CLINICAL PROTOCOL

Protocol No. M18-006

Title: **YOSEMITE**: A 3-Arm Phase 2 Double-Blind Randomized StudY of Gemcitabine, Abraxane® Plus PlacebO versuS GEMcitabIne, Abraxane® plus 1 or 2 TruncatEd Courses of Demcizumab in Subjects with 1st-Line Metastatic Pancreatic Ductal Adenocarcinoma

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OncoMed Pharmaceuticals

Protocol No. M18-006

Amendment 5: 19 December 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.

Principal Investigator Date

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Institution:

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Telephone Number:

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OncoMed Pharmaceuticals, Inc.

Protocol No. M18-006

Amendment 5: 19 December 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.

Signature of Sponsor Representative **Date**

Printed Name of Sponsor Representative

SYNOPSIS

Title of Study:

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

Study Period: Approximately 12–16 months	**Development Phase:** Phase 2

Objectives:

Primary Objective:

- To compare the efficacy of Arm 1 to the pooled decizumab arms (i.e., Arm 1 to Arms 2 and 3) (See Section 5.0 for description of Treatment Arms) in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

Secondary Objectives:

- To compare the efficacy of Arm 1 to Arm 2 and Arm 1 to Arm 3 in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To compare the safety of Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To determine the rate of immunogenicity against demcizumab when combined with Abraxane® and gemcitabine in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- . To determine population pharmacokinetics of demcizumab in subjects receiving demcizumab and Abraxane® and gemcitabine in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

Exploratory Objectives:

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

Study Design:

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

Gemcitabine will be given by intravenous (IV) infusion at a dose of 1000 mg/m^2 on Days 1, 8 and 15 of each 28-day treatment cycle (or until toxicity necessitates reducing or holding a dose). Abraxane® will be administered by IV infusion at a dose of 125 mg/m^2 over 30 minutes on Days 1, 8 and 15 of each 28-day treatment cycle. Demcizumab 3.5 mg/kg or placebo will be administered by IV infusion (prior to the administration of Abraxane® and gemcitabine) once every 2 weeks for either one (1st course through Study Day 70) or two (2nd course begun on Study Day 168 and continued through Study Day 238) 70 day courses.

Randomized subjects will be treated in the following manner (See Appendix A):

Arm 1 – Abraxane® and gemcitabine plus placebo (3 cycles), Abraxane® and gemcitabine (3 cycles), Abraxane® and gemcitabine plus placebo (3 cycles) and then Abraxane® and gemcitabine until disease progression

Arm 2 - Abraxane® and gemcitabine plus demcizumab (3 cycles), Abraxane® and gemcitabine (3 cycles), Abraxane® and gemcitabine plus placebo (3 cycles) and then Abraxane® and gemcitabine until disease progression

Arm 3 - Abraxane® and gemcitabine plus demcizumab (3 cycles), Abraxane® and gemcitabine (3 cycles), Abraxane® and gemcitabine plus demcizumab (3 cycles) and then Abraxane® and gemcitabine until disease progression

Dosing of gemcitabine, Abraxane® and demcizumab or placebo must be done within ± 2 days of the Study Day listed in the protocol. If a drug cannot be given within this 2 day window, then the dose of that drug is permanently missed. Subjects will only receive their second 70 day course of placebo or demcizumab if their Day 168 BNP is ≤100 pg/mL, peak tricuspid velocity is ≤ 3.0 m/s and LVEF is ≥50% and they did not develop pulmonary hypertension or heart failure while on study. Any subject who has two consecutive B-type natriuretic (BNP) values ≥100 pg/mL or one value ≥200 pg/mL will be unblinded by the Investigator through the IWRS system. If the subject is receiving demcizumab they will be started on an ACE inhibitor or carvedilol, unless the BNP elevation occurred more than 100 days after the discontinuation of demcizumab or there is a contraindication to administering these agents and if appropriate, referred to a cardiologist. If they are not receiving demcizumab they will be cared for according to standard medical practice.

Subjects will be assessed for disease status every 8 weeks and for safety at every visit and through 30 days following the termination visit. In all three arms, subjects should remain on study until disease progression, Immunogenicity will be assessed at baseline, every 8 weeks while on study and at treatment termination. Biomarker assessment will be performed at Days 0, 21, 35, 49 and 63 and at treatment termination. Plasma sample for PK analysis to be obtained prior to the demcizumab infusion on Days 0, 14, 56, 70, 168, 182, 224 and 238, and at the end of the demcizumab infusion (prior to chemo infusion) on Days 0, 56, 70, 168, 224 and at treatment termination. If all of the study drugs are discontinued prior to disease progression, the subject should remain on study until disease progression or withdrawal of consent. Once discontinuation criteria for the study are met (disease progression, use of other anti-cancer therapy, subject or investigator decision or protocol non-compliance) 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 and other assessments as required per protocol.

Study Population:

Subjects must have histologically confirmed metastatic pancreatic ductal adenocarcinoma. In addition, subjects must measurable disease per RECIST 1.1.

Diagnosis and Main Criteria for Eligibility (for Complete Eligibility Criteria, See Section 6.0):

Inclusion Criteria:

1. Subjects must have cytologically or histologically confirmed metastatic pancreatic ductal adenocarcinoma.. Prior chemotherapy and/or radiotherapy either in the adjuvant or neoadjuvant setting or for metastatic disease is not allowed.
2. Age ≥21 years
3. ECOG performance status 0 or 1 (see Appendix C)
4. Measurable disease per RECIST v1.1 (see Appendix D)

Exclusion Criteria:

1. Subjects with a neuroendocrine tumor of the pancreas, an acinar tumor of the pancreas or a pancreatic tumor with mixed histologies.
2. Subjects receiving heparin, warfarin, factor Xa inhibitors or other similar anticoagulants. Note: Subjects may be receiving low-dose aspirin and/or non-steroidal anti-inflammatory agents.
3. 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 E).
     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.
   - History of heart failure or pulmonary hypertension
   - Received a total cumulative dose of ≥400 mg/m^2 doxorubicin
   - Grade ≥2 ventricular arrhythmia

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 3.5 mg/kg or placebo) will be administered as an intravenous infusion over at least 30 minutes once every 2 weeks for 6 doses (e.g., the last dose given on Day 70). A second course of study drug (demcizumab at 3.5 mg/kg or placebo) will be administered once every 2 weeks for 6 doses starting on Day 168 (e.g., the last dose given on Day 238) if the subject's Day 168 BNP is ≤100 pg/mL, peak tricuspid velocity is ≤3.0 m/s and LVEF is ≥50%, and the subject did not develop pulmonary hypertension or heart failure while on study.

Duration of Treatment:

Subjects should remain on study until they develop progressive disease per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1, develop unacceptable toxicity or withdrawal consent. Disease progression should be based on radiographic assessment rather than an elevation of CA 19-9. If disease progression is suspected due to an elevation in CA 19-9 an early radiographic assessment may be performed to determine if progression has occurred. If all of the study drugs are discontinued prior to disease progression, the subject should still remain on study until disease progression.

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 every 14 days, doppler echocardiogram, anti-demcizumab testing, and subject interview on an ongoing basis (as outlined in the Schedule of Assessments) from randomization through 30 days following the termination visit.
Efficacy Evaluation: Subjects will be assessed for response using RECIST criteria 1.1 at Study Day 56 and then every 8 weeks. In addition, CA 19-9 levels will be obtained at baseline and then every 8 weeks. Disease progression should be based on radiographic assessment rather than an elevation of CA 19-9. If disease progression is suspected due to an elevation in CA 19-9 an early radiographic assessment may be performed to determine if progression has occurred. Investigator-assessed response rates, duration of response, time to progression, and survival will be evaluated. In addition, an optional independent assessment of the radiographs may be performed.
Immunogenicity: Subjects will be assessed at baseline and then every 8 weeks while the subject is on study. In addition, subjects will be assessed for immunogenicity at the time of treatment termination.
Pharmacokinetics: Sparse PK sampling will be obtained on all subjects. Plasma sample for PK analysis to be obtained prior to the demcizumab infusion on Days 0, 14, 56, 70, 168, 182, 224 and 238, and at the end of the demcizumab infusion (prior to chemo infusion) on Days 0, 56, 70, 168, 224 and at treatment termination.
Biomarker Evaluation: Whole blood will be obtained for biomarker evaluations on Study Days 0, 21, 35, 49 and 63, and at treatment termination as outlined in the Schedule of Assessments. 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
aPTT	activated partial thromboplastin time
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
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
IEC	Independent Ethics Committee
IGS	Invasiveness gene signature
IMP	Investigational Medicinal Product
INR	International normalized ration
IRB	Institutional Review Board
ITT	intent-to-treat (population)
IV	intravenous
IWRS	Interactive web randomization system
kg	kilogram(s)
LD	longest diameter (of a lesion)
LDH	lactic dehydrogenase
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Term	Definition/Explanation
mg	milligram(s)
mL	milliliter(s)
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NOAEL	no observed adverse effect level
PD	progressive disease
PK	pharmacokinetic(s)
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 (OMP-21M18) 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 Disease Background

Pancreatic cancer is an aggressive malignancy that is usually unresectable at the time of diagnosis, 80%–85%. As complete resection offers the only hope of cure, 5-year survival rates are less than 10%. For patients diagnosed locally advanced or metastatic pancreatic ductal adenocarcinoma the median survival is 8–12 months. Single agent chemotherapy, including the commonly used agents gemcitabine, Abraxane®, oxaliplatin, irinotecan, leucovorin, fluorouracil, produce objective partial responses in 5-15% of subjects. More recently, gemcitabine and Abraxane® has resulted in somewhat higher response rate, time to progression and survival (Ref 1). In addition, other combinations, such as FOLFIRINOX have reported encouraging activity. However, unresectable metastatic pancreatic ductal adenocarcinoma remains and incurable disease. Consequently, there is a significant need to develop novel approaches for the treatment of unresectable and metastatic pancreatic ductal adenocarcinoma.

3.3 Nonclinical Background

Many current cancer treatments, while producing an initial reduction in tumor burden and/or a prolongation of time to progression, have not resulted in meaningful long-term benefit. A possible explanation for this observation is the presence of cancer stem cells (CSC) (Ref 2, Ref 3), which represent a subset of the tumor, but are the most tumorigenic component driving growth and metastasis and are more resistant to traditional cytotoxic therapy, including both radiotherapy (Ref 4) and chemotherapy (Ref 5), than the remaining bulk of the tumor.

Consequently, efforts have been made to isolate cancer stem cells and then identify active pathways in these cells, which could serve as targets for antibody treatment. Using this approach, the Notch pathway was identified as a potential target. There are four Notch receptors (1–4) and five ligands, including two Jagged (1 and 2) and three Delta-Like Ligands (DLLs) (1, 3, and 4). There appears to be differential binding of these ligands to specific members of the Notch family, with DLL4, for example, having a higher specificity for Notch 1 than DLL1 (Ref 6). Among the breast, colon, and lung cancers assessed at OncoMed by IHC, all but two lung cancers expressed both Notch 1 and the Notch ligand DLL4. In addition to its important role on cancer stem cells, Notch 1 is also important in the cell signaling process of the remaining nontumorigenic cancer cells. Finally, DLL4 and Notch 1 have also been shown to be essential for angiogenesis (Ref 7). Blockade of DLL4 results in tumor-associated endothelial cell hyperproliferation, coupled to a non-productive angiogenesis associated with poor tumor perfusion, regional hypoxia and an inhibition of tumor growth (Ref 8, Ref 9). Thus, inhibition of the Notch pathway could potentially produce an anti-tumor effect by 1) impacting the growth of

the cancer stem cells, 2) impacting the growth of the remaining cancer cells, and 3) dysregulating tumor angiogenesis.

Demcizumab is a humanized IgG2 monoclonal antibody directed against DLL4. Demcizumab is not anticipated to exhibit a high rate of immunogenicity. The antibody binds to DLL4 with high affinity, as measured by Biacore, the affinity of demcizumab for human DLL4 is 0.64 nM. The binding of demcizumab to DLL4 blocks its interactions with Notch receptors however, the Notch signaling pathway may still be activated by other ligands, as demcizumab is specific for DLL4.

Nonclinical mouse xenograft studies have suggested that demcizumab possess anti-tumor activity via all three of the potential mechanisms described above. In mouse xenograft models, demcizumab and the murine antibody (m21M18) that was humanized to produce demcizumab have been demonstrated to have a direct effect on cancer stem cells, reducing the frequency of this population. In these same models, demcizumab and m21M18 have been shown to also have a direct effect on the nontumorigenic cancer cells. Finally, in these models, a phage-derived antibody against DLL4 that is capable of binding to murine DLL4, but not human DLL4, has been shown to have dys-angiogenic effects coupled to an inhibition of tumor growth.

3.3.1 Activity of Anti-DLL4 in Pancreatic Cancer Xenografts

Pancreatic cancer remains a disease with a generally poor clinical prognosis and one of the most difficult malignancies to treat effectively (Ref 10). The Notch pathway has been implicated in playing a role in normal pancreatic development where active Notch signaling is required for maintaining cells in undifferentiated state (Ref 11). Activation of Notch signaling has been also been associated with drug resistance in pancreatic cancer (Ref 12). We have found that blockade of Notch signaling with anti-DLL4 is efficacious in a variety of pancreatic xenograft models (Table 1). Representative tumor growth data is shown for PN4 in Figure 1. Inhibition of DLL4-Notch signaling in the tumor stroma and vasculature was associated with hyperproliferation of endothelial cells as shown by immunofluorescence with an anti-CD31 (data not shown) as was previously shown in colon tumors. Activity in reducing cancer stem cells was observed in both the PN4 (Figure 2) as well as the PN8 and PN13 xenograft models.

Table 1: Summary of the Activity of Anti-DLL4 (Demcizumab + 21R30) in Human Pancreatic Xenografts

Tumor	Single Agent	Combination	Reduction in CSCs
PN4	+	+	+
PN8	+	+	+
PN9	+	+	
PN13	+	+	+
PN16	+	+	
PN17	+	+	
PN21	+	+	
PN23	+	-	
PN35	+	+	
PN38		-	
PN40	-	+	
PN42		+	

Anti-DLL4 were tested as a single agent and in combination with gemcitabine or gemcitabine + Abraxane® in pancreatic tumors. The activity of anti-DLL4 treatment as a single agent or in combination with gemcitabine 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 the chemotherapeutic agent(s) plus control antibody ($p < 0.05$). For PN4, PN8 and PN13 tumors, anti-DLL4 treatment resulted in a reduction cancer stem cell frequency as shown by in vivo limiting dilution analyses.

Figure 1: Inhibition of Pancreatic Tumor Growth by Anti-DLL4 as a Single Agent and in Combination with Gemcitabine

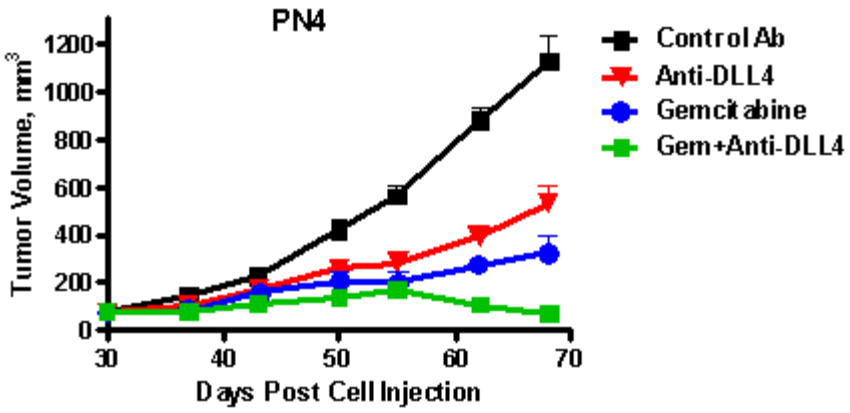
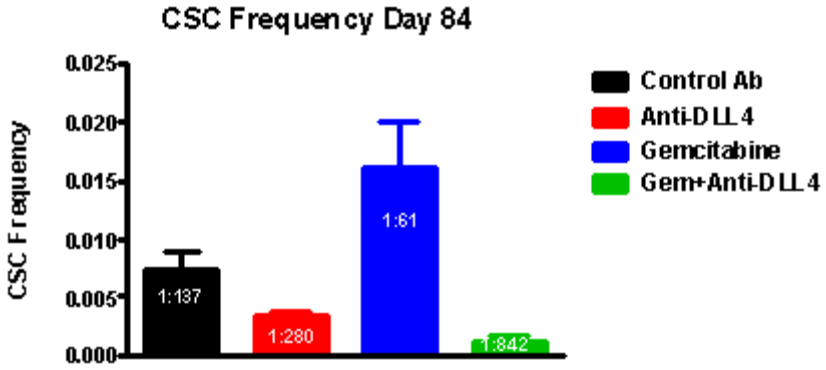


Figure 2: Reduction of Cancer Stem Cell Frequency after Treatment with Anti-DLL4



PN4 pancreatic tumors were treated with control Ab, anti-DLL4 (Demcizumab + 21R30), gemcitabine, or the combination of anti-DLL4. Following treatment, human tumor cells were isolated, and the tumorigenic cell frequency was determined by serial transplantation, in vivo limiting dilution analysis. Tumor growth frequency after 84 days of tumor growth was used to calculate the CSC frequency.

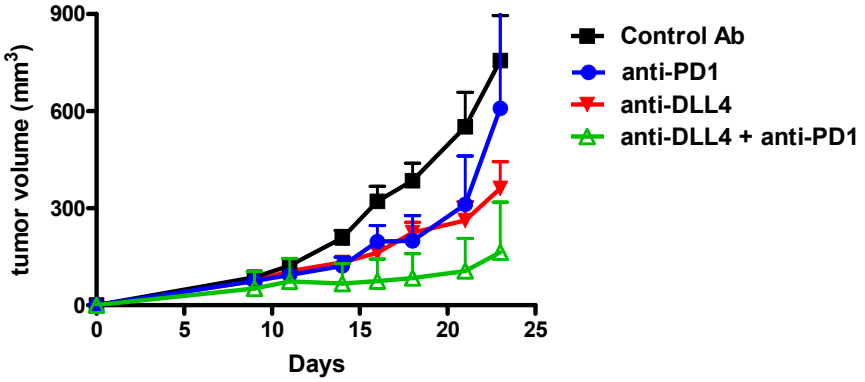
We determined that targeting DLL4-Notch signaling in both tumor and stromal/vasculature cells was required for anti-tumor efficacy (Ref 13). In addition to carrying combination studies with gemcitabine alone, we have tested anti-DLL4 in combination with gemcitabine plus Abraxane and observed combination activity in this setting as well. These data indicate that anti-DLL4 exhibits broad spectrum activity in pancreatic tumor models. Strikingly, synergy with gemcitabine or gemcitabine plus Abraxane was observed in the vast majority of the models (Table 1). The reduction in CSC frequency after anti-DLL4 treatment indicates that Notch signaling in the tumorigenic cells is required for CSC function.

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

Notch signaling is now known to play a key role in various aspects of the immune response (Ref 14). Notch signaling has been shown to upregulate PD1 expression during the immune response (Ref 15). Since PD1 functions to limit T-cell activation, inhibition of DLL4-Notch signaling might be expected to increase anti-tumor immune responses. Our previous studies were carried out using patient-derived xenografts that necessitated the use of immunocompromised mice and, thus, were not suitable for testing the effect of anti-DLL4 on the interaction of lymphocytes in the tumor microenvironment. To investigate the potential role of anti-DLL4 on the host immune response during tumor growth, we have carried out a series of experiments using murine tumors implanted in an isogenic murine host strain. An example combining anti-DLL4 and anti-PD1 is shown in Figure 5. This experiment utilized the CT26wt colon tumor model and was carried out in Balb/C mice. Anti-DLL4 reduced tumor growth as a single agent and showed additive activity in combination with anti-PD1 (Figure 3). Subsequent analyses indicated that the combination of anti-DLL4 and anti-PD1 increased the expression of

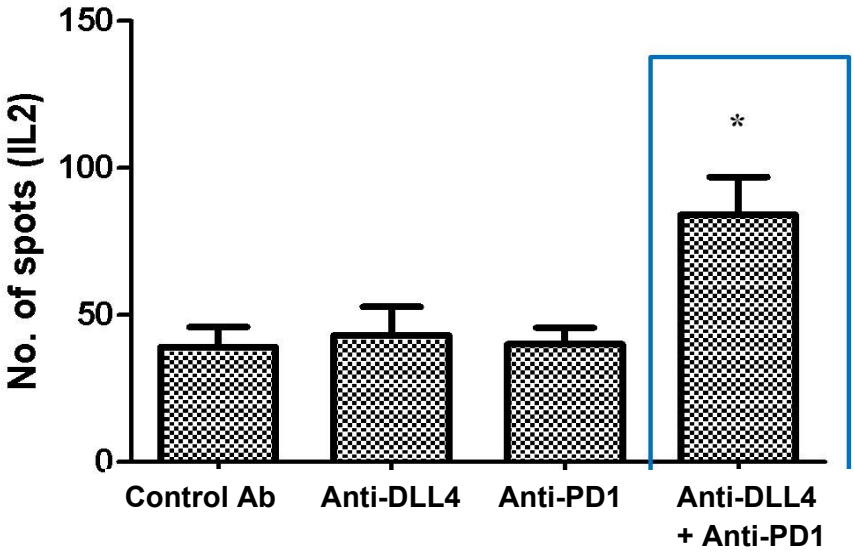
IL-2 in tumor-specific splenocytes (Figure 4). Furthermore, anti-DLL4 administration increased the fraction of memory T cells in the spleens of tumor-bearing mice (Figure 5). In addition to these results, we have observed in other experiments an increase in the cytotoxic activity of CD8+ T cells in killing tumor cells using an ex vivo assay (data not shown). Collectively, our experiments in immunocompetent animals suggest that anti-DLL4 may increase the anti-tumor immune response. Thus, in addition, to its previously characterized mechanisms of action (targeting CSCs and disrupting tumor vasculature), promotion of anti-tumor immunity may contribute to the efficacy of demcizumab treatment. This immune-mediated mechanism may be particularly important for the long-term, durable responses that have been observed in the Phase 1b clinical testing of demcizumab.

Figure 3: Activity of Anti-DLL4 in Combination with Anti-PD1 in Reducing the Growth of CT26wt Tumors in Immunocompetent Mice



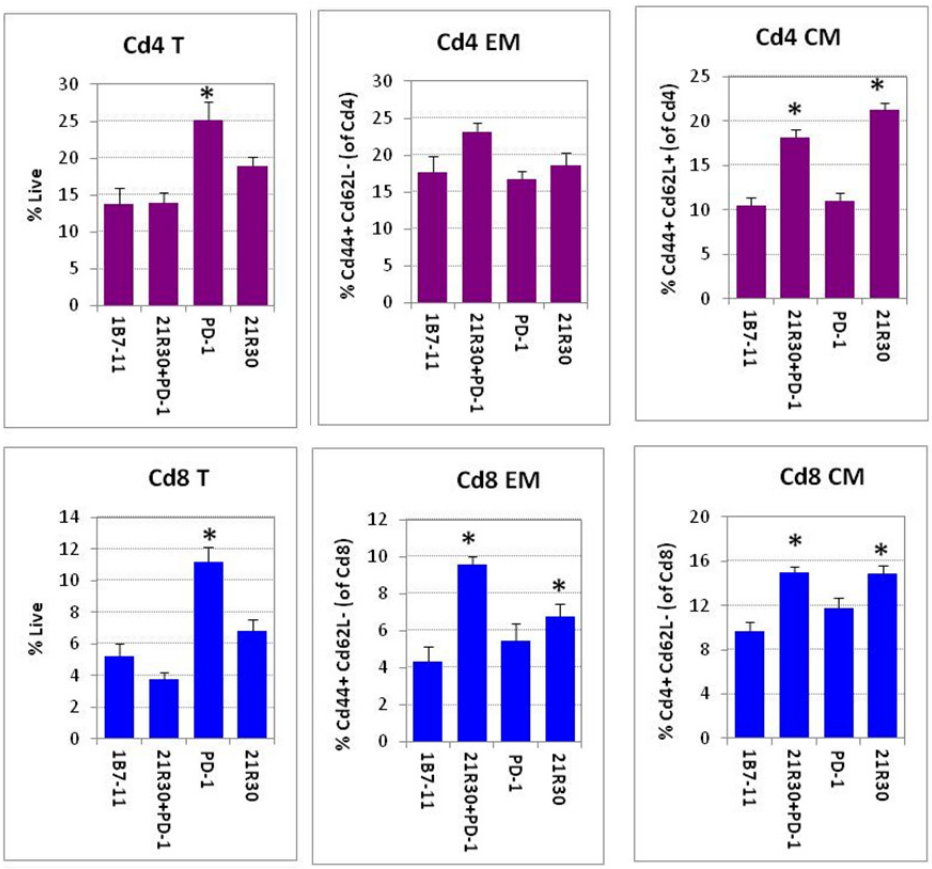
Anti-DLL4 treatment reduces tumor growth in an immune-competent mouse model. CT26wth murine colon tumors were implanted subcutaneously in Balb/C mice. Treatment was initiated on Day 7 with either control antibody, anti-PD1, anti-mDLL4 (OMP-21R30), or the combination of anti-DLL4 and anti-PD1. Anti-DLL4 inhibited tumor growth, either as a single agent or in combination with anti-PD1.

Figure 4: Increase in IL-2 Expression by Splenocytes after Treatment with Anti-DLL4 in Combination with Anti-PD1



Anti-DLL4 treatment increases IL-2 expression in combination with anti-PD1. Splenocytes from tumor-bearing mice from the four treatment groups shown in Figure 3 were analyzed for IL-2 expression by Elispot assay.

Figure 5: Anti-DLL4 Treatment Increases Memory T cells in Splenocytes of Tumor-Bearing Mice



Anti-DLL4 treatment increases memory T cells in splenocytes from tumor-bearing mice. Splenocytes from the four treatment groups shown in Figure 5 were analyzed for the total number of CD4+ or CD8+ T cells. Anti-PD1 treatment increased the percentages of both CD4+ and CD8+ T cells. Anti-DLL4 treatment increased the effector memory (EM) and central memory (CM) T cell populations in the CD+ subset and the CM population in CD4+ T cells. 1B7-11 = negative control antibody. 21R30 = anti-mDLL4.

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 demcizumab. 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 Abraxane® plus demcizumab in subjects with locally advanced or metastatic pancreatic ductal adenocarcinoma. 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 anti-hypertensives 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 (M18-004), 17 Sept 2014 (M18-002) and 21 August 2014 (M18-005), 104 subjects have been treated in these trials. Study M18-002 is an ongoing open-label Phase 1b study of gemcitabine or gemcitabine and Abraxane® plus demcizumab in subjects with locally advanced or metastatic pancreatic ductal adenocarcinoma. 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

Study M18-002 is an ongoing Phase 1b trial of demcizumab in combination with gemcitabine or gemcitabine and Abraxane® in subjects with previously untreated adenocarcinoma of the pancreas. Thirty-eight of the 52 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. Ten of the 22 (45%) evaluable subjects treated with Abraxane®, gemcitabine and demcizumab had a partial response, and 9 (41%) 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=52)

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

Dem = demcizumab; Gem = gemcitabine; Nab = Abraxane®; 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 Abraxane®, gemcitabine and demcizumab (truncated dosing regimen).

Figure 6 and Figure 7 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 Abraxane®, respectively.

Figure 6: Percent Change in Tumor Target Lesion Size - Study M18-002

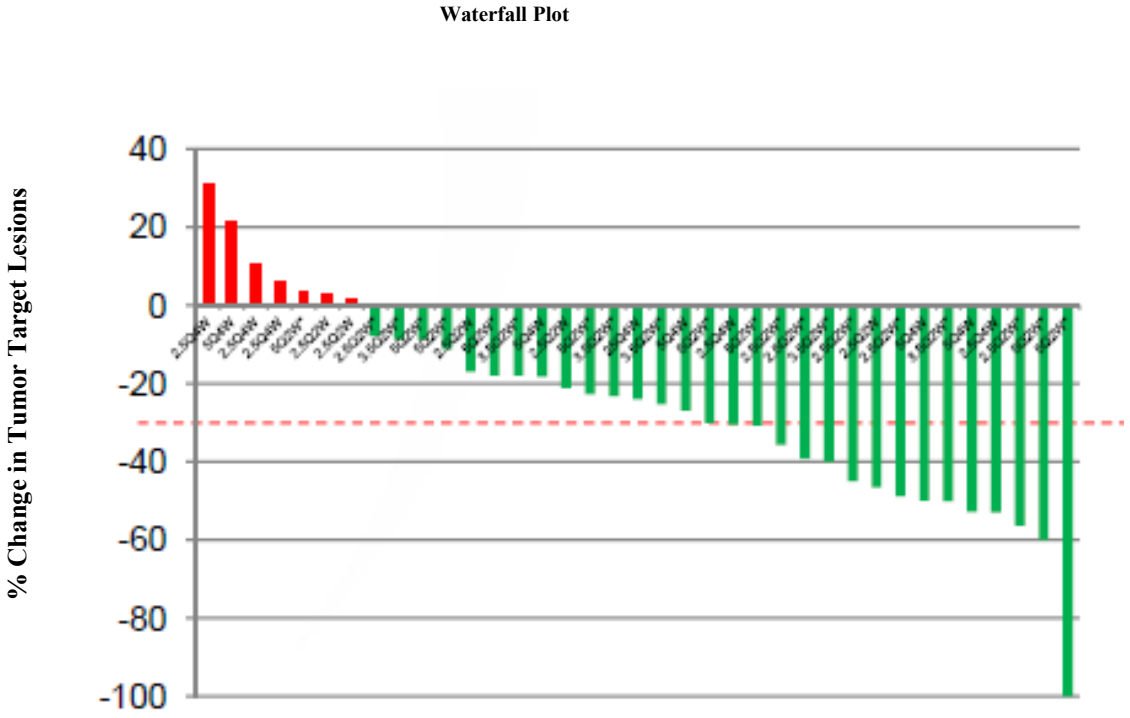
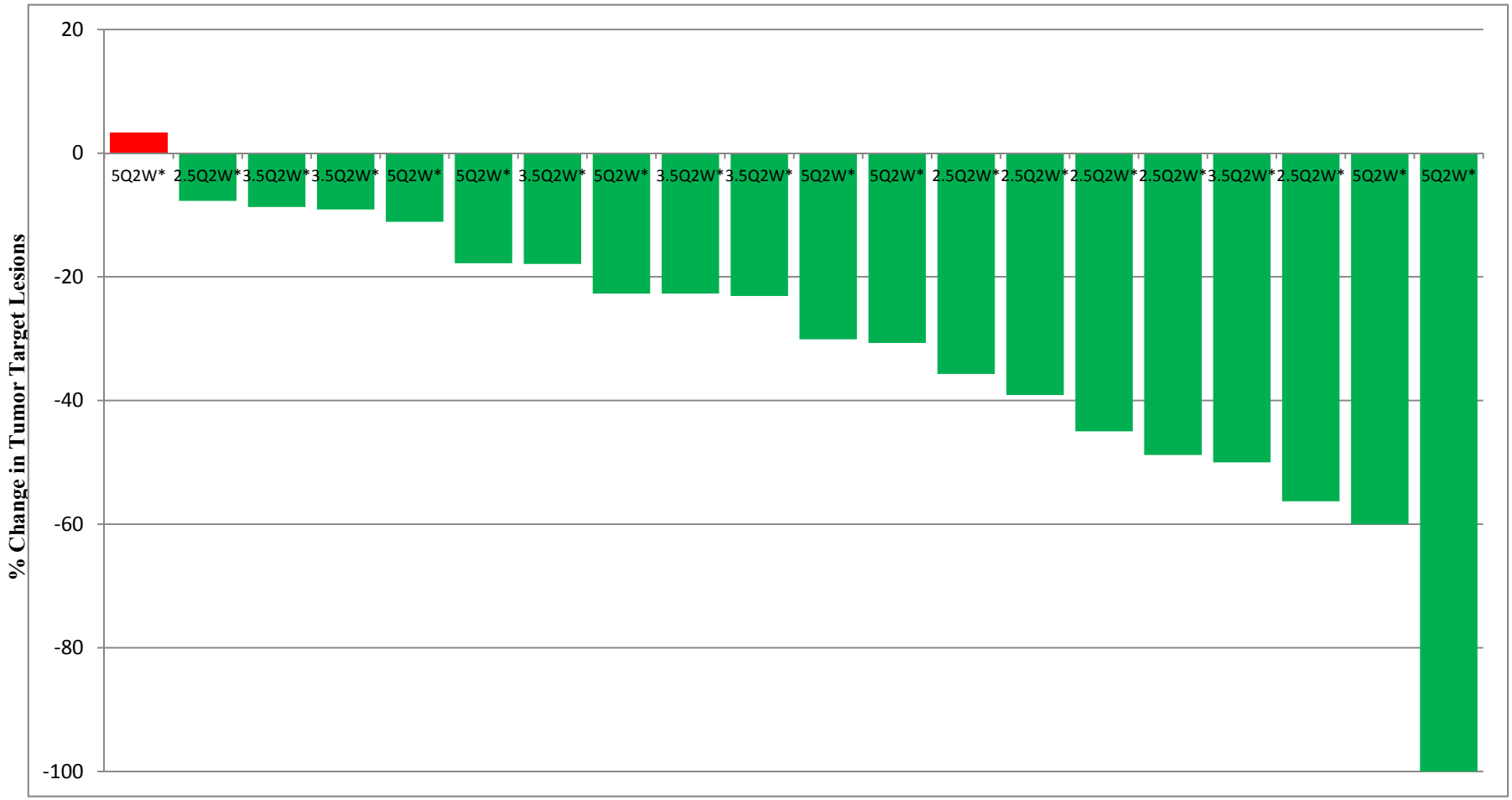


Figure 6 provides the best % change in tumor target lesion size for all subjects (i.e., subjects treated with gemcitabine and demcizumab and subjects treated with Abraxane®, gemcitabine and demcizumab) enrolled in study M18-002. Thirty-one of the 38 evaluable subjects had a reduction in the size of their 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 7: Percent Change in Tumor Target Lesion Size of the Abraxane®/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.

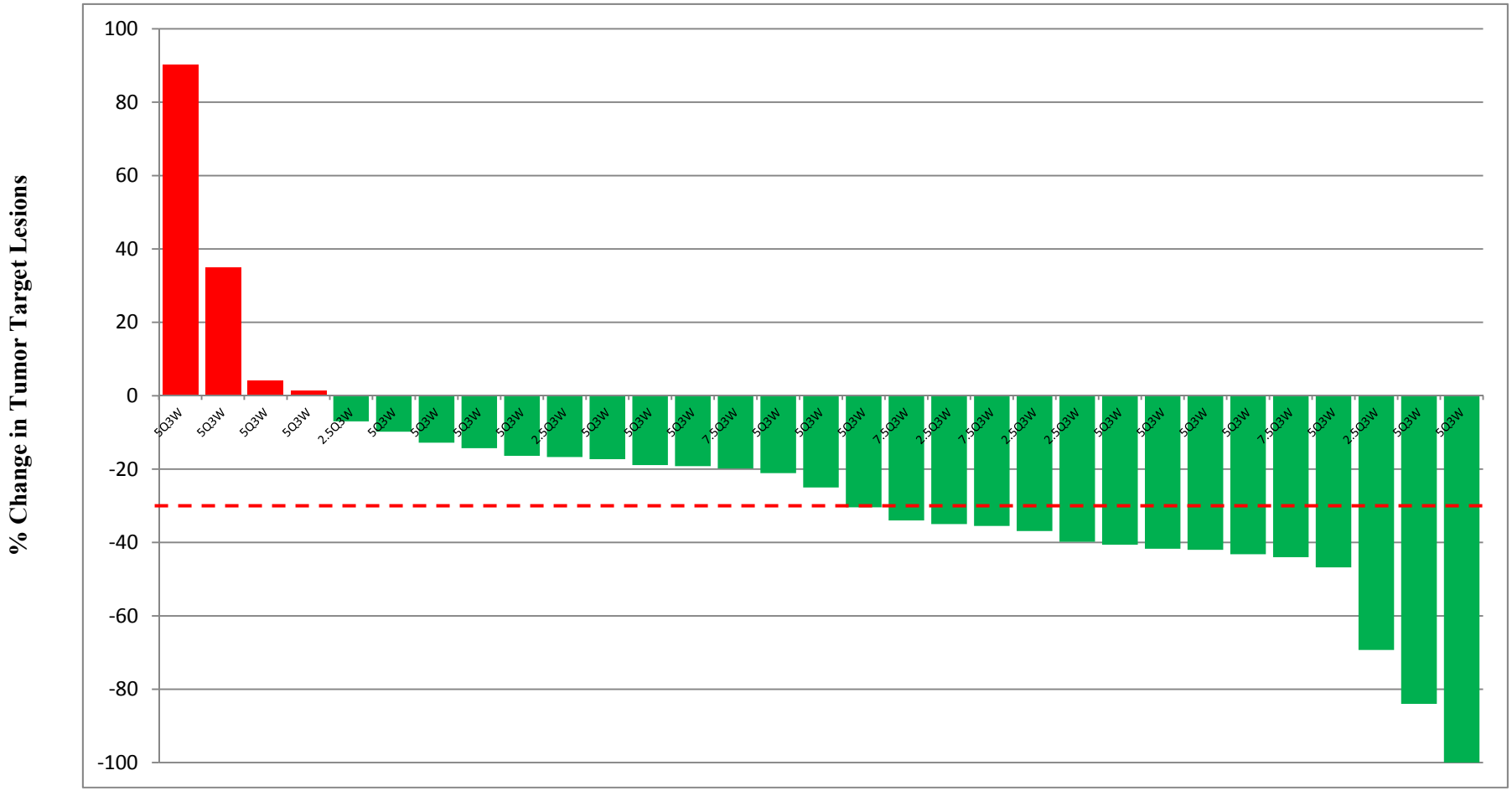
Table 3: Overall Response Assessment for Subjects in Study M18-004 (n =40)

	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 8 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 8: 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.

3.4.2.2 Phase 1b Safety Data

The treatment-emergent adverse events (AEs) in the 104 subjects treated 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 (44.2%), nausea (41.3%), hypertension/blood pressure increased (30.8%), vomiting (25%), edema peripheral (22.1%), diarrhea (21.1%), appetite decreased (17.3%), increased BNP (17.3%), anemia (13.5%), thrombocytopenia (13,5%), neutropenia (13.5%), dyspnea (11.5%), headache (10.6%) and pulmonary hypertension (10.6%).

The Grade 3-5 treatment-emergent AEs considered to be related to demcizumab that occurred in > 5% of subjects were hypertension/blood pressure increased (15.4%), neutropenia (7.7%) and thrombocytopenia (6.7%).

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 50 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 Risks/Benefits

The toxicology and pharmacokinetics of demcizumab were studied in the cynomolgus monkey. The toxicology findings in the initial definitive 8 week cynomolgus monkey study were limited to minor clinical pathology alterations, minimal effects on body weight (seen in selected monkeys that received 200 mg/kg), minimal-to-slight congestion or hemorrhage in the gastrointestinal tract, and dose-related degeneration/necrosis of the physis-metaphysis of the distal femur. The body weight, clinical pathology and gastrointestinal effects were not considered to be adverse. Based on the severity, the degeneration/necrosis of the physis-metaphysis of the distal femur noted at 50 and 200 mg/kg/week was considered adverse. Following recovery, degeneration/necrosis and loss of the physis-metaphysis of the distal femur was limited to one male that previously had been dosed at 200 mg/kg/week. Whether this finding was persistent or delayed in onset is uncertain. However, it should be noted that the monkeys that were treated in this study were adolescent monkeys with growth plates that were not yet fused. These finding would probably not have been observed if adult monkeys with fused growth plates had been studied. Similarly, as demcizumab will only be administered to patients who are at least 21 years of age in the human clinical trials this effect is unlikely to occur.

Based upon the results of this study, demcizumab was generally well tolerated at doses up to 200 mg/kg/week. The maximum tolerated dose (MTD) of demcizumab was at least 200 mg/kg/week, corresponding to a mean Day 50 AUC of 497 mg.hr/mL.

A subsequent cynomolgus monkey study was performed in which the animals received doses of demcizumab as a weekly infusion, 10, 30 or 100 mg/kg, for 26 weeks. In this study, long term administration of the two highest doses was not tolerated. Histopathologic findings present in the heart included hypertrophy, both of the cardiac myofibers and of the endothelial cells lining the small vessels within the myocardium, and myofiber degeneration and necrosis. In addition, test-article related changes in the liver included atrophy of centrilobular hepatocytes and dilation of the centrilobular sinusoids. Data from this study revealed that cardiotoxicity related to demcizumab occurred principally in monkeys that were treated with high doses (30 and 100 mg/kg) of demcizumab weekly, for prolonged periods of time. However, animals that received lower doses (10 mg/kg/week) of demcizumab did not manifest any clinical signs of cardiotoxicity with prolonged treatment (up to 6 months).

This nonclinical study, in addition to emerging clinical data, was pivotal to the redesign of the clinical trials of demcizumab to incorporate lower dose administration of the drug to patients and to institute the cardiac risk mitigation plan on the ongoing Phase 1b trials, although subsequently the use of truncated dosing was also incorporated. These findings prompted changes to the clinical protocols to include more frequent ECG monitoring and to add echocardiography and BNP measurements.

The emerging clinical data from the 5 demcizumab studies conducted to date suggest that the primary drug-related toxicities associated with demcizumab administration are hypertension,

bleeding, pulmonary hypertension and heart failure. Newly diagnosed hypertension or exacerbation of pre-existing hypertension occurred in about one-third to one-half of the subjects on the demcizumab clinical trials. Thus, subjects receiving demcizumab should be closely monitored for the development of hypertension or the exacerbation of pre-existing hypertension, and patients with hypertension should be treated according to the standard treatment guidelines for managing hypertension (Ref 16). Serious bleeding, primarily from luminal tumors in the gastrointestinal tract occurred in 5 subjects in the Phase 1 dose escalation study. As a result, subjects having luminal tumors were subsequently excluded from the demcizumab clinical trials and, subsequently, there was only 1 case of possible serious tumor-associated bleeding in the gastrointestinal tract in the Phase 1b or Phase 1b/2 studies. Grade 3 or greater right- and/or left-sided heart failure with or without Grade 3 pulmonary hypertension has occurred in 8 of the subjects treated with continuous demcizumab between Days 112-184. As a result, several modifications to the risk mitigation strategy, monitoring and dosing of demcizumab were instituted. Subsequent to implementation of this updated risk mitigation procedure, none of the 50 subjects treated according to this approach have developed Grade 2 or greater pulmonary hypertension or heart failure; i.e., only 1 patient has developed Grade 1 pulmonary hypertension. Strict adherence to the risk mitigation, monitoring and demcizumab dosing guidelines (provided in Section 7 of the Investigator Brochure) is required to avoid pulmonary hypertension and/or heart failure.

As the 5 clinical studies conducted to date have all been at the Phase 1 stage of development (with the exception of Phase 1b/2 study in patients with ovarian cancer, which at present has data reported on 5 subjects), the extent of efficacy data is limited. Nevertheless, there are observations of activity in the Phase 1b studies (see Section 6.4 of the Investigator's Brochure for a comprehensive overview). Most relevant for the upcoming Phase 2 study in pancreatic cancer is the ongoing Phase 1b study in subjects with 1st-line pancreatic cancer who were treated with demcizumab in combination with gemcitabine or gemcitabine plus Abraxane® (protocol M18-002). Four of the sixteen (25%) evaluable subjects treated with gemcitabine and demcizumab had partial response and 7 (44%) had stable disease and nine of the twenty-two (41%) evaluable subjects treated with Abraxane®, gemcitabine and demcizumab had a partial response and 10 (45%) had stable disease. In addition, twenty of the twenty-one evaluable subjects had a reduction in the size of their target lesions.

In summary, OncoMed has gained critical safety experience from the cynolmolgus monkey studies and from Phase 1 clinical development in understanding the primary risks associated with demcizumab treatment. OncoMed instituted a risk mitigation procedure early on in the program, as a result of histopathologic findings from the second cynomolgus study. The risk mitigation plan was further refined during clinical development, and subsequent to implementation of the updated risk mitigation plan, no patients have developed greater than Grade 1 cardiotoxicity to date. This risk mitigation strategy has been incorporated into the proposed Phase 2 protocol and is reviewed extensively in the Investigator's Brochure (Section 7). There have been observations of clinical activity in the Phase 1b trials as reviewed in Section 6.4 of the Investigator's Brochure and as briefly described above. Thus, the current risk/benefit assessment of demcizumab

supports the continued clinical development of this novel investigational anti-cancer therapeutic in a randomized, placebo-controlled Phase 2 trial, which will more rigorously assess the clinical potential of demcizumab in the treatment of1st line pancreatic cancer.

3.6 Dose Rationale

In the Phase 1b study of demcizumab and gemcitabine or demcizumab plus gemcitabine and Abraxane® (study M18-002), subjects in the 1st 3 dose cohorts received demcizumab doses of either 5 mg/kg once every 2 weeks or 2.5 or 5 mg/kg once every 4 weeks until disease progression. As 1 of the subjects in the 3rd dose cohort of this study and 2 additional patients in the ongoing non-small cell lung cancer Phase 1b study developed pulmonary hypertension and heart failure at approximately Day 168, the 38 subjects in the subsequent 4 cohorts received a truncated dosing regimen of 2.5, 3.5 or 5 mg/kg once every 2 weeks for 70 days (i.e., 6 doses over 70 days). No cases of Grade ≥2 pulmonary hypertension or heart failure were observed in any of these subjects. However, the data safety monitoring board (DSMB) for the study felt that the BNP and peak tricuspid velocity data of subjects in the.5 mg/kg cohort suggested that the dose may be too high and thus recommended that the truncated dosing regimen of 3.5 mg/kg once every 2 weeks be used for the Phase 2 study. Subjects in the 3rd arm of this study will receive 2 truncated courses of demcizumab at 3.5 mg/kg once every 2 weeks (one from Days 0-70 and one from Days 168-238). Only subjects who meet the original cardiac-related inclusion/exclusion criteria at Day 168 will receive the 2nd truncated course of demcizumab in this arm of the study. With a terminal half life of 16 days, the 3-month washout period will allow more than 99.5% of the drug to be eliminated before re-dosing. 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 and subjects have to meet stringent criteria for the second course of demcizumab. Furthermore, the DSMB for this study will be monitoring the emerging safety data very closely to ensure that this approach is safe for continued use in the trial.

3.7 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.

3.8 Subject Population

Subjects must be at least 21 years of age, have 1st line metastatic pancreatic ductal adenocarcinoma, have not received prior chemotherapy for their metastatic pancreatic ductal adenocarcinoma, have adequate organ and bone marrow function, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and have a life expectancy of more than 3 months. In addition, subjects must have measurable disease per RECIST 1.1.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

Primary Objective:

- To compare the efficacy of Arm 1 to the pooled decizumab arms (i.e., Arm 1 to Arms 2 and 3) (See Section 5.0 for description of Treatment Arms) in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma

Secondary Objectives:

- To compare the efficacy of Arm 1 to Arm 2 and Arm 1 to Arm 3 in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma
- To compare the safety of Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To determine the rate of immunogenicity against demcizumab when combined with Abraxane® and gemcitabine in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma**.**
- To determine population pharmacokinetics of demcizumab in subjects receiving demcizumab and Abraxane® and gemcitabine in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

Exploratory Objectives:

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

Primary Endpoint

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

Secondary Endpoints

- To compare the hazard of progression using the Investigator assessed progression-free survival time between subjects in Arm 1 and Arm 2 and Arm 1 and Arm 3 in 1st-line metastatic pancreatic ductal adenocarcinoma.
- To compare the Investigator-assessed RECIST response rate in Arm 1 to Arm 2 , Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic cancer.
- To compare the Investigator-assessed RECIST clinical benefit rate (i.e., the rate of complete response + partial response + stable disease) in Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To compare the Investigator-assessed progression-free survival at 6 months in Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To compare the Independent Review Facility (IRF)-assessed RECIST response rate and progression-free survival based solely on radiographs in Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled (Optional).
- To determine the half-life, volume of distribution and clearance of demcizumab when combined with Abraxane® and gemcitabine in with subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.
- To compare the safety profile through adverse event monitoring (including attribution of adverse events and serious adverse events [SAEs]), physical examination, vital signs, and clinical laboratory testing as outlined in the Schedule of Assessments (see Appendix B) between Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma. To compare the incidence of anti-demcizumab antibody development and neutralizing antibody development in subjects with 1st-line locally advanced or metastatic pancreatic ductal adenocarcinoma being treated with Abraxane® and gemcitabine plus demcizumab in Arm 1 to Arm 2, Arm 1 to 3 and Arms 1 to Arms 2 and 3 pooled.
- To compare the median survival in Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma
- The compare the Kaplan Meier estimates of survival at 6, 12, 18 and 24 months in Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled in subjects with 1st-line metastatic pancreatic ductal adenocarcinoma.

Exploratory Endpoints

- To compare the pharmacodynamic and predictive biomarkers for demcizumab and determine their correlation with response in Arm 1 to Arm 2, Arm 1 to 3 and Arm 1 to Arms 2 and 3 pooled (see Section 11.0).

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

5.0 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

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

Gemcitabine will be given by intravenous (IV) infusion at a dose of 1000 mg/m^2 on Days 1, 8 and 15 of each 28-day treatment cycle (or until toxicity necessitates reducing or holding a dose). Abraxane® will be administered by IV infusion at a dose of 125 mg/m^2 over 30 minutes on Days 1, 8 and 15 of each 28-day treatment cycle. Demcizumab 3.5 mg/kg or placebo will be administered by IV infusion (prior to the administration of Abraxane® and gemcitabine) once every 2 weeks for either one (1st course through Study Day 70) or two (2nd course begun on Study Day 168 and continued through Study Day 238) 70 day courses (i.e., 6 doses per course).

Randomized subjects will be treated in the following manner:

Arm 1 – Abraxane® and gemcitabine plus **placebo** (3 cycles), Abraxane® and gemcitabine (3 cycles), Abraxane® and gemcitabine plus **placebo** (3 cycles) and then Abraxane® and gemcitabine until disease progression

Arm 2 - Abraxane® and gemcitabine plus **demcizumab** (3 cycles), Abraxane® and gemcitabine (3 cycles), Abraxane® and gemcitabine plus **placebo** (3 cycles) and then Abraxane® and gemcitabine until disease progression

Arm 3 - Abraxane® and gemcitabine plus **demcizumab** (3 cycles), Abraxane® and gemcitabine (3 cycles), Abraxane® and gemcitabine plus **demcizumab** (3 cycles) and then Abraxane® and gemcitabine until disease progression

Dosing of gemcitabine, Abraxane® and demcizumab or placebo must be done within ± 2 days of the Study Day listed in the protocol. If a drug cannot be given within this 2 day window, then the dose of that drug is permanently missed. Subjects will only receive their second 70 day course of placebo or demcizumab if their Day 168 BNP is ≤100 pg/mL, peak tricuspid velocity is ≤3.0 m/s and LVEF is ≥50% and they did not develop pulmonary hypertension or heart failure while on study. Any subject who has two consecutive B-type natriuretic (BNP) values

≥100 pg/mL or one value ≥200 pg/mL will be unblinded by the Investigator (these subjects will remain on study) through the IWRS system. If the subject is receiving demcizumab they will be started on an ACE inhibitor or carvedilol, unless the BNP elevation occurred more than 100 days after the discontinuation of demcizumab or there is a contraindication to administering these agents and if appropriate, referred to a cardiologist. If they are not receiving demcizumab they will be cared for according to standard medical practice.

Subjects will be assessed for disease status every 8 weeks and for safety at every visit and through 30 days following the termination visit. In all three arms, subjects should remain on study until disease progression. Immunogenicity will be assessed at baseline, every 8 weeks while on study and at treatment termination. Biomarker assessment will be performed at Days 0, 21, 35, 49 and 63 and at treatment termination. Plasma sample for PK analysis to be obtained prior to the demcizumab infusion on Days 0, 14, 56, 70, 168, 182, 224 and 238, and at the end of the demcizumab infusion (prior to chemo infusion) on Days 0, 56, 70, 168, 224 and at treatment termination. If all of the study drugs are discontinued prior to disease progression, the subject should remain on study until disease progression or withdrawal of consent. Once discontinuation criteria for the study are met (disease progression, use of other anti-cancer therapy, subject or investigator decision or protocol non-compliance) 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 and other assessments as required per protocol.

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. Subjects must have cytologically or histologically confirmed metastatic pancreatic ductal adenocarcinoma. Prior chemotherapy and/or radiotherapy either in the adjuvant or neoadjuvant setting or for metastatic disease is not allowed.
2. Age ≥21 years
3. ECOG performance status 0 or 1 (see Appendix C)
4. Measurable disease per RECIST v1.1 (Appendix D)

5. Adequate organ and marrow function as defined below:
   - Absolute neutrophil count ≥1.5 x 10^9/L
     - Without granulocyte colony-stimulating factor support within 2 weeks prior to randomization
   - Hemoglobin ≥100 g/L
     - Without transfusion within 2 weeks prior to randomization
   - Platelets ≥125 X 10^9/L
     - Without transfusion within 2 weeks prior to randomization
   - Total bilirubin ≤1 X institutional upper limit of normal (ULN)
   - Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤5 X institutional ULN
   - Alkaline phosphatase ≤5 X institutional ULN
   - Albumin ≥ 3 g/dL
   - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) within 1.5 X the institutional ULN
   - Creatinine ≤1.5 X institutional ULN

   OR

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

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

     - For women, multiply the value from the equation above by 0.85.
     - Where age is in years, weight is in kg, and serum creatinine is in µmol/L
       - 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]
6. 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 (e.g., surgical sterilization, a reliable barrier method, birth control pills, or contraceptive hormone implants) 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.

7. Ability to understand and the willingness to sign a written informed consent document

6.2 Exclusion Criteria

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

1. Subjects with a neuroendocrine tumor of the pancreas, an acinar tumor of the pancreas or a pancreatic tumor with mixed histologies.
2. Subjects receiving any other investigational medicinal products or anti-cancer therapy.
3. Subjects with brain metastases (subjects must have a CT scan or MRI of the head within 28 days prior to randomization to rule out brain metastases), uncontrolled seizure disorder, or active neurologic disease
4. Subjects with leptomeningeal disease
5. Subjects with $\geq$ Grade 2 peripheral neuropathy
6. History of interstitial pulmonary disease or pneumonitis
7. Malignancies other than pancreatic cancer successfully treated within 3 years prior to randomization, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, treated superficial bladder cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent
8. Prior radiation to the chest wall or mediastinum if the radiation field involves the heart
9. History of a significant allergic reaction attributed to humanized or human monoclonal antibody therapy
10. Significant intercurrent illness that will limit the patient's ability to participate in the study or may result in their death over the next 18 months.
11. Pregnant women or nursing women
12. Subjects with known HIV infection
13. Known bleeding disorder or coagulopathy

14. Subjects receiving therapeutic doses of heparin, warfarin, factor Xa inhibitors or other similar anticoagulants. Note: Subjects may be receiving prophylactic doses of heparin, warfarin, factor Xa inhibitors or other similar anticoagulants, low-dose aspirin and/or non-steroidal anti-inflammatory agents.
15. Subjects with known clinically significant gastrointestinal disease including, but not limited to, inflammatory bowel disease
16. Subjects with a blood pressure of >140/90 mmHg. The BP should be taken using the method described in Section 9.3. Subjects taking antihypertensive medications must be taking ≤2 medications to obtain this level of BP control.
17. Subjects with tumors that are currently involving the lumen of the gastrointestinal tract
18. History of cerebral vascular accident (CVA) or transient ischemic attacks (TIAs) within 6 months prior to randomization, 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.
19. Subjects with an active infection requiring antibiotics
20. Subjects with an uncontrolled seizure disorder or active neurologic disease
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 E)

      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.
    - History of heart failure or pulmonary hypertension
    - Received a total cumulative dose of ≥400 mg/m^2 doxorubicin
    - Grade ≥2 ventricular arrhythmia
    - Inability to comply with study and follow-up procedures

7.0 REMOVAL OF SUBJECTS FROM STUDY

Subjects must be withdrawn from the study 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 (as assessed by the Sponsor)

Subjects who meet one of the above criteria will undergo the termination evaluations for the study (see Section 12.9). After the termination visit, subjects will have regular follow-up for survival and other assessments as required per protocol (see Section 12.10).

If a subject has permanently discontinued one, two or all three of the study drugs due to toxicities or any other reasons, the subject should remain on study until one of the above criteria is met. Subjects who have discontinued all study drugs and continue on study should have assessments performed as outlined in Section 12.0.

8.0 TREATMENT OF SUBJECTS

Dosing of gemcitabine, Abraxane® and demcizumab or placebo must be done within ± 2 days of the Study Day listed in the protocol. If a drug cannot be given within this 2 day window, then the dose of that drug is permanently missed. If one or more of these drugs needs to be temporarily or permanently discontinued the subject should continue to receive the other drug(s) and remain on study until disease progression.

8.1 Study Drug (DEMCIZUMAB OR PLACEBO)

8.1.1 Administration

Study drug (demcizumab at 3.5 mg/kg or placebo) will be administered once every 2 weeks for 6 doses (i.e., the last dose is given on Day 70). A second course of study drug (demcizumab at 3.5 mg/kg or placebo) will be administered once every 2 weeks for 6 doses starting at Day 168 if the subject's Day 168 BNP is ≤100 pg/mL, peak tricuspid velocity is ≤3.0 m/s and LVEF is ≥50%, and the subject did not develop pulmonary hypertension or heart failure while on study. No dose reductions of demcizumab/placebo are allowed 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 minutes as an infusion prior to the administration of Abraxane® and gemcitabine, 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 (+/- 2days) (See Section 12.0) , the missed dose cannot be administered at a later time point. Instead, no demcizumab/placebo is to be administered until the next scheduled dose.

8.1.2 Description

Demcizumab is an IgG2 humanized monoclonal antibody that is directed against the DeltaLike 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, 100mM Sodium Chloride, 45mM 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 study drug accountability log must be maintained and kept up to date at all times. Blinded study drug perforated labels must be kept for drug accountability.

8.1.5 Study 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 3.5 mg/kg, then the subject's dose would be 245 mg. Because the vials contain a concentration of 10 mg/mL, a total of 24.5 mL containing 245 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

Any subject who has two consecutive BNP values ≥100 pg/mL or one value ≥200 pg/mL will be unblinded by the Investigator through the IWRS system. If the subject is receiving demcizumab they will started on a cardioprotective agent such as an ACE inhibitor or carvedilol, unless the BNP elevation occurred more than 100 days after the discontinuation of demcizumab or there is a contraindication to the use of these agents and if appropriate referred to a cardiologist. If they are not on demcizumab they should be cared for according to standard medical practice. The selection and dose of the ACE inhibitor to be administered or the dose of carvedilol to be administered should be based on the recommendations in standard guidelines for treating heart failure (Ref 17). If there is a contraindication to administering both of these agents, the patient's treatment should be discussed with the OncoMed Medical Monitor.

In addition, any subject who develops a BNP of ≥300 pg/mL, a LVEF decline of ≥10% from baseline and a LVEF value that is <50%, clinically significant pulmonary hypertension (i.e., the subject has a peak tricuspid velocity >3.4 m/s on doppler echocardiogram and has been seen by a cardiologist and diagnosed with clinically significant pulmonary hypertension) and/or symptoms of heart failure must have their dose of demcizumab held, but administration of their chemotherapy may be continued. Dosing of demcizumab must continue to be held until the subjects BNP is <300 pg/mL, the decline in LVEF is <10% and a LVEF value that is >50%, their clinically significant pulmonary hypertension has resolved and symptoms of heart failure has resolved.

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

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

- BNP of ≥400 pg/mL
- ≥Grade 2 pulmonary hypertension
- Evidence of Grade ≥2 bleeding (except for readily manageable local bleeding, such as hemorrhoidal bleeding)
- Hypertensive crisis
- Hypertensive encephalopathy
- Blood pressure of ≥ 200/120 mmHg
- Need for therapeutic anti-coagulation
    - If therapeutic anti-coagulation is no longer required, the subject may receive any remaining demcizumab/placebo administrations.

If the demcizumab/placebo need to be held or discontinued, the administration of the chemotherapy should continue 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 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, permanently discontinue demcizumab therapy 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 Gemcitabine and Abraxane®

The dose of gemcitabine and Abraxane® should be modified according to the criteria in Section 8.2.3. All dose modifications are permanent. Dosing of gemcitabine and Abraxane® must be done within ± 2 days of the Study Day listed in the protocol. If a gemcitabine or Abraxane® cannot be given within this 2 day window, then the dose of that drug is permanently missed. The administration of the chemotherapy should not be held if the demcizumab/placebo needs to be held or discontinued.

8.2.1 Abraxane®

8.2.1.1 Administration

Abraxane® must be administered after the demcizumab, but before gemcitabine administration on days when three drugs are given. Abraxane® should be administered by IV infusion at a dose of 125 mg/m^2 over 30 minutes on Days 1, 8 and 15 of every 28-day cycle. The Study Day 0 weight should be used to calculate the body surface area that is used to calculate the total dose (mg) of Abraxane® throughout the study, unless the weight changes by >5%, in which case the current weight should be used to calculate the body surface area.

Subjects do not require premedication prior to Abraxane® administration, as hypersensitivity reactions are not expected. If a hypersensitivity reaction occurs, the infusion should be stopped and not restarted. If felt to be in the subject's best interest, at the investigator's discretion, treatment may continue on subsequent cycles using the premedication regimen the institution typically uses for solvent-based paclitaxel.

8.2.1.2 Description

Abraxane®, a microtubule inhibitor, is an albumin bound form of paclitaxel with a mean particle size of approximately 130 nanometers. The active agent in Abraxane® is paclitaxel. The chemical name for paclitaxel is 5β, 20-Epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate, 13 ester with (2R, 3S) –N-benzoyl-3-phenylisoserine.

8.2.1.3 Storage

Abraxane® vials must be stored as recommended in the label.

8.2.1.4 Packaging

The labeling of Abraxane® will comply with all applicable regulations.

8.2.2 Gemcitabine

8.2.2.1 Administration

Gemcitabine must be administered after the administration of demcizumab and Abraxane®. Gemcitabine should be administered by IV infusion at a dose of 1000 mg/m^2 over 30 minutes once weekly (Days 1, 8 and 15 of each 28 day cycle) for 3 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest every 28 days.

The Day 0 weight should be used to calculate the total dose (mg) of gemcitabine throughout the study, unless the weight changes by >5%, in which case the current weight should be used to calculate the dose. **Clearance in women and the elderly is reduced and women are somewhat less able to receive subsequent cycles.**

8.2.2.2 Description

Gemcitibine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2´-deoxy-2´, 2´-difluorocytidine monohydrochloride (-isomer).

8.2.2.3 Storage

Gemcitibine must be stored as recommended on the label.

The labeling of gemcit*a*bine will comply with all applicable regulations.

8.2.3 Gemcitabine and Abraxane® Dose Modification Guidelines

Dose reductions/modifications of gemcitabine and Abraxane® are permanent, except in some circumstances when the dose reduction was a result of neutropenia (see Section 8.2.3.1). Doses of gemcitabine and Abraxane® must be given within +/- 2 days of the Study Day specified in the protocol. If a dose is not given in the window it is permanently missed. Doses will be reduced for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.03.

Two levels of dose modifications are permitted according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction of either drug, further treatment with Abraxane® and gemcitabine should be discontinued, although demcizumab and/or placebo therapy should be continued.

Table 4: Dose Modifications

Dose Level	Abraxane® Dose (mg/m^2)[i.]	Gemcitabine (mg/m^2)
Study Dose	125	1000
-1	100	800
-2[ii.]	75	600

[i.] Dose reductions may or may not be concomitant, refer to Table 5. If the dose is withheld due to hematologic toxicity on Day 15, resume at the next lower dose level when the subject has adequate ANC and platelet counts to begin Day 1 of the next cycle. Refer to Table 5 for specific recommendations regarding dose modifications for Day 1.

[ii.] A maximum of 2 dose level reductions are allowed.

Subjects who have had two dose level reductions as outlined in Table 4 and are still unable to tolerate the gemcitabine/Abraxane regimen may receive the -2 dose levels on Days 1 and 15 (i.e., omit Day 8) of each 28 day cycle.

8.2.3.1 Dose Modifications

In the event dose modifications are required at the start of a cycle or within a cycle due to hematologic toxicities of neutropenia and/or thrombocytopenia, doses of Abraxane® and gemcitabine may be adjusted as detailed in Table 5. WBC growth factor may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in subjects with an ANC <500 cells/mm^3. Subject's not experiencing resolution of neutropenia within 21 days, despite uninterrupted WBC growth factor treatment, will discontinue gemcitabine and Abraxane®. In addition, WBC growth factors may be administered as supportive therapy to recover ANC adequately such that dosing levels may be maintained. If a dose reduction was required due to neutropenia, a dose re-escalation may be considered with continued growth factor support. If a dose reduction is required for a reason other than neutropenia, no dose re-escalation will be permitted for the duration of the study. If hematologic toxicity is restricted to platelet counts alone, dose modification of only gemcitabine could be considered after discussion with the sponsor.

Table 5: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	*Abraxane*® Dose	Gemcitabine Dose
Day 1	≥1500	AND	≥100,000	Treat on time at current dose levels	
	<1500	OR	<100,000	Delay doses until recovery	
Day 8	≥1000	AND	≥ 5,000	Treat on time at current dose levels	
	≥500 but <1000	OR	≥50,000 but <75,000	Reduce doses 1 dose level	
	<500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were given without modification:					
Day 15	≥1000	AND	≥75,000	Treat on time at current dose levels	
	≥500 but <1000	OR	≥50,000 but <75,000	Reduce doses 1 dose level from Day 8; consider following with WBC growth factors for support*	
	<500	OR	<50,000	Withhold doses	
Day 15: IF Day 8 doses were reduced:					
Day 15	≥1000	AND	≥75,000	Treat with same doses as Day 8; consider following with WBC growth factors for support*	
	≥500 but <1000	OR	≥50,000 but <75,000	Reduce doses 1 dose level from Day 8; consider following with WBC growth factors for support*	
	<500	OR	<50,000	Withhold doses	

Table 5: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle (Cont'd)

Day 15: IF Day 8 doses were withheld:				
Day 15	≥000	AND	≥75,000	Option A: Maintain dose level from Day 1 and follow with WBC growth factors for support* OR Option B: Reduce doses 1 dose levels from Day 1
	≥500 but <1000	OR	≥50,000 but <75,000	Option A: Reduce 1 dose level from Day 1 and follow with WBC growth factors for support* OR Option B: Reduce doses 2 dose levels from Day 1
	<500	OR	<50,000	Withhold doses

Abbreviations: ANC = absolute neutrophil count; WBC = white blood cell

*The use of WBC growth factors is only applicable if the dose limiting hematologic toxicity was limited to neutropenia or febrile neutropenia.

Dose modifications for other adverse drug reactions are provided in Table 6.

Table 6: Dose Modifications for Other Adverse Drug Reactions

Adverse Drug Reaction	**Abraxane® Dose**	**Gemcitabine Dose**
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC is ≥1500; resume at next lower dose level[b]	
Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improvement to ≤Grade 1; resume at next lower dose level	Treat with same dose
Cutaneous Toxicity: Grade 2 or 3	Reduce doses to next lower dose level; discontinue treatment if ADR persists	
For all other nonhematologic toxicities (except nausea, vomiting, alopecia and pulmonary embolism) of ≥Grade 3	Withhold doses until improvement to ≤Grade 1; resume at next lower dose level[i]	

Abbreviations: ADR, adverse drug reaction; ANC = absolute neutrophil count

[i] White blood cell growth factor may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in subjects with an ANC of <500 cells/mm^3

[b] See Table 5 for dose level reductions.

8.2.3.1.1 Administration of Abraxane® and Gemcitabine to Subjects with Abnormal Hepatic Function

Abraxane® and gemcitabine should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the subject is on study should prompt an evaluation to determine the cause, including the possibility of metastatic disease and hepatotoxicity from concurrent medications, alcohol use, or other factors.

8.2.3.1.2 Interstitial Pneumonitis

While participating in this study, subjects should be carefully monitored to prevent or minimize the occurrence of interstitial pneumonitis. Careful pre-study screening with continuous on-study monitoring for signs and symptoms is required. Should a subject develop symptoms of pneumonitis during this study, the timely initiation of appropriate management is required. Recommended guidelines are as follows:

1. Before randomization, evaluate candidate subjects for familial, environmental, or occupational exposure to opportunistic pathogens, and do not enroll those with a history of slowly progressive dyspnea and unproductive cough, or of conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, or multiple allergies.
2. During study treatment, provide close attention to episodes of transient or repeated dyspnea with unproductive persistent cough or fever. Radiographic evaluation with chest x-rays and CT scans (normal or high resolution) may be indicated to evaluate for infiltrates, ground-glass opacities, or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.
3. Infections should be ruled out with routine immunological/ microbiological methods. Transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.
4. Administration of Abraxane® and gemcitabine must be permanently discontinued from upon the diagnosis of interstitial pneumonitis. However, the administration of the demcizumab or placebo should be continued, unless contraindicated. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Subjects with an added immunological agent may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

8.2.3.1.3 Prophylaxis Against Sepsis

In the MPACT metastatic pancreatic ductal adenocarcinoma Phase 3 study, an increase in cases of non-neutropenic sepsis was observed with the combination of Abraxane® and gemcitabine. An exploratory analysis suggested that the presence of biliary stents may have increased the risk of sepsis in that population. Investigators were to provide oral broad spectrum antibiotics to subjects who were then to initiate these antibiotics at the first occurrence of fever. Subjects enrolled in this clinical trial may not have the same risk of sepsis as metastatic pancreatic ductal adenocarcinoma patients. Subjects should be advised that there could be an increased risk of serious infection and they should contact their physician for evaluation when they develop a fever. Fever or similar symptoms should be fully evaluated as an early sign of a serious infection. Broad spectrum antibiotics such as fluoroquinolones may be provided to subjects to treat or as prophylaxis for infection at the discretion of the treating physician.

8.2.3.1.4 Hypersensitivity Reactions

Hypersensitivity reactions are infrequent with Abraxane®. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of IP administration and aggressive symptomatic therapy.

Subjects who develop a severe hypersensitivity reaction to Abraxane® should not be rechallenged.

8.3 Anti-Emetics and Hematopoietic 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.

8.4 Concomitant and Prohibited Therapy

All concomitant medication administered from randomization through 30 days following treatment termination 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 subjects' specific tumor type) may not be administered from randomization through treatment termination. 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 after consultation with the OncoMed medical monitor. 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.

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, and the subject should continue on study with continued gemcitabine plus Abraxane® administrations and regular assessments to ensure close follow-up. Once the therapeutic anti-coagulation is discontinued, subjects may receive any remaining scheduled demcizumab/placebo infusion.

8.5 Treatment Compliance

Demcizumab, gemcitabine and Abraxane® 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 eCRF in Medidata. In addition, drug accountability will be performed.

9.0 SAFETY ASSESSMENTS

Safety will be assessed by adverse event 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 B – Schedule of Assessments)

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 Adverse Events from the time of randomization through 30 days after discontinuation from the study (i.e., 30 days from the date of the treatment termination visit) **must** be documented in the medical record and reported on the AE Case Report Form (CRF).

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). The grading of the adverse events will be done using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. In addition, for each adverse event the Investigator must indicate the attribution of AE to study drug (i.e., related or unrelated) and the attribution of the AE to the malignancy.

The principal investigator is responsible for assessing whether an adverse event is **related** (or possibly related) to participation in the research.

In general, adverse events are considered **related to participation in the research** if there is not a clear alternative explanation. Adverse events 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 adverse event 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 adverse event unless the condition worsens in intensity or frequency after randomization (e.g., Grade 2 nausea prior to randomization becomes Grade 3 nausea after randomization). 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 9.1.3). 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** 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
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- any other adverse event that, based upon the Investigators 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)

9.1.2.1 Disease Progression and Death

Disease progression (including progression of pancreatic cancer, 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 a serious adverse event, 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.

9.1.3 Serious Adverse Event Reporting Procedures

SAEs that occur during the study must be clearly documented in the medical record. SAEs should be reported by completing the AE page in Medidata within 24 hours of the Investigator's knowledge of the event. By completing the 'serious' information, this will generate an auto-notification to PVG. Only in the event of a system outage, a manual SAE form must be completed and faxed or emailed to PPD PVG (also within 24 hours of the Investigator's knowledge of the event). The following is the contact information for PPD Drug Safety.

9.1.3.1 Pharmacovigilance telephone contacts:

- EMEA/APAC: [redacted]
- United States: [redacted]

9.1.3.2 Pharmacovigilance fax contacts:

- EMEA/APAC: [redacted]
- United States: [redacted]

9.1.3.3 Pharmacovigilance email contact (all regions)

- EMEAAsiaSafetyCentral.SM@ppdi.com

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

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 at baseline.

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 and then every 14 days while on treatment, and at the time of treatment termination. BNP will be measured using any Alere Triage POC device (or if approved by OncoMed the site's laboratory). BNP must be drawn on the day of dosing and assessed prior to dosing (or if approved by OncoMed it may be drawn the day before dosing and assessed prior to dosing) and elevations will be managed per Section 8.1.6.

9.2.4 Urinalysis

Urinalysis (with microscopic analysis) will be obtained during screening, at Study Days 28, 56, and every 56 days thereafter, and at the time of treatment termination.

9.2.5 Pregnancy Testing

For women of childbearing potential, a serum pregnancy test is required during Screening, every 56 days while on study, at the termination visit and 56 and 112 days following the treatment 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 other week while on treatment and at treatment termination. 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 Schedule A. Blood pressure should be measured with the subject in the same position. The same cuff method should be used to measure blood pressure throughout the study. 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 by following the guidelines for the management of high blood pressure in adults (Ref 16). 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 it is ≤150/90 mmHg over a 4-week period with every-2-week BP measurements.

9.4 Cardiac Studies

Twelve-lead electrocardiograms (ECGs) with assessment of PR interval, QRS duration, and QTc interval will be obtained at Screening, every 28 days, and at the termination visit.
A transthoracic Doppler echocardiogram with left ventricular ejection fraction, right ventricular systolic pressure and peak tricuspid velocity determination will be obtained at Screening and then every 28 days. The Day 168 Doppler echocardiogram must be performed prior to the Day 168 visit, so that the peak tricuspid velocity and left ventricular ejection fraction values are available at the time of the Day 168 visit. The Doppler echocardiograms may also be sent to an Independent Cardiologist of the Sponsor's choice for central review. A CT pulmonary angiogram (CTPA) should be performed if pulmonary hypertension is diagnosed (i.e., the subject has a peak tricuspid velocity >3.4 m/s on Doppler echocardiogram, has been seen by a cardiologist and was diagnosed with clinically significant pulmonary hypertension) 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

Subjects will be assessed during screening and then every 8 weeks while the subject is on study. In addition, subjects will be assessed for immunogenicity at the time of treatment termination. 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

Sparse PK sampling will be done in all subjects on the study. Plasma samples for PK analysis will be obtained prior to the demcizumab infusion on Days 0, 14, 56, 70, 168, 182, 224 and 238, and at the end of the demcizumab infusion (prior to chemo infusion) on Days 0, 56, 70, 168, 224 and at treatment termination. The PK samples must be drawn from a location that is different from the site of study drug administration. If the study drug is administered via a vein in the arm, *post-dose* 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 8 weeks. The schedule of every 8 weeks is to be maintained throughout the study and will not be shifted if there are dose holds (see Appendix B). Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response, progression-free survival and duration of response will be assessed using the RECIST criteria v1.1 (see Appendix D) (Ref 18). The primary response outcomes will be based on the Investigator's assessment. 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 CA 19-9 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 CA 19-9.

Overall survival will be assessed by collecting survival data including the date and cause of death. Once a patient has completed the treatment termination visit, overall survival follow up will be performed every three months for up to 5 years. Follow up may be conducted by telephone interview or chart review.

The same imaging method used at screening must be used throughout the study. A documented standard-of-care tumor assessment performed within Study Days -28 to 0 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.

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 specimens obtained at the time of surgical resection or from a core biopsy will be collected for protein and gene expression biomarker analysis. Exploratory predictive biomarkers such as tumor endothelial cell DLL4 expression will be measured in FFPE tumor specimens. Gene expression biomarker analysis including Notch pathway-related predictive biomarker 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, Abraxane® and gemcitabine treatment.

Blood Biomarkers: A predose sample of 9 mL of blood will be drawn on Study Days 0, 21, 35, 49 and 63 and at treatment termination to evaluate changes in plasma proteins by immunochemistry (e.g., VEGF, βFGF, SDF1, PLGF, SCF, 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 sample will also be obtained at the time of treatment termination unless one has been obtained during the prior 14 days.

Optional Pharmacogenomics: For subjects who sign the optional Pharmacogenomics Informed Consent (Appendix G), 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 may influence safety, tolerability, or pharmacodynamic effects of demcizumab 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 gemcitabine metabolism may also be performed (e.g., CMPK and DCK).

12.0 STUDY VISIT SCHEDULE AND ASSESSMENTS

Subjects must sign and date the Informed Consent Form (Appendix F) 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 form in the PPD IWRS system and submit it electronically for approval. Once OncoMed or its representative has approved the randomization form, the investigator/study coordinator will use the IWRS system to randomize the subject. The IWRS system will then assign a subject number and the subject will be officially enrolled in the study. 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. All on-study evaluations (i.e., those done from Day 0 and beyond) must be done within the following timeframe:

- Dosing of gemcitabine, Abraxane® and demcizumab or placebo must be done within ± 2 days of the Study Day listed in the protocol. If a drug cannot be given within this 2 day window, then the dose of that drug is permanently missed.
- Laboratory evaluations within ± 3 days of the Study Day listed in the protocol, except for BNP which must be done on the day of demcizumab/placebo dosing and must be done prior to the demcizumab/placebo dose.
- Imaging studies (e.g., CT scans, MRI), ECG, and transthoracic Doppler echocardiogram within ± 7 days for the Study Day listed in the protocol.

Unless otherwise indicated, all assessments must be performed prior to dosing for all study visits when dosing occurs. **BNP must be drawn on the day of dosing and assessed prior to dosing (or if approved by OncoMed it may be drawn the day before dosing and assessed prior to dosing).**

For subjects who have discontinued demcizumab/placebo, all assessments as outlined in Appendix B should continue.

12.1 Screening

All screening tests must be performed within Study Days -28 to 0, unless otherwise indicated.

- Informed Consent (must be obtained before any study specific procedures are performed)
- Past medical history
- Physical examination
- Peripheral neuropathy assessment
- Vital signs
- Height
- Weight
- ECOG performance status

- CBC with differential and platelet count
- Serum chemistry
- INR/aPTT
- B-type natriuretic peptide (BNP) measured using an Alere Triage POC device (or if approved by OncoMed the site's laboratory)
- Urinalysis with microscopic analysis
- Electrocardiogram (ECG) including PR interval, QRS duration, and QTc interval
- Transthoracic doppler echocardiogram with LVEF, and peak tricuspid velocity determination
- Tumor marker: CA 19-9
- Serum pregnancy test for all females of childbearing potential (a negative result must be obtained prior to randomization) (must be done within 7 days prior to randomization).
- Tumor assessment: Diagnostic-quality, contrast-enhanced CT scans of chest, abdomen, and pelvis (MRI scans may be performed in lieu of CT scans; see Section 10.0) performed as outlined by the RECIST criteria v1.1 (see Appendix D). Note: The same radiographic technique of each region must be used consistently throughout the study.
- MRI of the brain, or CT scan of the brain with IV contrast (see Section 10.0)
- Colonoscopy and/or upper gastrointestinal endoscopy to rule out gastrointestinal involvement in subjects having symptoms suggestive of possible gastrointestinal involvement.
- FFPE (if tissue blocks are available; i.e., FNA is not adequate). Note: FFPE may be shipped any time after enrollment.

12.2 Study Day 0

- Demcizumab or placebo
- Abraxane®
- Gemcitabine
- Abbreviated physical examination
- Vital signs (prior to demcizumab or placebo infusion, 15 minutes after start of infusion, end of infusion, and 15 minutes post infusion).
- Weight
- ECOG performance status
- CBC with differential and platelets **(unless previously obtained on Study Days -3 to -1)**
- Serum chemistry **(unless previously obtained on Study Days -3 to -1)**
- Serum for anti-demcizumab antibody collected prior to demcizumab or placebo infusion
- Concomitant medications

- Adverse event recording
- Peripheral neuropathy assessment
- Blood for biomarkers **(must be obtained prior to dosing)**
- Blood for pharmacogenomics **(Optional and only if subject has signed the separate pharmacogenomics Informed Consent Form)**
- Plasma for pharmacokinetics prior to the demcizumab or placebo infusion and at the end of the infusion (i.e., within 30 minutes prior to and post infusion, but prior to chemotherapy)

12.3 Study Days 7, 14, 21, 28, 35, 42, and 49

- Demcizumab or placebo **-** Days 14, 28 and 42
- Abraxane® **-** Study Days 7, 14, 28, 35, and 42**)**
- Gemcitabine - – Study Days 7, 14, 28, 35, and 42)
- Abbreviated physical examination (Study Days 14, 28, and 42 only)
- Vital signs (prior to demcizumab or placebo infusion, 15 minutes after start of infusion, end of infusion, and 15 minutes post infusion) (Study Days 14, 28 and 42 only)
- Vital signs obtained once: Study Days 7, 21, 35 and 49 only)
- Weight
- ECOG performance status
- CBC with differential and platelet count
- Serum chemistry
- BNP measured using an Alere Triage POC device (or if approved by OncoMed the site's laboratory) **(Study Days 14, 28, and 42)**
- Urinalysis with microscopic analysis **(Study Day 28 only)**
- ECG including PR interval, QRS duration, and QTc interval **(Study Day 28** only**)**
- Transthoracic doppler echocardiogram with LVEF and peak tricuspid velocity determination **(Study Day 28 only)**
- Concomitant medication
- Adverse event recording
- Peripheral neuropathy assessment **(Study Day 28 only)**
- Blood for biomarkers **(Study Days 21, 35 and 49 only)**
- Plasma for pharmacokinetics prior to the infusion (i.e., with 30 minutes pre- infusion) **(Study Day 14 only)**

12.4 Study Day 56

- Demcizumab or placebo
- Abraxane®
- Gemcitabine
- Abbreviated physical examination
- Vital Signs (prior to demcizumab or placebo infusion, 15 minutes after start of infusion, end of infusion, and 15 minutes post infusion)
- Weight
- ECOG performance status
- CBC with differential and platelet count
- Serum chemistry
- BNP measured using any Alere Triage POC device (or if approved by OncoMed the site's laboratory)
- Urinalysis with microscopic analysis
- ECG including PR interval, QRS duration, and QTc interval
- Transthoracic doppler echocardiogram with LVEF and peak tricuspid velocity determination
- Tumor marker: CA 19-9 (if elevated at baseline)
- Serum pregnancy test for all females of childbearing potential
- Tumor assessment: Diagnostic-quality, contrast-enhanced CT scans of chest and abdomen, as well as imaging of all other known sites of disease, performed as outlined by the RECIST criteria v1.1 (see Appendix D). Note: If another imaging method was used at baseline, the same imaging method must be used consistently throughout the study.
- Serum for anti-demcizumab antibody **(**prior to demcizumab or placebo infusion)
- Concomitant medication
- Adverse event recording
- Peripheral neuropathy assessment
- Plasma for pharmacokinetics prior to the demcizumab or placebo infusion and at the end of the infusion (i.e., within 30 minutes prior to and post infusion, but prior to **chemotherapy)**

12.5 Study Days 63, 70

- Demcizumab or placebo – **(Study Day 70 only)**
- Abraxane®
- Gemcitabine
- Abbreviated physical examination **(Study Day 70 only)**
- Vital signs (prior to demcizumab or placebo infusion, 15 minutes after start of infusion, end of infusion, and 15 minutes post infusion) **(Study Day 70 only)**
- Vital signs obtained once **(Study Day 63 only)**
- Weight
- ECOG performance status
- CBC with differential and platelet count
- Serum chemistry
- BNP measured using an Alere Triage POC device (or if approved by OncoMed the site's laboratory) **(Study Day 70 only)**
- Concomitant medication
- Adverse event recording
- Blood for biomarkers **(Study Day 63 only)**
- Plasma for pharmacokinetics prior to the infusion and at the end of infusion (i.e., with 30 minutes pre- and post infusion) (**Study Day 70 only**)

12.6 Study Day 77

- Vital signs measured once
- Weight
- ECOG performance status
- CBC with differential and platelet count
- Serum chemistry
- Concomitant medication
- Adverse event recording

12.7 Study Days 84, 91, 98

- Abraxane®
- Gemcitabine
- Abbreviated physical examination **(Study Days 84 and 98 only)**

- Vital signs obtained once
- Weight
- ECOG performance status
- CBC with differential and platelet count
- Serum chemistry
- BNP measured using an Alere Triage POC device (or if approved by OncoMed the site's laboratory) **(Study Days 84 and 98 only)**
- ECG including PR interval, QRS duration, and QTc interval **(Study Day 84 only)**
- Transthoracic doppler echocardiogram with LVEF and peak tricuspid velocity determination **(Study Day 84 only)**
- Concomitant medication
- Adverse event recording
- Peripheral neuropathy assessment **(Study Day 84 only)**

12.8 Study Day 105

- Vital signs obtained once
- Weight
- ECOG performance status
- CBC with differential and platelet count
- Serum chemistry
- Concomitant medication
- Adverse event recording

As long as the subject has stable disease or a response, the subject should continue to be treated and beginning weekly at Day 112 will undergo the tests designated for Study Days 84, 91, 98, and 105. In addition, the following will be done every 8 weeks beginning at Day 112:

- a CT, spiral CT, or MRI of the chest, abdomen, and pelvis performed as outlined by the RECIST criteria 1.1 (see Appendix D),
- a CA 19-9 level obtained (if elevated at baseline),
- Serum pregnancy test for all females of childbearing potential
- a urinalysis with microscopic analysis
- a serum sample for anti-demcizumab antibody

Finally, a second course of demcizumab or placebo once every 2 weeks for 70 days will be given starting on Day 168 (see Section 8.1.1) and plasma for pharmacokinetics will be obtained prior to demcizumab or placebo infusion on Day 168, 182, 224 and 238, and at the end of demcizumab or placebo infusion on Day 168 and 224.

12.9 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. The following assessments must be performed on the day of study drug termination:

- Abbreviated physical examination
- Vital signs measured once
- Weight
- ECOG performance status
- CBC with differential and platelet count
- Serum chemistry
- BNP measured using an Alere Triage POC device (or if approved by OncoMed the site's laboratory) (unless performed within the last 28 days)
- Serum for anti-demcizumab antibody
- Plasma for pharmacokinetics
- Urinalysis with microscopic analysis **(unless performed within the last 28 days)**
- ECG including PR interval, QRS duration, and QTc interval
- Transthoracic doppler echocardiogram with LVEF and peak tricuspid velocity determination **(unless done within the last 28 days)**
- Tumor marker: CA 19-9 (if elevated at baseline)
- Serum pregnancy test for all females of childbearing potential
- Tumor assessment: **unless performed within 7 days of termination or at a prior response evaluation that documented progressive disease**: Diagnostic-quality, contrast-enhanced CT scans of chest and abdomen, as well as imaging of all other known sites of disease, performed as outlined by the RECIST criteria v1.1 (see Appendix D). Note: If another imaging method was used at baseline, the same imaging method must be used consistently throughout the study.
- Concomitant medication **(through 30 days following treatment termination)**
- Adverse event recording at the time of treatment termination and through 30 days following treatment termination

- Peripheral neuropathy assessment
- Blood for biomarkers (unless performed within the last 14 days)

12.10 Follow-up after Termination Visit

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

Serum pregnancy test for all females of childbearing potential 56 and 112 days following the treatment termination visit.

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 patients who have not progressed at the time of treatment termination until they receive subsequent treatment. 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 termination, 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.

SURVIVAL DATA: Once a patient has completed the treatment termination visit, overall survival follow up will be performed every three months +/- 1 week or more frequently at the request of the Sponsor for up to 5 years. Follow up may be conducted by telephone interview or chart review

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) 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 the RDC system. The clinical data and the site-specific laboratory data will be entered by site personal into the RDC system. Analysis of samples for antibodies to demcizumab will be performed by ICON Development Solutions. 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 CROs, and records retention for the study data will be consistent with the standard procedures for these organizations.

14.0 STATISTICAL PLAN

Table 7 presents the power to detect the difference between the control arm and the pooled demcizumab arms in the trial for the primary endpoint of PFS. Type 1 error is controlled at the 0.10 one sided level. Two hundred and one subjects followed until 125 PFS events have been observed will provide 80 percent power to detect a hazard ratio of 0.67 which corresponds to an increase in median PFS from 5.5 months to 8.2 months.

Table 7: Power for a Two Arm Comparison

Total #Subjects	Median Control	Median Treatment	Hazard Control	Hazard Treatment	Hazard Ratio	End of Study (months)	Total #Events	Events Control	Event Treat	Type1 Error	Power
201	5.5	5.5	0.126027	0.126027	1.000000	23	123.6	42.6	81.0	0.1	0.1000
201	5.5	6.0	0.126027	0.115525	0.916669	24	124.9	43.7	81.1	0.1	0.2068
201	5.5	6.5	0.126027	0.106638	0.846152	24	123.1	43.7	79.4	0.1	0.3466
201	5.5	7.0	0.126027	0.099021	0.785713	25	124.2	44.7	79.6	0.1	0.5033
201	5.5	7.5	0.126027	0.092420	0.733335	26	125.2	45.4	79.7	0.1	0.6507
201	5.5	8.0	0.126027	0.086643	0.687496	26	123.6	45.4	78.2	0.1	0.7664
201	5.5	8.2	0.126027	0.084530	0.670729	26	123.0	45.4	77.6	0.1	0.8041
201	5.5	8.5	0.126027	0.081547	0.647060	27	124.5	46.1	78.4	0.1	0.8563

In addition to PFS, subjects will also be followed for the overall survival endpoint. At the time of the PFS final analysis, which is anticipated to occur when approximately 87 deaths have been observed, an interim analysis for OS will take place. After this final analysis for PFS, there will be two more planned analyses for OS, one based on all deaths as of June 1 2017 and the final analysis based on all deaths as of November 1 2017. Table 8 presents the interim analysis plan for OS along with the power to detect a hazard ratio of 0.675 with type 1 error of 0.10. The efficacy boundary is determined from the O'Brien Fleming spending function while the futility boundary simply allows the study to continue while the estimated hazard ratio is less than 1 in favor of a survival benefit for demcizumab. The rejection boun dary for OS may have to be adjusted using the O'Brien Fleming spending function for the number of deaths actually observed at times of the interim analyses (100% information = 131 deaths).

Table 8: Summary of Power and Type 1 Error

	Interim 1 PFS Final Analysis	Interim 2 Deaths as of June 1 2017	Final Analysis Deaths as of Nov 1 2017
Z-Statistic (reject the null)	1.72	1.52	1.42
Z-Statistic (reject the alt)	0	0	1.42
Events Total	87	112	131
Events Control	34	43	49
Events Treatment	53	69	82
Cumulative Power (HR=0.675)	0.531	0.713	0.8
Cumulative Type 1 Error (1-sided)	0.043	0.076	0.1
Cumulative Prob. of Stopping for Futility (Alt)	0.036	0.042	0.201
Cumulative Pro. of Stopping for Futility (Null)	0.5	0.577	0.9

The study will have 80 percent power to detect a hazard ratio of 0.675 with a type 1 error of 0.10 one-sided. The study followup for overall survival will stop for futility at either the OS analysis done at the time of the PFS analysis or the subsequent interim analysis for OS if the hazard ratio is greater than 1 suggesting that treatment with demcizumab may shorten survival. The first analysis for OS will be based on all subjects who have died as of the data cutoff date for PFS.The final two analyses for OS will be based on all deaths on or prior to June 1 and November 1 2017. The probability of stopping for futility at the first interim when there is no treatment benefit is 0.5. The probability of stopping for futility at the first interim when demcizumab has an overall suvival benefit described by a hazard ratio of 0.675 is 0.036.

14.1 Data Safety Monitoring Board

A data safety monitoring board consisting of a Chairman, at least 2 medical oncologists and a statistician will meet quarterly to review the emerging data from the trial. In addition to the planned Data Review meetings, the sponsor and/or DSMB may convene ad hoc meetings, should they be deemed necessary. Specifically, the DSMB will review all adverse events (i.e., all Grades regardless of attribution to study drug) and safety data by treatment arm.

14.2 Study Stopping Rules

These stopping rules apply to all subjects randomized on the study. 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 v. 4.03) 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 non-small cell lung 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 9 presents the probability of exceeding the 15 percent threshold either at the formal interim or the final analyses of the trial.

Table 9: Probability CHF Rate will Exceed 15 Percent over Control

Control Rate	Dem Rate	Prob of exceeding 15 pct at Interim (67 subjects enrolled in demcizumab treated arm, 67 subjects in the control arm)	Prob of exceeding 15 pct at final (134 subjects with demcizumab, 134 subjects with control)	Prob of Not exceeding 15 pct at final	Total Prob of exceeding 15 pct	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.

14.3 Subject Populations for Analysis

As noted above, 201 evaluable subjects will be enrolled in the trial.

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

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

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

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

Missing values will not be imputed.

14.4 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.

14.5 Treatment Exposure

Treatment exposure will be summarized as duration on treatment and extent of exposure to demcizumab in Arms 2 and 3. 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.

14.6 Endpoints

14.6.1 Safety Endpoints

Safety endpoints include AEs; SAEs; physical examination; vital signs; clinical laboratory testing including assessment of BNP every 14 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; and anti-demcizumab testing. Safety endpoints will be analyzed by treatment arm using the Safety Population.

14.6.1.1 Adverse Events

All reported adverse events 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 adverse events in each treatment arm will be tabulated by seriousness, severity, and relationship to study drug.

14.6.1.2 Clinical Laboratory Assessments and Vital Signs

Clinical laboratory data (hematology, serum chemistry, and urinalysis with microscopic analysis) 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.

14.6.1.3 BNP Assessment

The proportion of subjects with at least two consecutive BNP assessments above 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 elevation ≥400 pg/mL will be summarized by treatment group.

Among the subjects in the demcizumab groups with two BNP measurements above 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 to ≥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.

14.6.1.4 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.

14.6.1.5 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 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.

14.6.2 Immunogenicity Endpoints

Immunogenicity endpoints will be analyzed using the ITT Population. The incidence of anti-demcizumab antibody development in each treatment arm 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.

14.6.3 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.

14.6.4 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.

14.6.4.1 Best Overall Response

The best overall response is defined as the best response recorded from the start of the treatment until disease progression (see detailed definition in Appendix D) 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 and for the pooled demcizumab arms.

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

14.6.4.2 Clinical Benefit Rate

The Investigator-assessed RECIST clinical benefit rate (i.e., the rate of complete response + partial response + stable disease) will be calculated for the pooled demcizumab arms and will be compared with control. In addition, the rates in each individual demcizumab arm will also be compared with control.

14.6.4.3 Progression-Free Survival and Duration of Response

The primary endpoint, 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 RECIST criteria for the ITT Population. The Kaplan-Meier method will be used to estimate the proportion of subjects without progression or death over time and the median progression-free survival time in the pooled demcizumab arms as well as each individual arm of the trial. The 95% confidence intervals for median progression-free survival time will also be calculated for the pooled demcizumab arms as well as each treatment arm. The p-values for the demcizumab treatment effects (pooled versus control as well as each individual demcizumab arm versus control) will be generated using a stratified Cox proportional hazards model. The stratification factors will be performance status (0 or 1), region (United States/ Canada or Europe/Australia) and CA19-9 (0 – ULN, >ULN – 59ULN, >59ULN). Subjects who have not experienced death (within 56 days of the last tumor assessment) 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 CA19-9 (0 – ULN, >ULN – 59ULN, >59ULN) 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 one or both of the 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 dependent covariate to capture the effect 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 demcizumab will be used. The variable will be zero unless a subject has started a second course of demcizumab in 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).

14.6.5 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 criteria and determined by 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, 9 weeks post-baseline, and 18 weeks post-baseline. These summary statistics will also be presented for differences from baseline at 9 and 18 weeks post-baseline. Along with the summary statistics, the 95% confidence intervals of the mean tumor length for each treatment arm and the pooled demcizumab arms at each of the three timepoints will also be presented. An ANCOVA model will be used to test the hypothesis that there is no difference between treatment arms as well as no difference between the pooled demcizumab arms and control with regard to changes from baseline tumor length at scheduled tumor assessments. Treatment and ECOG PS and region will be factors in the model and baseline tumor length will be used as a covariate. Missing values will not be imputed.

In 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 t 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 adverse event, 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 thearms of the study as well as between the pooled demcizumab arms and control.

14.6.6 Duration of Response

The Investigator and IRF (optional) assessed 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. The Kaplan-Meier method will be used to estimate the duration of response. The 95% confidence intervals for duration of response will also be calculated for the pooled demcizumab arms as well as each treatment arm. The p-value for treatment effect (pooled versus control and each demcizumab arms versus control) will be generated using a Cox proportional hazards model. Subjects who have not experienced death or progression by their last contact will be censored at the time of their last radiographic response assessment.

14.6.6.1 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 arms pooled demcizumab arms and control as well as the individual demcizumabarms versus control 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.

14.6.7 Overall Survival

A comparison of the overall survival between the pooled demcizumab arms and control as well as each individual demcizumab arm versus control will be performed. Overall survival is defined as the number of days from randomization until death occurs. 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 intervals for median survival times will also be calculated. A p-value for treatment effect will also be generated using a stratified Cox proportional hazards model. The stratification factors will be performance status and CA19-9 (0 – ULN, >ULN – 59ULN, >59ULN). Subjects who have not experienced death by their last contact date will be censored at that time and the number and percentage of these subjects will be displayed. If there is a disparity in discontinuation rates between treatment arms, a sensitivity analysis will be performed to assess the impact.In addition, a robust test procedure that adaptively weights which time points receive the greatest weights in the construction of the test (Ref 19) will be applied to the OS data. This test is based on a weighted Kaplan Meier 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 Kaplan Meier curves between the

two arms restricted up to the time point T, which is the minimum of the two largest observed death times from the two arms combined. Landmark Survival

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

14.7 Termination Criteria

Randomization will be terminated when at least 201 subject have been randomized. Randomization may be extended beyond 201 subjects to ensure that 201 evaluable subjects are enrolled. All ongoing subjects will continue to be dosed until disease progression, subject withdrawal, or the Investigator withdraws subjects from the study.

14.8 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 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 all regulatory requirements and the 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 adverse events.

Investigators are required to follow their respective IRB or IEC requirements for the reporting of Serious Adverse Events and written safety reports to the IRB or IEC. Investigators must immediately forward to their IRBs or IECs any updates 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., Clinical Research Associate [CRA]) to inspect study data, subjects' medical records, and electronic data capture (EDC) fields in accordance with current GCPs. During the site visit, the OncoMed CRA or representative will review the following:

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

The OncoMed CRA or representative will be responsible for reviewing completed EDC 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 EDC system. The EDC screens should be completed in accordance with instructions from OncoMed.

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

17.6 Investigational Medicinal Product Accountability

All IMP (demcizumab and placebo) required for completion of this study will be provided by OncoMed or its agent.

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 Drug 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.

18.0 REFERENCES

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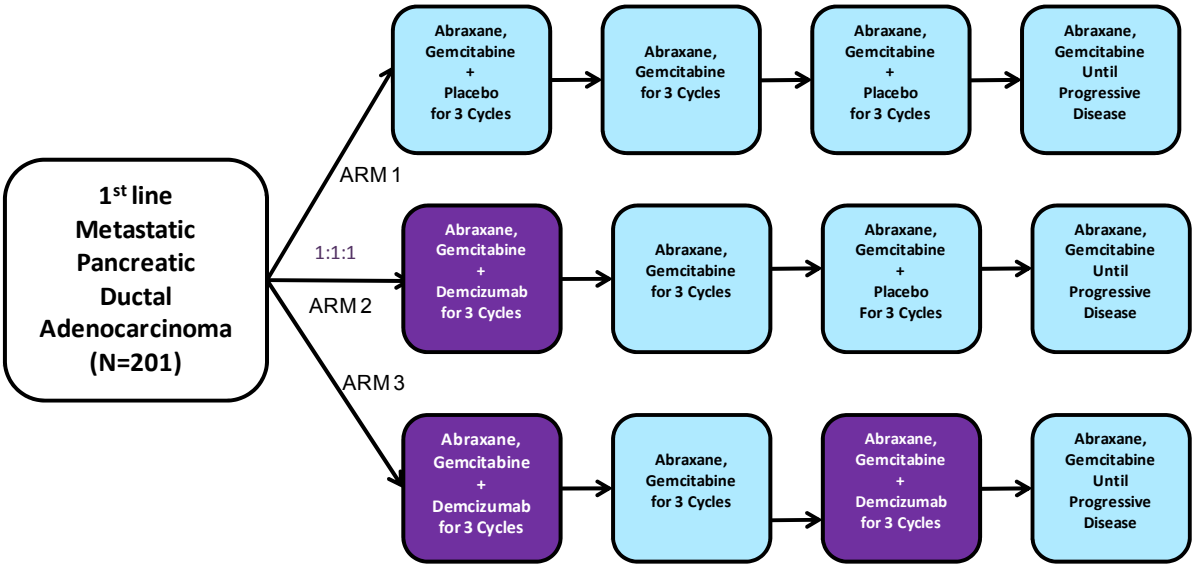
APPENDIX A: STUDY SCHEMA

1st Line Metastatic Pancreatic Ductal Adenocarcinoma:

1:1:1 Randomization (n = 201)



If a drug cannot be administered within the specified time window (See Section 12.0) , the missed dose cannot be administered at a later time point. Instead, the drug is to be administered until the next scheduled dose.

APPENDIX B: SCHEDULE OF ASSESSMENTS

Day(s)	-28 to 0	0	7	14	21	28	35	42	49	56	63	70	77	84	91	98	105[r]	Termination Visit	Follow-up after termination visit
Informed consent[a]	X																		
Abraxane®[b]		X	X	X		X	X	X		X	X	X		X	X	X[r]			
Gemcitabine[b]		X	X	X		X	X	X		X	X	X		X	X	X[r]			
Demcizumab or placebo[b]		X		X		X		X		X		X							
Past medical history	X																		
Physical exam[c]	X	X		X		X		X		X		X		X		X		X	
Vital signs [d,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[s]	
Height	X																		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
INR/aPTT	X																		
BNP[g]	X			X		X		X		X		X		X		X		X[t]	
Anti-demcizumab antibody		X[u]								X[u]								X[u]	
Urinalysis with microscopic analysis	X					X				X[y]								X[t]	
ECG[h]	X					X				X				X				X	
Transthoracic doppler echocardiogram with LVEF and peak tricuspid velocity determination[i]	X					X				X				X				X[t]	
Tumor marker CA 19-9	X									X[q]								X[q]	

APPENDIX B: SCHEDULE OF ASSESSMENTS (CONT'D)

Day(s)	-28 to 0	0	7	14	21	28	35	42	49	56	63	70	77	84	91	98	105[r]	Termination Visit	Follow-up after termination visit
Serum pregnancy test[l]	X									X								X	X
Chest, abdomen, and pelvis radiographic evaluation[k]	X									X								X[v]	
CT pulmonary angiogram (if applicable)[aa]		If pulmonary hypertension is diagnosed, ……..perform CT pulmonary angiogram (or other appropriate study) to rule out pulmonary embolism……																	
Concomitant meds[l]		X …… X																	
Adverse event evaluation[l]		X …… X																	
Peripheral neuropathy assessment	X	X				X				X				X				X	
Pharmacokinetics		X[p]		X[p]						X[p]		X[p]						X	
Blood for biomarkers[m]		X			X		X		X		X							X	
Optional Pharmacogenomics[n]		X																	
Colonoscopy and/or upper GI endoscopy[o]	X																		
Head CT or MRI	X																		
FFPE (if tissue blocks available)[w]	X																		
Survival data including date and cause of death[x]																			X[x]
Subsequent anti-cancer therapies[y]																			X
Response assessment data[z]																			X

NOTES TO APPENDIX B

a. Written informed consent is required before performing any study-specific tests or procedures and may be obtained at any time prior to such tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 0 may be used for screening assessments rather than repeating such tests.b. Demcizumab or placebo and gemcitabine and Abraxane® must be dosed as described in Section 8.0. Dosing of gemcitabine, Abraxane®, and demcizumab or placebo must be administered within ± 2 days of the Study Day listed in the protocol. If a drug cannot be given within this 2 day window, then the dose of that drug is permanently missed.

c. A full physical examination will be done at screen[i]ng. Subsequently, an abbreviated physical examination will performed at Day 0, every other week while on treatment and at treatment termination. 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.

d. On the day of demcizumab or placebo dosing, pre-infusion, 15 minutes after start of infusion, end of infusion, and 15 minutes post infusion on the days of dosing.

e. Vitals obtained once at the visits where demcizumab or placebo is not administered (Study Days 7, 21, 35, 49 63, 77, 84, 91, 98 and 105).

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

g. BNP measured using an Alere Triage POC device (or if approved by OncoMed the site's laboratory).

h. A 12-lead ECG must be performed and must include assessment of the PR interval, QRS duration, and QTc interval.

i. A doppler echocardiogram with left ventricular ejection fraction and peak tricuspid velocity determination to be repeated every 28 days while subjects remain on therapy.

j. Serum pregnancy test (women of childbearing potential only) must be obtained within 7 days prior to randomization, every 56 days while on study, at the termination visit and 56 and 112 days following the termination visit

k. Conventional CT, Spiral CT, or MRI of the chest, abdomen, and pelvis performed as outlined by RECIST 1.1 (see Appendix D). Note: The same radiographic technique of each region must be used consistently throughout the study.

l. To be collected for 30 days after treatment termination..

m. A predose sample of a total of 9 mL of blood will be drawn on Days 0, 21, 35, 49 and 63 and at treatment termination, unless one has been obtained during the prior 14 days for subjects continuing on study drug to evaluate changes in plasma proteins (4 mL) (e.g., VEGF, βFGF, SDF1, PLGF, SCF, 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.

n. Pharmacogenomics: 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.

o. Colonoscopy and/or upper gastrointestinal endoscopy to rule gastrointestinal involvement in subjects having symptoms suggestive of possible gastrointestinal involvement.

p. Plasma samples for PK analysis to be obtained at the end of the demcizumab or placebo infusion on Days 0, 56, 70, 168 and 224; prior to the demcizumab infusion on Days 0, 14, 56, 70, 168, 182, 224 and 238 (prior to the paclitaxel infusion) and at treatment termination. Instructions for the collection handling, storage, and shipment of these samples are provided in the Study Reference Binder.

q. If elevated at baseline.

r. As long as the subject has stable disease or a response, the subject may continue to be dosed weekly for 3 weeks followed by a week of rest for gemcitabine and Abraxane® and will undergo the tests designated for Study Days 84, 91, 98, and 105. In addition, 1) every 8 weeks the subject will have a conventional CT, spiral CT, or MRI of the chest, abdomen, and pelvis performed as outlined by the RECIST criteria 1.1 (see Appendix D), 2) every 8 weeks the subject will have a CA 19-9 level obtained, 3) a urinalysis with microscopic analysis will be performed every 56 days and 4) every 4 weeks the subject will have a transthoracic doppler echocardiogram with LVEF and peak tricuspid velocity determination. 5) A second course of demcizumab or placebo once every 2 weeks for 70 days will be given starting on Day 168, 6) plasma for pharmacokinetics will be obtained prior to demcizumab or placebo infusion on Day 168, 182, 224 and 238, and at the end of demcizumab or placebo infusion on Day 168 and 224. Note: The same radiographic technique of each region that was used at baseline must be used throughout the study.

s. Any subject with demcizumab- induced or -exacerbated hypertension will continue to have their BP monitored once every 2 weeks for 8 weeks. If the BP is not <150/90 mmHg at the end of the 8-week period, then the BP will continue to be monitored once every 2 weeks until it is <150/90 mmHg for a 4-week period.

t. Unless done within last 28 days. If a subject has a BNP of ≥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 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.

NOTES TO APPENDIX B CONT'D

u. Serum sample for immunogenicity to be obtained at baseline, every 8 weeks (prior to demcizumab or placebo infusion) while the subject is on study and at treatment termination. Instructions for the collection, handling, storage, and shipment are provided in the Study Reference Binder.

v. Perform tumor assessment at screening (Study Days -28 to -8), every 8 weeks thereafter until disease progression, and at the termination visit (unless performed within 7 days of termination or at a prior response evaluation that documented progressive disease). The schedule of every 8 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 within Study Days -28 to -8 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 D).

w. If available, archival FFPE tumor specimens obtained at the time of surgical resection or from a core biopsy 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.

x. 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).

y. 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 aa.).

z. 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.

aa. A CT pulmonary angiogram (CTPA) should be performed if pulmonary hypertension is diagnosed (i.e., the subject has a peak tricuspid velocity >3.4 m/s on Doppler echocardiogram, has been seen by a cardiologist and was diagnosed with clinically significant pulmonary hypertension) 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.

APPENDIX C: 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 D: RECIST CRITERIA 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 13) 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 portion 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 patient with 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 patient with 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.

- 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 E: 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 patients.

APPENDIX F: SAMPLE INFORMED CONSENT

PROTOCOL M18-006: YOSEMITE: A 3-Arm Phase 2 Double-Blind Randomized Study of Gemcitabine, Abraxane® Plus Placebo versus Gemcitabine, Abraxane® plus 1 or 2 Truncated Courses of Demcizumab in Subjects with 1st-line Metastatic Pancreatic Ductal Adenocarcinoma

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 1st-line Metastatic Pancreatic Ductal Adenocarcinoma.

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 compare the efficacy and safety of 1 or 2 truncated courses of a new experimental drug, demcizumab, when given in combination with gemcitabine and Abraxane® to gemcitabine and Abraxane (plus placebo). The administration of Gemcitabine and Abraxane® is a standard treatment for subjects with pancreatic cancer. You also may be given antiemetic therapy and/or hematopoietic growth factors and/or red blood cell/platelet transfusions, if your study doctor considers it appropriate

Demcizumab is a humanized monoclonal antibody and was developed to target cancer stem cells. Demcizumab may block the growth of cancer stem cells, 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 Administration (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

Up to 201 subjects will be enrolled at up to 65 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.

If enrolled in the study you will receive intravenous (in the vein) infusions of the demcizumab (or placebo) once every 2 weeks for the duration defined by your treatment group stated in the next section. Abraxane® and Gemcitabine will be administered on Days 1, 8 and 15 of each 28-day treatment cycle and will continue until toxicity necessitates reducing or holding a dose). The treatment arms are defined in the next section. 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. You will undergo assessments every 8 weeks to determine the status of your *disease* and for safety at every visit and through 30 days following the termination of study drug

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; and B-type natriuretic peptide [BNP], which indicate how well your heart if 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 samples for special tests will be sent to OncoMed Pharmaceuticals, 800 Chesapeake Dr., Redwood City, California, U.S.A, 94063 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 pancreatic cancer is: CA 19-9. If your baseline: CA 19-9 tumor marker is not elevated, the test will not be repeated during the study.

- 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, , at baseline and then every 8 weeks, and at treatment termination, to determine if you are developing antibodies to demcizumab. . The anti-demcizumab antibody samples will be sent to ICON, [redacted].

- Pharmacokinetic Analysis: Blood samples will be obtained prior to your demcizumab (or placebo) infusion on Study Days 0, 14, 56, 70, 168, 182, 224 and 238, and at the end of the demcizumab infusion (prior to chemo infusion) on Days 0, 56, 70, 168, 224 and at treatment termination visit to determine how the demcizumab is distributed and eliminated from your body. The PK samples will be sent to ICON, [redacted].

- Biomarkers: At specified time points blood samples will be obtained to assess whether the demcizumab is producing desired changes to the genes and proteins related to your cancer. A predose sample of 9 mL of blood will be drawn on Study Days 0, 21, 35, 49 and 63 and at treatment termination.

- In addition, archival tumor tissue sections (formalin-fixed paraffin-embedded (FFPE)) will be collected if available for gene and protein testing of biomarkers related to your cancer.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, gemcitabine and Abraxane treatment.

In addition, you will have an ECG and doppler echocardiogram performed during screening, then every 28 days on study and at treatment termination. 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 a head CT or MRI at baseline and CT scans and/or other radiographs performed every 56 days to assess the status of your tumor. A CT pulmonary angiogram (CTPA) (or MR angiogram or VQ scan if you have an allergy to the contrast dye) may be performed if you are diagnosed with pulmonary hypertension to see if you might 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. Results of your standard of care tests or examinations before signing this informed consent form and within 28 days prior to Day 0 may be used for screening assessments rather than repeating such tests. Your doctor will:

- Conduct a review of your physical health and medical history, including a review of any medications you are or have been taking.
- Conduct a physical exam including height and weight will be performed, Peripheral neuropathy assessment and vital signs including your pulse, blood pressure, breathing rate and temperature will be measured.
- Collect blood and urine samples for routine testing.
- Collect blood for testing of tumor markers. Approximately 3 tablespoons of blood will be taken at this visit.
- Complete an electrocardiogram (ECG), doppler echocardiogram, and either a computerized tomography (CT) scan or magnetic resonance imaging (MRI) of your chest, abdomen, pelvis, and head.
- Order a colonoscopy and/or upper gastrointestinal endoscopy if your tumor involves your esophagus, stomach, or intestinal tract or if you have symptoms that suggest that that your tumor may involve these areas, to ensure that your tumor does not currently involve your gastrointestinal tract.
- Complete a serum pregnancy test within 7 days prior to the first dose of demcizumab if you are a female of childbearing potential, 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 3.5 mg/kg demcizumab or placebo as shown in the treatment arms, below. A placebo looks like the demcizumab, but does not contain any medication. Dosing of Gemcitabine, Abraxane® and Demcizumab or placebo must be done within ± 2 days of the Study Day listed in the protocol. If a drug cannot be given within this 2 day window, then the dose of that drug is permanently missed.

Demcizumab 3.5 mg/kg or placebo will be administered by IV infusion (prior to the administration of Abraxane® and Gemcitabine) once every 2 weeks for either one (1st course through Study Day 70) or two (2nd course begun on Study Day 168 and continued through Study Day 238) 70 day courses. You will receive 6 doses of demcizumab or placebo during the 1st 70 day course of treatment and an additional 6 doses of demcizumab or placebo during the 2nd

70 day course of treatment (beginning on Day 168). You will be randomly (by chance) assigned to one of the three treatment arms:

Arm 1:

- Abraxane® and gemcitabine plus **placebo** (3 cycles), then
- Abraxane® and gemcitabine (3 cycles), then
- Abraxane® and gemcitabine plus **placebo** (3 cycles), then
- Abraxane® and gemcitabine until disease progression

Arm 2:

- Abraxane® and gemcitabine plus **demcizumab** (3 cycles), then
- Abraxane® and gemcitabine (3 cycles), then
- Abraxane® and gemcitabine plus **placebo** (3 cycles), then
- Abraxane® and gemcitabine until disease progression

Arm 3:

- Abraxane® and gemcitabine plus **demcizumab** (3 cycles), then
- Abraxane® and gemcitabine (3 cycles), then
- Abraxane® and gemcitabine plus **demcizumab** (3 cycles), then
- and then Abraxane® and gemcitabine until disease progression

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, or whether you are receiving demcizumab or placebo.

Abraxane®

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

Gemcitabine

Gemcitabine must be administered after the administration of demcizumab and Abraxane®. Gemcitabine should be administered by IV infusion at a starting dose of 1000 mg/m^2 over

30 minutes once weekly for 3 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest every 28 days. The dose of gemcitabine may be reduced over time if necessary to reduce toxicity.

Study Day 0: This is considered your randomization visit where you will start your study treatment. This visit will take approximately (3) hours. The following assessments will be done prior to the infusion of demcizumab or placebo, Abraxane®, and Gemcitabine: abbreviated physical examination including weight; Peripheral neuropathy assessment 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.

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

- **Study Days 7, 14, 21, 28, 35, 42, and 49:** demcizumab or placebo will be given on Days 14, 28 and 42 only, Abraxane®, and Gemcitabine will be given on Study Days 7, 14, 28, 35 and 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 your receive demcizumab or placebo, and also your BNP will be measured those days. At Day 28 only, Peripheral neuropathy assessment

Blood will be taken for routine testing. On Day 28, blood will be taken before the infusion of demcizumab (or placebo), for pharmacokinetic testing. At Day 21, Day 35 and Day 49, 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.

- At Day 28 only, a urine specimen will be obtained for routine testing. On Day 28, an ECG and doppler echocardiogram will be done.

Study Day 56: The following assessments will be obtained on Day 56: 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 and abbreviated physical exam BNP measured, urine specimen for routin*e* testing, Peripheral neuropathy assessment.

Blood will be obtained for routine testing, pharmacokinetics, immunogenicity and if you are a female of child-bearing potential for a serum pregnancy test. Approximately 3 tablespoons of blood will be drawn during this visit. An ECG and doppler echocardiogram will be done. Tumor marker: CA 19-9 (if elevated at baseline) will be done, In addition, on Day 56, you will undergo a CT scan or MRI of the chest, abdomen, and pelvis, 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, Abraxane®, and Gemcitabine

If the CT scan or MRI shows disease progression, you will be taken off the study and will undergo assessments listed under **Treatment Termination**. At this point, your study doctor will discuss alternate treatment options.

Study Days 63 and 70: demcizumab or placebo, will be given on Day 70 only, Abraxane®, and Gemcitabine will be given on Day 63 and 70. 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 on the day that your receive demcizumab (or placebo).

Blood will be taken for routine testing, blood will also be taken for biomarkers on day 63, and blood will also be taken for pharmacokinetics on day 70. Approximately 3 tablespoons of blood will be drawn on Study Days 63 and 70. BNP will be also measured

Study Day 77: 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. Approximately 3 tablespoons of blood will be taken for routine testing. An abbreviated physical examination will be performed

Study Days 84, 91 and 98: Abraxane®, and Gemcitabine. 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; Peripheral neuropathy assessment (Day 84 only) ,and vital signs. An abbreviated physical examination will be performed on Days 84 and 98 only, and BNP measured on Days 84 and 98 only.

Blood will be taken for routine testing. On Study Day 84 only, blood will also be obtained for testing for antibody formation to demcizumab. Approximately 3 tablespoons of blood will be drawn on Study Days 84, 91, and 98.

On Day 84 only an ECG and doppler echocardiogram will be done.

Study Day 105: 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.

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

As long as your disease is stable or shows a response, you may continue to be treated. You will undergo the tests listed for Study Days 84, 91, 98, and 105. In addition, every 8 weeks you will

undergo a CT scan or MRI of the chest, abdomen, and pelvis, to assess whether your cancer has improved, progressed, or is stable.

In addition, every 8 weeks blood will be obtained for tumor markers, if applicable and if you are a female of child-bearing potential for a serum pregnancy test. You will also have a doppler echocardiogram every 4 weeks.

TERMINATION VISIT

When your tumor has progressed or you are going to be removed from the study for another reason 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; Peripheral neuropathy assessment and vital signs.

Blood samples will be obtained for routine testing (including BNP), antibody formation to demcizumab, pharmacokinetic testing, and 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. In addition, if you are a female of child-bearing potential, blood will be obtain*ed* for a serum pregnancy test. A urine specimen will be obtained unless one was obtained within 28 days of treatment termination. An ECG will be done and a doppler echocardiogram will be performed. A repeat CT scan or MRI of the chest, abdomen, and pelvis will be obtained unless performed within 7 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 Termination 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.

If you are a female of child-bearing potential, you will have a serum pregnancy test done 56 and 112 days after your termination visit.

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 greater than 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 less than or equal to 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. Below is a table that summarizes the treatment and tests that will be performed through Day 105. Similar testing will continue to be performed after Day 105 until you are removed from the study.

Day(s)	-28 to 0	0	7	14	21	28	35	42	49	56	63	70	77	84	91	98	105	Termination Visit	Follow-up after termination visit
Informed consent Past medical history/ height/INR/aPTT Serum pregnancy test Head CT or MRI FFPE (if tissue blocks available) Colonoscopy and/or upper GI endoscopy (in subjects having symptoms of possible gastrointestinal involvement)	X																		
Abraxane/ Gemcitabine		X	X	X		X	X	X		X	X	X		X	X	X			
Demcizumab or placebo		X		X		X		X		X		X							
Physical exam	X	X		X		X		X		X		X		X		X		X	
Weight and vital signs/ ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant meds/ Adverse event evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC w/diff, plts/ Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BNP	X			X		X		X		X		X		X		X		X	
Peripheral neuropathy assessment	X	X				X				X				X				X	
Anti-demcizumab antibody/ ECG/ Transthoracic doppler echocardiogram	X					X				X				X				X[t]	
Urinalysis	X					X				X								X	
Tumor marker CA 19-9 Chest, abdomen, and pelvis radiographic evaluation	X									X								X	
Blood for biomarkers		X			X		X		X		X							X	
Pharmacokinetics		X		X						X		X						X	
Optional Pharmacogenomics		X																	
Survival data including date and cause of death) Subsequent anti-cancer therapiesy Response assessment data																			X

POSSIBLE RISKS AND DISCOMFORTS

You may have side effects while you are in the study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study treatment that are unknown at this time. You should tell the study doctor/staff about anything that is bothering you or any side effects you have, even if you do not think they are related to the study drug.

The following is a list of the most medically significant or most common side effects reported in completed studies of demcizumab, Abraxane® and/or gemcitabine. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study treatment/therapy and some may never go away. The study doctor may alter the dosage regimen of one or more of these drugs (if allowed by the study) or give you medicines to help lessen the side effects. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

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, 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 addition, 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 3 months. As a result, demcizumab will not be given on an ongoing basis in this study. Instead, a shortened regimen of 6 doses over 70 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 70-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. It is possible that you may receive a lower dose of gemcitabine and/or Abraxane® than you would have received if you were not participating on this study due to additional toxicities caused by demcizumab.

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)

Abraxane®

Very common (a 10% or more chance that this will happen):

- anemia (a decrease in the number of red blood cells (which may make you feel weak or tired)
- low number of white blood cells with or without fever (that may make it easier get infections)
- a decrease in the number platelets, the cells that help your blood to clot (which may lead to unusual bleeding or bruising under the skin)
- constipation
- diarrhea
- nausea
- vomiting
- stomach pain
- pain, swelling or sores on the inside of the mouth
- neuropathy, a disorder of the nerves which can cause tingling or numbness, with weakness, or decreased sensation or movement
- dizziness
- headache
- feeling tired or weak
- pain (including muscle, joints, bone, and chest pain)
- swelling caused by fluid held in the tissues, especially of the ankles, feet or fingers
- fever
- chills
- decreased appetite
- change in taste
- weight loss
- difficulty sleeping
- depression
- cough
- shortness of breath
- hair loss
- rash, possibly red, bumpy or generalized
- itchiness
- changes in nails, including discoloration or separation from nailbed
- abnormal liver function test results
- dehydration (loss of water and minerals in the body)
- nose bleed

Common (between a 1% to less than 10% chance that this will happen):

- bone marrow depression which is a severe reduction of red or white blood cells and platelets (at nearly the same time) which can cause weakness, bruising, or make infections more likely
- infections, including pneumonia or of the lung, mouth, gallbladder, urinary tract, nail, or hair follicle, (which may be bacterial, fungal or viral)
- a very severe infection of the blood which may include a decrease in blood pressure
- inflammation of the lung passages
- thickening, inflammation or scarring in the lungs which may cause breathlessness, cough
- inflammation of the bowel causing abdominal pain or diarrhea
- blockage of the intestine
- trouble swallowing
- indigestion or upset stomach
- abnormal chemistry or electrolyte blood test results
- abnormal kidney function test results
- acute kidney failure
- blood in the urine
- lack of muscle coordination
- muscle weakness
- anxiety
- nasal congestion
- mouth or throat pain
- dry mouth, nose, and throat
- coughing up blood or bloody sputum
- blood clot in the lungs or in deep vein
- fluid in the chest cavity
- red or flushed skin
- dry skin
- hand-foot syndrome, involving reddening, swelling, numbness and peeling of palms and soles of feet
- high blood pressure
- low blood pressure
- faster heart beat
- watery eyes
- changes in vision or blurry vision
- infusion site reactions (described as discomfort, bleeding or bruising/swelling at the needle site, and in some instances infection or leaking of IV fluid outside of blood vessel into the surrounding tissue)
- localized swelling due to build up of lymph fluid

Uncommon (between a 0.1 to less than 1% chance that this will happen):

- a decrease in the heart's ability to pump blood to all parts of the body and possibly heart failure
- irregular or slow heart beat
- stopping of the heart
- allergic reaction (may include skin inflammation, rash, trouble breathing, trouble speaking, fever), sometimes fatal
- syndrome involving abnormal blood clotting, with decreased platelets, bruising (including tiny red or purple spots under the skin) and possibly leading to blood clots
- edema/swelling and cyst formation of the macular area of the retina
- irritation and redness of the thin membrane covering the eye
- inflammation of the cornea
- too much fluid in the body
- feeling unwell
- sleepiness
- scaly or peeling skin
- hives
- a loss of nerve function in the muscles of the face

Additional side effects observed during post-marketing surveillance of Abraxane, not otherwise noted above include:

- a loss of nerve function in the muscles of the face or the eyes
- lack of movement in the vocal cords with possible voice changes
- skin sensitivity to sunlight
- potentially life threatening skin rash with skin blistering
- skin or tissue damage from prior radiation therapy can become damaged again, when a person receives chemotherapy after having had radiation therapy. This is referred to as radiation recall and may involve redness, peeling, pain, and swelling. Skin changes have been noted to range from mild redness to tissue death. Radiation recall may also occur in the lungs and other internal organs.

Abraxane® in Combination with Gemcitabine

In subjects with metastatic pancreatic cancer, who received the combination of Abraxane® and gemcitabine, there may be an increase of blood infections. Contact your study doctor immediately if you develop a fever. Your study doctor will evaluate if your fever is an early sign of a serious infection, which may require treatment.

A particular lung illness, known as pneumonitis (thickening, inflammation or scarring in the lungs with breathlessness, or cough), appears to occur more often (4%) when the two drugs are given together. This lung illness requires early detection and treatment as it may be life-threatening or even fatal. Therefore, it is important that you promptly tell your study doctor if you have worsening shortness of breath, difficulty breathing, fever, or a dry cough (not productive), for further evaluation and possible treatment.

In addition, acute renal or kidney failure and hemolytic uremic syndrome (a syndrome involving abnormal blood clotting, with decreased platelets, bruising including tiny red or purple spots

under the skin, and possibly leading to blood clots) have been reported commonly and uncommonly, respectively, in combination of Abraxane® with gemcitabine.

Gemcitabine

clinically important side effects of gemcitabine

Very common (a 10% or more chance that this will happen):

- blood and protein in the urine
- fluid retention (swelling of the hands, feet or face)
- difficulty breathing

Uncommon (between a 0.1 to less than 1% chance that this will happen):

- acute kidney failure (which can include hemolytic uremic syndrome)
- severe hepatic toxicity (example: hepatic failure, hepatic veno-occlusive disease)
- severe pulmonary toxicity (example: interstitial pneumonitis, pulmonary edema, adult respiratory distress syndrome

Additional side effects observed during post-marketing surveillance of gemcitabine, not otherwise noted above include:

- posterior reversible encephalopathy syndrome (a very rare condition known as posterior reversible encephalopathy syndrome has occurred when gemcitabine is given alone or in combination with other chemotherapy medications. Therefore, you should tell your study doctor if you have one or more of the following symptoms; headache, abnormal shaking of body, sleepiness, increased blood pressure, feeling confused, abnormal vision including loss of vision, loss of muscle control or muscle weakness, numbness or tingling in extremities)
- capillary leak syndrome (A very rare condition known as capillary leak syndrome that causes leaking of fluid outside of blood vessels has occurred when gemcitabine is given alone or in combination with other chemotherapy medications. Therefore, you should tell your study doctor if you have one or more of the following symptoms: fatigue; lightheadedness or fainting; pain in arms, legs, or stomach or all over body; swelling in face or body; difficulty breathing; low blood pressure)
- pulmonary fibrosis (excess of fibrous tissue in the lung and a severe pulmonary toxicity)
- vasculitis (an inflammation of the small blood vessels described as pain, heat, and redness to the affected part of the body)
- gangrene (dying tissue due to lack of blood supply described as skin discoloration, severe pain, foul smelling leakage from a sore, and may include swelling, and increased temperature to the affected region of the body)

You should inform your study doctor if you are planning any dental work while on study, as some study subjects have an increased risk of bleeding. It may be advisable to use a soft-bristled tooth-brush and to be careful when using dental floss and toothpicks.

Infusions:

Demcizumab or placebo, Abraxane and Gemcitabine 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

Pregnancy Risk with study treatments

There is a very high risk that demcizumab may be harmful to an unborn baby (embryo or fetus) or newborn child. In addition, Abraxane® and gemcitabine can cause harm to an unborn child if given to a pregnant woman. You cannot take part in this study if you are pregnant or breast-feeding. Because of the possible risks to an unborn child, if you are a female who can become pregnant, you will be asked to take a pregnancy test prior to starting study treatment. It is important that both men and women take steps to prevent pregnancy through the use of adequate contraception (for example, a barrier or hormone method or abstinence) prior to study entry during the study and for 6 months after completion of the study.

Females: If you decide to take part in this study, you should avoid becoming pregnant while receiving the study treatment. You must commit to complete abstinence from heterosexual contact, or agree to use medical doctor-approved contraception throughout the study and for 6 months following completion of the study without interruption. If you become pregnant while on the study or within 6 months following completion of the study, you must tell the study doctor right away. If this happens while you are on the study, the study treatment will be discontinued. The study doctor will follow you and your pregnancy to completion.

Males: If you have a partner of childbearing potential, you should avoid fathering a child while receiving study treatment and for 6 months after completion of the study. You must agree to complete abstinence from heterosexual contact or use a condom during sexual contact with a

female of child bearing potential while receiving study treatment and within 6 months after completion of the study. If your partner becomes pregnant while you are receiving study treatment or within 6 months after completion of the study, you must tell the study doctor right away. If your partner becomes pregnant while you are on study, you will remain on the study. If your partner becomes pregnant during the study or within 6 months after completion of the study, 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, or 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 subjects 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.

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 Web site 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 (to be used only for clinical purposes), 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 access 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 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. Your date of birthmay 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 countries outside of the EEA, that do not have the same protections as your country we will make sure that your information will be treated with a goodlevel 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).). Following the end of the study, or after you have withdrawn from the study before its conclusion, your study doctor (or appointed delegate) may seek to establish your long term health status by accessing your hospital records, or publicly available sources such as national registries, newspaper obituaries and social networking websites. Attempts may also be made to contact you or your relatives to ascertain this information. If you do not want this information about you to be collected, you may record your objection with your study doctor at any time.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*n* 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

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 Subject or Subject'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 G: SAMPLE PHARMACOGENOMICS AND TUMOR DNA TESTING INFORMED CONSENT

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 OMP-21M18 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 OMP-21M18 (the study drug), the Notch/DLL4 pathways (the targets of the OMP-21M18) and/or other genes related to your cancer. Only DNA research related to OMP-21M18 or to the diseases for which this drug is 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 OMP-21M18 and gemcitabine 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.

You can also decide not to take part at all in DNA research. 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?

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 Subject number from the main study. After the study is officially over, the Subject 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 Subject 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 Food and Drug Administration (FDA) or the European Medicines Evaluation Agency (EMEA)

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 OMP-21M18 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 subjects' 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

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 provide the Optional Pharmacogenomics Specimen

☐ **Yes** ☐ **No**

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

☐ **Yes** ☐ **No**

_____
Printed Name of Subject or Subject's Authorized Representative

_____ _____
Signature of Subject or Subject'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 Ethics Committee deems a witness signature is necessary.

APPENDIX H: PROTOCOL AMENDMENTS SUMMARY OF CHANGES

AMENDMENT 1: 24 NOVEMBER 2014

RATIONALE

Study M18-006 has been amended for the following reasons:

The following changes were made at the request of the FDA. The inclusion criteria for bilirubin was reduced to 1 X ULN, ≥Grade 2 pulmonary hypertension was added as a treatment termination criteria, a section was added regarding the role of the DSMB and clarifying the data that they will review and the sample informed consent was revised to clarify that patients will receive 6 doses of demcizumab or placebo during each of the two 70 day truncated courses of therapy and that patients may receive less intensive gemcitabine/Abraxane therapy than if they were not on the study due to demcizumab toxicity.

In addition, minor changes were made in the protocol to ensure consistency throughout the document and/or provide clarity.

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.

Synopsis	
Section 5.0	OVERALL STUDY DESIGN AND PLAN – DESCRIPTION
Section 8.1.6	Treatment Modification and Termination Criteria
Section 8.4	Concomitant and Prohibited Therapy
Section 12.9	Termination Visit
Section 12.10	Follow-up after Termination Visit
Section 14.1	*Data Safety Monitoring Board*
Section 14.2	Study Stopping Rules
Section 14.6.1.3	BNP Assessment
Appendix B	Schedule of Assessments
Notes to Appendix B	
Appendix F	SAMPLE INFORMED CONSENT

AMENDMENT 2: 10 FEBRUARY 2015

RATIONALE

Study M18-006 has been amended for the following reasons:

The requirement for mandatory FFPE (either from archival tissue or from a fresh core biopsy) was removed and instead FFPE will only be collected if available; i.e., subjects who do not have archival tissue will not undergo a core biopsy to obtain fresh tumor tissue. In addition, the requirement for subjects who have two BNP values > 100 pg/mL or one value > 200 pg/mL to be referred to a cardiologist has been changed to state that such subjects will be referred to a cardiologist if appropriate. Definitions were added to the protocol for "women of child-bearing potential" and "adequate contraception". Additional serum pregnancy tests were added every 56 days while on study, at the termination visit and at 56 and 112 days following the termination visit for women of child-bearing potential. Finally, a few minor typos have been corrected.

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.

Synopsis	
Section 5.0	OVERALL STUDY DESIGN AND PLAN – DESCRIPTION
Section 6.1	Inclusion Criteria
Section 8.1.6	Treatment Modification and Termination Criteria
Section 9.2.5	Pregnancy Testing
Section 11.0	EXPLORATORY ASSESSMENTS
Section 12.1	Screening
Section 12.4	Study Day 56
Section 12.8	Study Day 105
Section 12.9	Termination Visit
Section 12.10	Follow-up after Termination Visit
Appendix B	Schedule of Assessments
Notes to Appendix B	
Appendix F	SAMPLE INFORMED CONSENT

AMENDMENT 3: 28 MAY 2015

RATIONALE

Study M18-006 has been amended for the following reasons:

The primary purpose of this amendment was to make the following modifications to the Inclusion/Exclusion Criteria. Inclusion criterion 1 were modified to allow patients with a cytologic diagnosis to be eligible. Exclusion criterion 6 was modified to provide a definition of clinically significant ascites. The previous exclusion criterion 7 was removed so that patients with plastic biliary stents are eligible. The previous exclusion criterion 10 (now exclusion criterion 9) was modified to clarify that patients with prior chest wall radiotherapy are excluded only if the radiation field involved the heart. The previous exclusion criterion 16 (now exclusion criterion 15) was modified to state that patients on prophylactic doses of heparin, warfarin, factor Xa inhibitors or other similar anti-coagulates are eligible.

In addition, Section 13 was modified to clarify that the BNP measurement must be obtained on the Day of the demcizumab dosing and the result reviewed prior to dosing and the Sample Informed Consent was modified to clarify the objectives of the study. In addition, modifications were made to clarify the appropriate radiologic assessments to obtain. Finally, minor typos were corrected throughout the protocol and other minor changes were made for clarification purposes.

Finally, a few minor typos have been corrected.

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.

Synopsis	
Section 6.1	Inclusion Criteria
Section 6.2	Exclusion Criteria
Section 8.2.1.1	Administration
Section 8.2.2.1	Administration
Section 9.2.3	BNP Assessment
Section 9.4	Cardiac Studies
Section 9.6	Pharmacokinetic Assessments
Section 10.0	Efficacy Assessments
Section 12.0	STUDY VISIT SCHEDULE AND ASSESSMENTS
Section 12.1	Screening
Section 12.2	Study Day 0
Section 12.3	Study Days 7, 14, 21, 28, 35, 42, and 49
Section 12.4	Study Days 56
Section 12.5	Study Days 63, 70
Section 12.7	Study Days 84, 91, 98
Section 12.9	Termination Visit
NOTES TO APPENDIX B	
Appendix F	SAMPLE INFORMED CONSENT

AMENDMENT 4: 31 MARCH 2016

RATIONALE

The primary purpose of this amendment is to change the method for analyzing the primary endpoint of progression-free survival. The previous approach for the primary endpoint analysis involved comparing Arm 1 to Arm 2 and Arm 1 to Arm 3, seperately. This approach required that 80% of patient achieve the PFS endpoint (i.e., either progress or died). However, a blinded review of the data to date suggests that only about 69% of the patients are having a progression-free survival event. Thus, it appears that there may not be an adequate number of events at the end of the study to conduct the PFS analysis initially described in the protocol. Thus, the method for this analysis has been modified to compare Arm 1 to a pooled dataset of Arms 2 and 3 which requires lower percentage of pateints to achieve a PFS endpont.

In addition, the wording of the study objectives and endpoints were modified to account for this modification. A statement that standard of tests performed prior to the informed consent date may be used for screening purposes if they were done within 28 days of Day 0. Also, wording was added to allow the BNP to be drawn the day prior to dosing at a site if approved by the Sponsor. Other minor changes were made for consistency purposes and the typographical errors were fixed.

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.

Synopsis	
Section 4.1	Study Objectives
Section 9.2.3	BNP Assessment
Section 11.0	EXPLORATORY ASSESSMENTS
Section 12.0	STUDY VISIT SCHEDULE AND ASSESSMENTS
Section 14.0	STATISTICAL PLAN
Section 14.2	Study Stopping Rules
Section 14.3	Subject Populations for Analysis
Section 14.6.4.1	Best Overall Response
Section 14.6.4.2	Clinical Benefit Rate
Section 14.6.4.3	Progression-Free Survival and Duration of Response
Section 14.6.5	Continuous Variable Assessment of Tumor Length
Section 14.6.6	Duration of Response
Section 14.6.6.1	Sites of Progression
Section 14.6.7	Overall Survival
Section 14.6.8	Landmark Survival
Notes to Appendix B	
Appendix F	SAMPLE INFORMED CONSENT

AMENDMENT 5: 19 DECEMBER 2016

RATIONALE

The primary purpose of this amendment is to add two additional analyses of overall survival to be conducted on all deaths through June 1, 2017 and November 1, 2017, respectively. In addition, the protocol was modified to state that subjects in long-term follow-up would have their survival status updated every 3 months or sooner at the request of the Sponsor. In addition, changes were made to the Abraxane/gemcitabine dosage modification section to 1) delete the statement that subjects having their gemcitabine/Abraxane therapy held for 21 days due to drug related toxicity should have their gemcitabine and Abraxane stopped and 2) to add a statement that subjects who had undergone two dose reductions of gemcitabine/Abraxane and still were unable to tolerate that treatment could receive gemcitabine/Abraxane on Days 1 and 15 (i.e., omit Day 8) of each 28 day cycle.

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.

Section 8.2.3	Gemcitabine and Abraxane® Dose Modification Guidelines
Section 12.10	Follow-up After Termination Visit
Section 14.0	STATISTICAL PLAN
Section 14.6.7	Overall Survival