like to do DNA tests related to demcizumab and the diseases for which this drug is developed. The DNA tests are only for research. The tests are not for your medical care. All volunteers taking part in the main study are also being invited to take part in DNA research (where possible).

WHAT AM I BEING ASKED TO DO?

You are being asked to give one small blood sample (10 mL, about 2 teaspoons) at Study Day 0. Blood will be drawn from a vein using a needle. DNA will be extracted from your blood sample.

Your DNA may be tested for specific genes relevant to demcizumab, carboplatin and/or pemetrexed (the study drugs), the Notch/DLL4 pathways (the targets of demcizumab) and/or other genes related to your cancer. Only DNA research related to demcizumab, carboplatin, or pemetrexed or to the diseases for which these drugs are developed will be performed. No blood sample for DNA research will be taken from you unless you sign and date this Informed Consent Form.

In addition, if a piece of your tumor was previously collected as part of your diagnosis, you are being asked to have DNA testing performed on your tumor. DNA will be extracted to help to identify biomarkers that could be used in the future to predict which patients are more likely to respond to demcizumab, carboplatin and pemetrexed treatment. Analysis of candidate genes and/or proteins relevant to the Notch pathway may be performed (e.g., Notch1, Hey L, FBW7, etc.). No DNA research will be performed on your tumor unless you sign and date this Informed Consent Form.

The Sponsor will store the samples until there is no DNA left.

The sampes will be retained at OncoMed Pharmaceuticals, 800 Chesapeake Dr., Redwood City, California, U.S.A, 94063.You can also decide not to take part at all in DNA research. No blood sample for DNA research will be taken from you unless you sign and date this Informed Consent Form. Your decision to give, or not to give, a DNA sample will not affect the medical care that you receive from your study doctor or his/her staff. Your participation is voluntary.

HOW WILL MY IDENTITY AND RESULTS BE KEPT CONFIDENTIAL?

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you or your family against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Also, GINA does not prohibit discrimination of individuals with a genetic disorder that has been diagnosed.

The Sponsor has taken several steps to keep your identity and results confidential. These are described below.

a) Coding of your DNA Sample

Your DNA sample will not have your name or address on it. Your DNA sample will be coded with your Patient number from the main study. After the study is officially over, the Patient number will be removed from your DNA sample. Your DNA sample and results will be labeled with a new number.

b) Restricted Access to Your DNA Sample

The Sponsor will control your DNA sample. Your DNA sample will be stored in a secure room at a facility in Redwood City, CA, or other site designated by the sponsor. Only authorized staff are allowed to enter the room. Your DNA sample may be transferred to other research partners working with the Sponsor. DNA samples transferred to research partners will not contain your

Patient number. Your DNA sample will not be sold, loaned, or given to any other independent groups for their own use. Research partners working with the Sponsor are not allowed to share DNA samples with anyone else.

c) Restricted Access to Results

Your DNA results will be stored by the Sponsor both on paper and in computer records. You will not be identified by name in these records. Your results will only be labeled with a code number. This is to protect your privacy. Your results will be kept as long as necessary. The following people may see your test results:

- The Sponsor
- Research partners working with the Sponsor
- Independent Ethics Committees/Institutional Review Boards
- Regulatory authorities, like the Australian Health Authority or EMA

Unless the law requires it, your individual results will not be given to anyone who is not listed above. For example, your results will not be given to employers, insurance companies or family members. Research partners working with the Sponsor may not use or share your results without permission from the Sponsor.

DNA results from the study may be published or added to public databases. They also may be presented in public meetings. No publication or presentation will identify you by your code number or name.

d) Separate Storage of DNA Forms

Your study doctor will keep your signed DNA informed consent form, and any other DNA forms, separate from your other medical files. People who have access to your medical files (such as insurance companies) would not know that you took part in a DNA research study by looking at your medical files. You will be given a copy of your signed DNA consent form.

WHAT IF I CHANGE MY MIND LATER?

If you change your mind and decide later that you no longer want to take part in DNA research, you may ask for your DNA sample to be destroyed as long as the study is not officially over. You can stay in the main study even if you change your mind about taking part in DNA research.

WILL I GET MY DNA TEST RESULTS?

The tests will be performed in a research laboratory. Results from a research laboratory may not always be exact. They cannot be used to make a diagnosis about your health. Also, research laboratories cannot give advice on health or health risks. For these reasons, the results of your DNA tests will not be given to you or your study doctor (or his/her staff).

WHAT ARE THE BENEFITS?

You will not directly benefit from taking part in this DNA research. This research could provide information about demcizumab or the diseases for which this drug is developed. This information could help others in the future.

WHAT ARE THE RISKS?

There may be some pain or bruising from the needle stick used to draw the blood. Some people may faint when their blood is drawn. Very rarely, there may be an infection at the place where the needle went into the skin. Any problem that you have from drawing blood will be handled the same way as in the main study. Your research results cannot be used to make a diagnosis about your health.

WILL I BE PAID FOR TAKING PART OR FOR THE USE OF MY RESULTS?

You will not be paid for taking part in the DNA research part of the study. You will not be paid for any use of your DNA sample or results or for any inventions that are made from them. If you take part, you are providing your DNA sample for use by the Sponsor. The Sponsor intends to own any use of the results, treatments, or inventions that can be made from the research.

QUESTIONS

If you have any question about the study and/or its procedure or safety, you may contact Dr. (Name of Investigator) at (telephone number). In the event of any injury, you may contact Dr. (name) at (telephone number). You may also call (Name) at (telephone number) for information on experimental patients' rights.

If at any time during this research study you feel that you have not been adequately informed of your rights with respect to the privacy of your health information, or you feel that the privacy of your health information has not been adequately protected, you may contact or visit (Site's) privacy office during normal working hours at (Privacy Office name) at (telephone number and address).

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

PROTOCOL M18-007: A Three 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

Your decision to participate in this part of the study is entirely voluntary and you may choose not to participate in this part of the study without prejudice or loss of benefits to which you are otherwise entitled in the remainder of the study. A signed copy of this consent form will be given to you for your records and a copy will be retained by the investigator for his or her files.

By signing the form below, you acknowledge that you have read the above information about this research study, and have had a chance to ask questions to help you understand your participation in this study and how your information will be used.

I consent to the processing of my personal data, including any sensitive personal data, as set out above and to the transfer of such data to countries outside of the European Economic Area

☐ Yes ☐ No

I consent to provide the Optional Pharmacogenomics Specimen

☐ Yes ☐ No

I consent to allow my tumor specimen to be analyzed for DNA

☐ Yes ☐ No

_____

Printed Name of Patient or Patient's Authorized Representative

_____ _____

Signature of Patient or Patient's Authorized Representative Personally **Date**

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent Personally **Date**

_____

Printed Name of Witness*

_____ _____

Signature of Witness* Personally **Date**

*If the Principal Investigator or Institutional Review Board deems a witness signature is necessary.

APPENDIX G: PROTOCOL AMENDMENT SUMMARY OF CHANGES

AMENDMENT 1: 8 OCTOBER 2014

RATIONALE

The changes in the protocol described below are being made to comply with the request made by the FDA. Italics below and in the protocol indicate new text. Strike-through indicates text that has been removed. Additional changes were made to improve clarity.

SUMMARY OF CHANGES:

Synopsis

Previously Read:

2. NSCLC with known EGFR mutation or anaplastic lymphoma kinase (ALK) gene translocation (such as EML4-ALK)

Now Reads:

2. NSCLC with EGFR mutation or anaplastic lymphoma kinase (ALK) gene translocation (such as EML4-ALK)

The following change in Section 4.1, Study Objectives (Endpoints, Primary Endpoint) was made to improve clarity.

Section 6.2, Exclusion Criteria

Previously Read:

2. NSCLC with known EGFR mutation or anaplastic lymphoma kinase (ALK) gene translocation (such as EML4-ALK). Note: testing for these mutations is not a prerequisite to study entry.

Now Reads:

2. NSCLC with EGFR mutation or anaplastic lymphoma kinase (ALK) gene translocation (such as EML4-ALK)

    - *Negative results for these genetic aberrations must be documented in order for a subject to be eligible*.

AMENDMENT 2: 4 MARCH 2016

SUMMARY OF CHANGES AND RATIONALE

Study M18-007 has been amended for the following reasons.

1. To provide more specific information regarding the criteria that need to be met for further treatment with demcizumab/placebo starting on Day 168 (Section 3.5, Section 5.0 and Section 8.1.1).
2. To remove the requirement for mandatory FFPE tumor tissue in order to make the study available to more NSCLC subjects (Section 6.0 and Section 11.0).
    - FFPE tumor tissue, if available, must be provided for exploratory biomarker analyses.
3. To clarify that subjects with metastatic disease after initial NSCLC resection with curative intent and no adjuvant therapy are allowed to enter the study regardless of time from NSCLC resection, as metastatic disease must have been present at time of initial diagnosis but was not detected (Section 6.0).
4. To add additional eligibility criteria for albumin, prior radiation to chest wall or mediastinum, arterial aneurysms, interstitial lung disease and pneumonitis (Section 6.0).
    - Ongoing feedback from investigators of this study indicated that these additions may further enhance the safety of subject participants.
5. To base creatinine clearance calculations as it pertains to pemetrexed-related safety on the Cockcroft and Gault formula using actual body weight, as was done for pemetrexed safety data summarized in the pemetrexed prescribing information (Section 6.0 and 8.2.6).
6. To clarify the terms of ‘women of childbearing potential’ and ‘effective forms of contraception (Section 6.0).
7. To clarify and correct some aspects of demcizumab-related treatment modification and termination criteria (Section 8.1.6).
8. To specify a second approach to pemetrexed and carboplatin dose modification in which chemotherapy is delivered 3 or more days after the fixed day of demcizumab/placebo administration for chemotherapy-related or other reasons (Section 8.4 with Figure 20). This enables dose modification for chemotherapy that is more in line with what is typically done in daily practice.
9. To stop BNP, ECG and Doppler echocardiogram assessments after ≥105 days of regularly scheduled assessments after the last dose of demcizumab/placebo (depending on when discontinuation occurred), unless results for BNP and Doppler echocardiogram do not meet eligibility criteria (Sections 9.2.3 and 9.4, Appendix A).
    - It was deemed acceptable for subject safety to stop the outlined assessments at a time point when more than six half-lives of demcizumab have passed.

10. To simplify PK assessments for demcizumab and stop them after Day 336 (Section 9.6 and Appendix A).
11. To reduce the number of assessments for blood biomarkers to one on-study assessment seven days after demcizumab/placebo administration (Day 28) and remove assessments for circulating tumor cells (Section 11.0 and Appendix A).
    - This reduces the amount of blood drawn from subjects and will provide adequate information regarding blood-based pharmacodynamics biomarkers, considering that >50 subjects will have undergone more extensive blood biomarker assessments by the time this amendment is active.
12. To simplify protocol text for study visit schedule and assessments and make Appendix A the primary reference (Section 12.0).
13. To provide additional flexibility in the timing of pemetrexed administrations and associated assessments after discontinuation of carboplatin and demcizumab/placebo (Section 12.2).
14. To clarify which assessments are required in case of discontinuation of all study drugs (Section 12.2).
15. To reduce the frequency of chemistry assessments to every three weeks and of hematology assessments to every three weeks starting with Day 42 (Cycle 3 of carboplatin and paclitaxel, assuming no dosing delays; Appendix A).
    - This reduces the amount of blood drawn from subjects, is more in line with standard of care and poses no safety risk to subjects given the large clinical safety experience with pemetrexed and carboplatin.
16. To clarify and revise tables for protocol assessments to make them consistent with protocol changes (Appendix A).
17. To clarify and revise the informed consent form to make it consistent with protocol changes (Appendix E).

SUMMARY OF CHANGES:

As a result, all the corresponding sections in the table below have been updated to reflect the changes outlined above. Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the previous amendments.

Synopsis	
Section 3.2	Stage IV Non-Small Cell Lung Cancer
Section 3.3.2	Potential for Immune-Mediated Mechanism of Action for Anti-DLL4
Section 3.4.2.1	Phase 1b Efficacy Data
Section 3.4.2.2	Phase 1b Safety Data
Section 3.5	Dose Rationale
Section 4.1	Study Objectives
Section 4.2	Endpoints
Section 5.0	OVERALL STUDY DESIGN AND PLAN – DESCRIPTION
Section 6.1	Inclusion Criteria
Section 6.2	Exclusion Criteria
Section 7.0	REMOVAL OF SUBJECTS FROM ON-STUDY PART OF PROTOCOL
Section 8.1.1	Administration
Section 8.1.4	Drug Ordering, Storage, and Accountability
Section 8.1.6	Treatment Modification and Termination Criteria
Section 8.2.5	Vitamin Supplementation and Dexamethasone Administration
Section 8.2.6	Renally Impaired Subjects
Section 8.3.1	*Administration*
Section 8.4	Pemetrexed and Carboplatin Dose Modification/Treatment Delay
Section 9.1.2	Definition of Serious Adverse Event
Section 9.1.4	Serious Adverse Event Reporting Procedures
Section 9.2	Clinical Laboratory Assessments
Section 9.2.1	Hematology
Section 9.2.3	BNP Assessment
Section 9.3	Vital Signs and Other Physical Findings
Section 9.4	Cardiopulmonary Studies
Section 9.5	Immunogenicity Assessments
Section 9.6	Pharmacokinetic Assessments
Section 10.0	EFFICACY ASSESSMENTS
Section 11.0	EXPLORATORY ASSESSMENTS
Section 12.0	STUDY VISIT SCHEDULE AND ASSESSMENTS
Section 12.1	Screening
Section 12.2	Assessments for On-study Part of Protocol (Day 0 up to Termination Visit)
Section 12.3	Termination Visit
Section 12.4	Follow-up after Termination Visit
Section 14.0	STATISTICAL PLAN

Section 14.3	Treatment Exposure
Section 14.4.1	Safety Endpoints
Section 14.4.2	Immunogenicity Endpoints
Section 14.4.4	Efficacy Endpoints
Section 14.4.9	Exploratory Endpoints
Section 17.6	Investigational Medicinal Product Accountability
Section 18.0	REFERENCES
Appendix A	SCHEDULE OF ASSESSMENTS
Notes to Appendix A	
Appendix E:	SAMPLE INFORMED CONSENT
Appendix F:	PHARMACOGENOMICS INFORMED CONSENT

AMENDMENT 3: 29 NOVEMBER 2016

SUMMARY OF CHANGES AND RATIONALE

The M18-007 protocol has been amended in order to update the primary and secondary endpoints of the study, as well as, the statistical plan. The reason for this amendment is that enrollment of the full 201 subject trial is not feasible given major competition for enrollment, and the study should test an efficacy hypothesis with a smaller sample size.

Due to significant enrollment competition in the first-line metastatic non-small cell lung cancer (NSCLC) treatment setting it has become apparent that enrollment of the planned 201 subjects would take a very long time and be very cost prohibitive. The M18-007 study achieved first-patient-in in February 2015 and was planned to complete enrollment of 201 subjects by March 2016, however, as of October 2016 the study had enrolled 82 subjects. Over the course of the last 6 months the M18-007 study has enrolled between 1 and 6 subjects per month (on average 2.5 patients per month) across 40 open study sites--thus, completion of the planned enrollment of 201 subjects would take several more years. The challenge to enrollment is driven by many competing clinical trials of novel immune-oncology agents that have been initiated recently in the first-line NSCLC treatment space. This includes over 7 global Phase 3 trials with many thousands of subjects to be enrolled. These studies are directly competing with the M18-007 trial due to the overlapping eligibility criteria and the significant enthusiasm that exists for immune-oncology agents (particularly anti-PD1 and anti-PDL1 therapy) in NSCLC.

Due to the above, the sponsor (OncoMed) and our corporate partner (Celegene) have made the decision to discontinue enrollment on the M18-007 study. However, 82 subjects have been enrolled on this double-blinded Phase 2 M18-007 study. It is the feeling of OncoMed and the participating investigators that there are informative data that can be derived from this clinical trial. In this amendment, OncoMed will continue to treat and follow subjects enrolled (as per protocol) and will change the primary endpoint of the study to be more suitable for a double blinded 82 subject Phase 2 experiment. OncoMed will pool the two demcizumab experimental arms (arms 2 and 3 in the study) to compare the outcome of these subjects to the outcome of the control arm (arm 1). The primary endpoint will be changed from progression free survival to response rate. The Phase 1b data for demcizumab with carboplatin and pemetrexed chemotherapy in NSCLC suggested that the addition of demcizumab augmented response rate in these subjects. As such OncoMed feels that response rate is an acceptable and scientifically based efficacy endpoint for the M18-007 study. The statistical plan has been amended for this primary endpoint of response rate and to accommodate the smaller sample size of 82 subjects. The progression free survival endpoint has been changed from a primary to a secondary efficacy endpoint.

SUMMARY OF CHANGES:

As a result, all the corresponding sections in the table below have been updated to reflect the changes outlined above. Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the previous amendments.

Sponsor Contacts	
Synopsis	
Section 4.1	Study Objectives
Section 4.2	Endpoints
Section 5.0	OVERALL STUDY DESIGN AND PLAN – DESCRIPTION
Section 14.0	STATISTICAL PLAN
Section 14.1	Subject Populations for Analysis
Section 14.4.4	Efficacy Endpoints
Section 14.4.4.7	Overall Survival
Section 14.5	Termination Criteria
Section 18.0	REFERENCES