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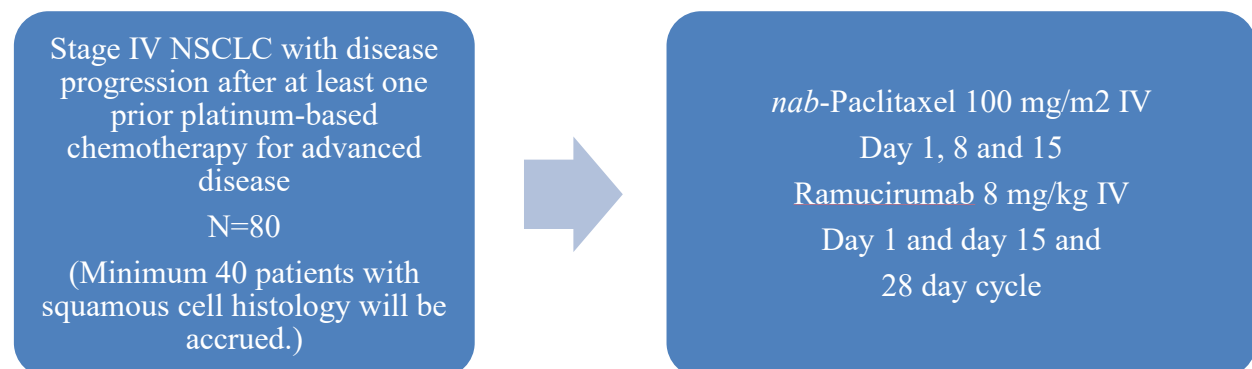
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SCHEMA

Ramucirumab is a human IgG1 (Immunoglobulin G) monoclonal antibody that targets the extracellular domain of VEGFR-2 (vascular endothelial growth factor receptor). A recent double-blind, placebo-controlled phase III clinical trial (REVEL) evaluated the addition of ramucirumab to docetaxel compared with docetaxel and placebo in patients with Stage IV squamous and non-squamous NSCLC in the 2nd-line treatment setting. [2] This study demonstrated a superior overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) with the combination therapy compared with docetaxel with placebo. This effect was seen across histologic subtypes, in the absence of excess toxicity in patients with squamous cell histology. This finding is intriguing, as prior study of bevacizumab in patients with NSCLC of squamous cell histology was associated with excess pulmonary hemorrhage. This provides the rationale for further investigation of ramucirumab in patients with squamous cell NSCLC.

nab-Paclitaxel is a formulation of paclitaxel complexed with albumin that is readily soluble in saline and allows administration of paclitaxel without the use of lipid-based solvents and the need for corticosteroid and antihistamine premedication. *nab*-Paclitaxel was approved for the 1st line treatment of NSCLC based on a trial by Socinski et al. which demonstrated a superior ORR with the addition of *nab*-paclitaxel to carboplatin compared with carboplatin/paclitaxel in patients with advanced and metastatic NSCLC, as well as prolonged PFS and OS without statistical significance. The subgroup analysis by tumor histology demonstrated a statistically significant advantage for *nab*-paclitaxel/carboplatin in terms of best overall response rate (41% vs 24%, $p < 0.001$), and numerically better PFS and OS in squamous NSCLC. [3]

This is a single-arm phase II clinical trial, in which patients with previously treated NSCLC will be treated with ramucirumab/*nab*-paclitaxel until disease progression, unacceptable treatment-related toxicity or withdrawal of consent with the primary endpoint of progression-free survival. A minimum of 40 patients with squamous cell histology will be required for determination of the co-primary endpoint. We hypothesize that the addition of ramucirumab to *nab*-paclitaxel is well-tolerated and associated with a superior PFS compared with single agent taxane-based therapy.

**Primary objectives:**

- To evaluate the safety of the addition of ramucirumab to *nab*-paclitaxel
- To evaluate the efficacy of ramucirumab/*nab*-paclitaxel as determined by PFS in the histologically unselected population

- To evaluate the efficacy of ramucirumab/*nab*-paclitaxel as determined by PFS in patients with squamous cell histology

Secondary objectives:

- To evaluate the efficacy of ramucirumab/*nab*-paclitaxel as determined by ORR and OS in all patients and in patients with squamous cell histology
- To evaluate patient-reported symptoms and quality-of-life using the EuroQoL Five Dimensions questionnaire (EQ-5D-5L) [1].

Interim analysis:

- Ramucirumab/*nab*-paclitaxel is a novel combination, but a dose finding study is not planned since prior addition of monoclonal antibodies to cytotoxic therapies has been safe and tolerable, in the absence of overlapping toxicities. However, enrollment will be halted for a safety review after C2D21 for the 6th patient with squamous cell histology, and separately for the first 6 patients without squamous cell histology. Dose delivered and adverse events for those patients will be examined, and the decision to continue as planned or modify the protocol in any way will be made by the disease center Data and Safety Monitoring Board (DSMB) and the University of Pittsburgh Cancer Institute (UPCI) Data and Safety Monitoring Committee (DSMC).

Statistical Methods:

- For the unselected population (squamous and non-squamous) and for the subgroup of squamous NSCLC only, the PFS curve and a 90% confidence interval for the median PFS will be estimated by standard methods (the Kaplan-Meier method for survival, and the Greenwood variance formula applied to log-transformed survival). Sampling weights will be used to approximate PFS for the unselected population, in which about 25% of the study population has disease with squamous histology [2].
- Power calculations assume accrual of 80 patients at a uniform rate over 2 years, with 10 months of additional follow-up. A minimum of 40 patients with NSCLC of squamous cell histology will be accrued, e.g. after 40 patients with non-squamous histology have been enrolled, the remaining patients must have squamous cell histology. Simulating data with median 5 months PFS (exponential distribution), the lower bound of the 90% confidence interval for median PFS was greater than 3 months for 93% of 10,000 simulated datasets of size n=80 and 75% for size n=40. Therefore, we conclude that with two-sided alpha=0.1, the study has 93% power to conclude that the median PFS is unlikely to be 3 months or less in an unselected population, and 75% power for the squamous histology subgroup. The average width of the confidence interval for median PFS for squamous histology is expected to be about 3.8 months (ie, 90% confidence interval 3.6-7.4 months). The null rate of 3 months is from the median TTP of 2.7 months (median OS of 7 months) in previously treated advanced stage NSCLC patients treated with single agent docetaxel [4].
- Patient-reported symptoms and quality-of-life will be assessed using the EuroQoL Five Dimensions questionnaire[1].

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
AUC _{0-last}	AUC from time zero to the last quantifiable time point
AUC _{0-∞}	AUC from time zero to infinity
AUC _{0-inf}	AUC from time zero to infinity
BP	blood pressure
BUN	blood urea nitrogen
C _{max}	maximum plasma concentration
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DVT	deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EKG	electrocardiogram
EQ-5D-5L	EuroQoL Five Dimensions questionnaire
FDA	Food and Drug Administration
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
HCC	hepatocellular carcinoma
HR	hazard ratio
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin G
INR	International Normalized Ratio
IRB	Institutional Review Board
MI	myocardial infarction
MTD	maximum tolerated dose
NCI	National Cancer Institute
NRP-1	Neuropilin-1
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PE	pulmonary embolism
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic
PR	partial response
PT	prothrombin time

PTT	partial thromboplastin time
QTc	corrected QT
RPLS	reversible posterior leukoencephalopathy syndrome
RR	response rate
SAE	serious adverse event
SD	stable disease
TK	toxicokinetic
TKI	tyrosine kinase inhibitor
TIA	transient ischemic attack
ULN	upper limit of normal
VEGF(R)	vascular endothelial growth factor (receptor)

1. OBJECTIVES

1.1 Primary Objectives

- To evaluate the safety of the addition of ramucirumab to *nab*-paclitaxel
- To evaluate the efficacy of ramucirumab/*nab*-paclitaxel as determined by PFS in the histologically unselected population
- To evaluate the efficacy of ramucirumab/*nab*-paclitaxel as determined by PFS in patients with squamous cell histology

1.2 Secondary Objectives

- To evaluate the efficacy of ramucirumab/*nab*-paclitaxel as determined by ORR and OS in all patients and in patients with squamous cell histology
- To evaluate patient-reported symptoms and quality-of-life using the EuroQoL Five Dimensions questionnaire (EQ-5D-5L)

2. BACKGROUND

2.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer mortality in the United States and worldwide[5]. An estimated 224,210 new cases of lung cancer will be diagnosed in 2014 in the United States alone, and 159,260 lung cancer deaths are estimated to occur[4]. Historically, palliative chemotherapy in the metastatic non-small cell lung cancer (NSCLC) setting resulted in modest survival prolongation and preservation of quality of life.[6-10] A series of large randomized controlled phase 3 clinical trials established platinum-based doublets as the standard of care in the 1st line treatment of metastatic NSCLC with response rates (RR) of 20 to 30% and a median survival of 8 to 11 months.[11-15] Currently approved 2nd line therapies for advanced NSCLC include docetaxel, erlotinib and pemetrexed[4, 16-18]. Treatment in the 2nd line setting is associated with a limited ORR of less than 10%, a median PFS of less than 4 months and a median OS of 7-9 months[19]. Treatment of patients with squamous cell histology NSCLC in particular is an unmet need because of lack of driver mutations associated with response to currently approved agents and significant risk of hemoptysis associated with treatment of monoclonal antibodies targeting vascular endothelial growth factor (VEGF).

Overexpression VEGF has been found in most human tumors, including NSCLC, and is associated with increased tumor recurrence, metastasis and death [20-24]. The angiogenic phenotype is considered a hallmark of the malignant process whereby proangiogenic mechanisms overwhelm or circumvent the negative regulators of angiogenesis[25]. The VEGF/VEGF-receptor (VEGFR) pathway plays a pivotal role in normal and pathologic angiogenesis[26]. VEGF pathway activation leads to endothelial cell survival, mitogenesis, migration and differentiation and mobilization of endothelial progenitor cells from the bone marrow into the peripheral circulation [26].

The VEGF-related gene family is composed of six secreted glycoproteins referred to as VEGF-

A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placenta growth factor (PlGF) -1 and -2[27-29]. VEGF-A (commonly referred to as VEGF) is an endothelial specific mitogen with a diverse range of angiogenic activities[30]. VEGF-A undergoes alternate splicing to yield isoforms of 121, 165, 189 and 206 amino acids, which have distinct tissue specific expression patterns, suggesting defined roles in vasculogenesis and tumor angiogenesis[28, 29, 31-33]. The VEGF ligands mediate their effect through several receptor tyrosine kinases [26]. All isoforms of VEGF bind to VEGFR-1 and VEGFR-2, whereas PlGF-1 and -2 and VEGF-B specifically bind and activate VEGFR-1[34-36]. While VEGFR-1 is critical for physiologic and developmental angiogenesis, the precise function of VEGFR-1 in angiogenesis is unclear [26]. The majority of the effects of VEGF are mediated through binding of VEGFR-2, which leads to microvascular permeability, invasion, migration and survival [37-39]. Other mediators of the VEGF ligands include VEGFR-3, which may be involved in cardiovascular development and vascular remodeling during embryogenesis and lymphangiogenesis in the adult, and Neuropilin-1 (NRP-1) and NRP-2, which are likely to serve as co-receptors for VEGF[26].

Recognition of the VEGF pathway as a key mediator of angiogenesis has led to the clinical study of several VEGF targeted therapies in lung cancer. These targeted therapies include neutralizing antibodies to VEGF (bevacizumab and aflibercept) and VEGFR-2 (ramucirumab) and receptor tyrosine kinase inhibitors (TKIs) with preferential selectivity for the VEGFRs.

Ramucirumab is a fully human IgG1 monoclonal antibody that specifically binds to the VEGFR-2 extracellular domain with high affinity, preventing binding of all VEGF ligands and receptor activation and signaling[52]. Two phase II clinical trials have assessed the addition of ramucirumab to platinum doublet chemotherapy in the 1st line setting. Camidge et al. enrolled squamous and non-squamous patients on a single arm trial of carboplatin/paclitaxel/ramucirumab and demonstrated tolerability of this regimen, a RR of 55%, a median PFS of 7.9 months and OS of 17.9 months[53]. Of interest in this single-arm trial, the single-nucleotide polymorphism (SNP) rs2981582 on the VEGFR-2 gene had significant associations with improved overall survival, PFS, and best overall response. Doebele et al. randomized patients with non-squamous NSCLC to either platinum/pemetrexed or platinum/pemetrexed/ramucirumab and demonstrated no statistically significant improvements in PFS (5.6 versus 7.2 months, respectively, HR 0.75, P = 0.132), OS (10.4 versus 13.9 months, HR 1.03, P = 0.892), and RR (38.0% and 49.3%, respectively, P = 0.180) and no new or unexpected safety findings[40].

The REVEL clinical trial is a randomized phase III clinical trial which assessed the addition of ramucirumab to docetaxel compared with docetaxel/placebo in patients with squamous or non-squamous advanced NSCLC after platinum based chemotherapy. This trial met its primary endpoint demonstrating an OS advantage with the addition of ramucirumab (9.1 months with docetaxel/ramucirumab versus 10.5 months with docetaxel/placebo, HR 0.86, P = 0.023), in addition to a PFS prolongation (4.5 versus 3.0 months, respectively, HR 0.76, p<0.0001; Table 1; Figure 2b) and improvement in RR (23% versus 14%, respectively, OR 1.89, p<0.0001; Table 1[2]). Although this study was not powered for subgroup analyses, most subgroups of patients had numerically longer survival with the addition of ramucirumab compared with docetaxel/placebo, including patients with non-squamous disease (11.1 versus 9.7 months, respectively, HR 0.83, 95% CI 0.71–0.97), patients with squamous disease (9.5 versus 8.2 months, HR 0.88, 95% CI 0.69–1.13), and responders to first-line platinum therapy (11.2 versus

10.3 months, HR 0.84, 95% CI 0.71–0.99). The most common grade 3 or worse adverse events were neutropenia (49% patients in the ramucirumab group versus 40% in the placebo group), febrile neutropenia (16% versus 10%), fatigue (14% versus 10%), leukopenia (14% versus 12%), and hypertension (6% versus 2%). The numbers of deaths from adverse events (5% versus 6%) and grade 3 or worse pulmonary hemorrhage (1% versus 1%) did not differ between the treatment groups. The efficacy of ramucirumab in combination with docetaxel across NSCLC histologies and the safety with regard to the risk of pulmonary hemorrhage make ramucirumab of particular interest in patients with squamous cell NSCLC.

nab-Paclitaxel is a formulation of paclitaxel complexed with albumin that is readily soluble in saline and allows administration of paclitaxel without the use of lipid-based solvents and the need for corticosteroid and antihistamine premedication. *nab*-Paclitaxel was approved for the 1st line treatment of NSCLC based on a trial by Socinski et al. which demonstrated a superior ORR with the addition of *nab*-paclitaxel to carboplatin compared with carboplatin/paclitaxel in patients with advanced and metastatic NSCLC, as well as numerically longer PFS and OS without statistical significance. The subgroup analysis by tumor histology demonstrated a statistically significant advantage for *nab*-paclitaxel/carboplatin in terms of best overall response rate (41% vs 24%, $p < 0.001$), and numerically better PFS and OS in squamous NSCLC [2]. More importantly, the overall toxicity profile, with the exception of anemia and thrombocytopenia favor *nab*-paclitaxel over paclitaxel.

Toxicity	Nab-paclitaxel + carboplatin (n=514) %		Paclitaxel + carboplatin (n=524) %		p value
	Grade 3	Grade 4	Grade 3	Grade 4	
Nonhematologic					
Neuropathy	3	0	11	<1	<.001
Myalgia	<1	0	2	0	.011
Arthralgia	0	0	2	0	.008
Hematologic					
Neutropenia	33	14	32	26	<.001
Thrombocytopenia	13	5	7	2	<.001
Anemia	22	5	6	<1	<.001

2.2 Agents

2.2.1 Ramucirumab

Mechanism of Action

Ramucirumab (IMC-1121B [LY3009806]) drug substance is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream intracellular signaling components, including Erk1/Erk2, neutralizing ligand induced proliferation and migration of human endothelial cells[41-46].

Potent antiangiogenic and antitumor effects have been demonstrated in murine models with the administration of DC101, a rat antibody to murine ortholog of VEGF Receptor 2 (ramucirumab does not cross-react with the murine VEGF Receptor 2; therefore, DC101 was used in murine models as a proof-of-principle surrogate antibody)[47-49]. DC101 administration resulted in a reduced rate of tumor growth and in lower tumor microvessel density characteristic of antiangiogenic agents. Thus, the primary mechanism of action of DC101 appropriately models the expected primary mechanism of the antitumor effect of ramucirumab [26, 50, 51]. The efficacy of DC101 has been demonstrated in numerous mouse xenograft solid tumor models, providing a rationale for evaluation of ramucirumab in clinical studies in patients with multiple malignancies.

Clinical Data

A comprehensive clinical development program to evaluate ramucirumab focusing on tumors where VEGF ligands (including VEGF-A) and VEGF Receptor 2 are overexpressed and/or where the unmet medical need is high was initiated following Phase 1 studies evaluating dose, schedule, and toxicity. As of 31 December 2013, ramucirumab DP or ramucirumab DP/placebo has been administered either as a single agent or in combination with various antineoplastic agents to approximately 7000 patients with different oncologic conditions in Phase 1/1b, Phase 2, and Phase 3 clinical trials. Based upon actual exposure data from completed clinical trials and the enrollment/ randomization schemes for ongoing trials (for which the development program team remains blinded), an estimated 4002 patients have received ramucirumab with 932 patients receiving single-agent ramucirumab and 3070 patients receiving ramucirumab in combination with antineoplastic agents.

Ramucirumab has shown clinical efficacy in patients with gastric cancer in 2 randomized Phase 3 trials: REGARD (I4T-IE-JVBD; IMCL CP12-0715) (ramucirumab monotherapy with best supportive care [BSC]) and RAINBOW (I4T-IE-JVBE; IMCL CP12-0922) (ramucirumab in combination with paclitaxel). A Phase 3 trial (ROSE [I4T-IE-JVBC; IMCL CP12-0606]) examining the combination of ramucirumab with docetaxel in previously untreated metastatic breast cancer failed to meet its primary endpoint of investigator-assessed progression-free survival (PFS). In ROSE, while investigator-assessed PFS numerically favored ramucirumab, this difference was not statistically significant.

Safety

The nonclinical toxicity of ramucirumab DP was investigated in cynomolgus monkeys. This toxicology evaluation involved a 5-week study (administration of 4 ramucirumab DP doses over 5 weeks [dose range, 4-40 mg/kg]) and a 39-week study (weekly ramucirumab DP for up to 39 weeks [dose range, 5-50 mg/kg]). Clinically observable, ramucirumab DP-related adverse events (AEs) were infrequent and mild in these evaluations. The most notable AEs were renal toxicity (observed in the 39-week study at 16- and 50-mg/kg/week doses), manifested by elevations in blood urea nitrogen, serum creatinine, and urinary protein, and diffuse glomerulonephritis at necropsy. Thickening and osteochondropathy of the epiphyseal growth plates (observed in the 39-week study at 5-mg/kg/week doses and greater) were also noted.

As of 31 December 2013, AE information was available for 2485 patients receiving ramucirumab DP on 7 Phase 1/1b studies, 18 open-label or unblinded Phase 2 studies, and 3 completed Phase 3 studies, including monotherapy and combination therapy with cytotoxic chemotherapy agents. Placebo-controlled blinded clinical trials are ongoing (1 Phase 2 study, 3 Phase 3 studies); unblinded safety data for these studies are not available. Detailed AE information based on a review of Phase 1/1b, Phase 2, and completed Phase 3 clinical studies of ramucirumab DP (N=2485) is available in Section 6.2.1 and Section 7.3.8 of the ramucirumab Investigator Brochure.

Adverse drug reactions (ADRs; AEs for which a causal relationship to the investigational drug was considered at least possible) of special interest include AEs which have been associated with antiangiogenic agents and therapeutic monoclonal antibodies and include the following categories: infusion-related reaction (IRR), hypertension, proteinuria, arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), bleeding/hemorrhagic events, gastrointestinal (GI) perforation, and congestive heart failure (CHF) when used in combination with mitoxantrone or following prior anthracycline therapy.

Infusion-related reaction is considered an adverse event of special interest (AESI), as it has been observed in association with other approved and investigational therapeutic monoclonal antibodies. With the exception of liver injury/liver failure, the AESIs discussed are potentially associated with other agents that inhibit VEGF- or VEGF Receptor 2-mediated angiogenesis. Some AESIs also have been reported in clinical trials of ramucirumab DP, although in some instances a causal association with ramucirumab DP could not be clearly established. Liver failure and/or other significant liver injury events were included as an AESI in August 2012, following the independent data monitoring committee (IDMC) recommendations in an ongoing Phase 3 study in patients with advanced hepatocellular carcinoma (HCC; Study I4T-IE-JVBF [IMCL CP12-0919; REACH]).

Animal studies have not been specifically conducted to evaluate the effect of ramucirumab on female reproduction and fetal development, and there are no studies in pregnant women (See Section 7.3.7 of the ramucirumab Investigator Brochure for details on use during pregnancy and lactation). No formal studies have been performed to evaluate the safety and efficacy of ramucirumab DP in the treatment of children or elderly patients.

Pharmacokinetics

The pharmacokinetics (PK) and toxicokinetics (TK) of ramucirumab in cynomolgus monkeys were obtained in the 5-week and 39-week repeat-dose toxicology studies, and after a single dose in a wound-healing study. In the 5-week study, animals were administered intravenous (I.V.) doses of 0, 4, 12, or 40 mg/kg ramucirumab DP weekly and blood samples for ramucirumab concentration analysis in serum were obtained after the first dose. In the 39-week study, animals were administered I.V. doses of 0, 5, 16, or 50 mg/kg ramucirumab DP weekly and blood samples were obtained after the first, 12th, and 39th doses.

Noncompartmental analysis of the concentration-vs-time data from the monkey toxicology studies indicated that the PK behavior of ramucirumab was nonlinear over the 4- to 50-mg/kg

dose range. Area under the concentration-vs-time curve extrapolated to infinity (AUC_{0-inf}) and maximum concentration (C_{max}) increased in a greater than dose-proportional manner. Ramucirumab half-life increased and clearance decreased with increasing dose. The steady-state volume of distribution was approximately equal to the vascular space at each dose level. Mean ramucirumab AUC_{0-inf} in the 50-mg/kg group increased between the first and 39th doses, indicating that drug accumulation occurred. Antibodies against ramucirumab were detected in the 4-, 12-, and 40-mg/kg dose groups in the 5-week study, and in the 5- and 16- mg/kg dose groups in the 39-week study. In summary, the PK behavior of ramucirumab in monkeys was nonlinear and typical of monoclonal antibodies.

The PK of ramucirumab were determined after a single 10-minute I.V. infusion dose of 5, 15, or 50 mg/kg in a wound-healing study. Similar to previous studies in monkeys, the systemic exposure to ramucirumab as indicated by C_{max} and area under the concentration-vs-time curve (AUC) increased with increasing dose and the apparent volume of distribution was in the range of plasma volume for monkeys, indicating that ramucirumab did not substantially distribute beyond the vasculature.

Rationale for Starting Dose

The REVEL clinical trial evaluated ramucirumab at a dose of 10 mg/kg IV on day 1 in combination with docetaxel given IV at 60 to 75 mg/m² on day 1 of a 21 day cycle. Ramucirumab has been approved in gastric and gastroesophageal cancer at 8 mg/kg IV every 2 weeks. The dosing schedule of ramucirumab in the proposed study has been selected to coincide with weekly dosing of *nab*-paclitaxel.

2.2.2 nab-Paclitaxel

Mechanism of Action

Paclitaxel is an anti-microtubule agent that has a broad spectrum of activity against human cancers. It was first authorized in the proprietary product Taxol® (paclitaxel) Injection, manufactured by Bristol-Myers Squibb, New York, New York, which is now available as generic equivalents. Taxol consists of paclitaxel dissolved in a proprietary solvent, Cremophor® ELb (BASF, Ludwigshafen, Germany) and ethanol.

nab-Paclitaxel (ABRAXANE® for Injectable Suspension [Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation, Summit, New Jersey, United States; hereafter referred to as “Celgene”], ABI-007) is a proprietary solvent-free, protein-stabilized formulation of paclitaxel comprised of paclitaxel in a noncrystalline amorphous state and human albumin with mean particle size of approximately 130 nanometers. *nab*-Paclitaxel has been developed to improve the therapeutic index of paclitaxel, also reducing the toxicities associated with Taxol and the CrEL and ethanol vehicle. This may be achieved in part by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumor. Because *nab*-paclitaxel does not contain a solvent vehicle, micellar entrapment observed with Taxol does not occur[52-54]. *nab*-Paclitaxel displays linear pharmacokinetic (PK) characteristics. The novel albumin-bound particle formulation of paclitaxel in *nab*-paclitaxel conferred the ability to

achieve a higher maximum tolerated dose (MTD) based on every 3-weeks dosing: 300 mg/m² for nab-paclitaxel (Study DM97-123) versus 175 mg/m² for Taxol [55]. The use of albumin-bound paclitaxel also enables *nab*-paclitaxel to be given in a shorter, more convenient infusion time of 30 - 40 minutes compared with 3 hours to 24 hours with Taxol. Due to its distinct pharmacological and PK properties and therapeutic index, *nab*-paclitaxel has been approved by regulatory authorities worldwide in over 40 countries/regions as a new product, rather than as a generic formulation of Taxol.

nab-Paclitaxel may be given without steroid and anti-histamine premedication, which is required for Taxol to prevent solvent-related HSRs (Taxol US prescribing information). Cremophor EL has been shown to leach plasticizers, specifically di(2-ethylhexyl)phthalate (DEHP), from polyvinyl chloride (PVC) bags and polyethylene-lined tubing [56-61]. Although no controlled epidemiologic toxicity studies have been conducted in humans exposed to DEHP, severe effects (eg, carcinogenicity, cardiopulmonary toxicity, hepatotoxicity, and nephrotoxicity) have been observed in experimental models. The Taxol prescribing information instructs users to prepare, store, and administer solutions in glass, polypropylene, or polyolefin containers; non-PVC-containing infusion sets (eg, those with polyethylene lining) should be used (Taxol US prescribing information). By comparison, standard tubing and intravenous (IV) bags may be used for the IV administration of *nab*-paclitaxel [52, 55].

Clinical Data and Safety

As of October 2014, *nab*-paclitaxel is approved under the trade name of ABRAXANE in 51 countries worldwide for the treatment of patients with metastatic breast cancer. ABRAXANE is also approved in 8 countries worldwide for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), and in 40 countries for the first-line treatment of metastatic adenocarcinoma of the pancreas, and it is approved in Japan for treatment of advanced gastric cancer.

Nonclinical toxicity studies revealed no evidence for unique and previously unseen risks with *nab*-paclitaxel and the results were similar to the nonclinical toxicology profile of solvent-based paclitaxel. The known adverse effects for paclitaxel were not masked by its formulation with albumin, but were generally not exacerbated in comparison to Taxol. The primary toxicities based on the results of animal studies and the known toxicities of paclitaxel when administered as Taxol include myelosuppression, testicular degeneration, and neuropathy. In nonclinical studies with mice-bearing adult and pediatric tumor xenografts, repeat-dose administration of *nab*-paclitaxel was generally well-tolerated. In *in vitro* studies with human liver microsomes and tissue slices, it has been shown that paclitaxel is metabolized primarily to 6 α -hydroxypaclitaxel by CYP-2C8 and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6 α , 3'-p-dihydroxypaclitaxel, by CYP-3A4.

A Phase 3 randomized, controlled study (Study CA012-0) conducted in patients with metastatic breast cancer compared *nab*-paclitaxel (260 mg/m²) with solvent-based paclitaxel (175 mg/m²) both given on Day 1 of a 21-day cycle. *nab*-Paclitaxel demonstrated greater efficacy (higher response rates, longer times to tumor progression [TTP], and longer progression-free survival [PFS] in patients previously treated for metastatic disease) with toxicity similar to that of

solvent-based paclitaxel, despite the higher dose of active agent achieved with *nab*-paclitaxel. Grade 4 neutropenia occurred less frequently in the *nab*-paclitaxel group, and did not appear to be related to cumulative dose. Instances of neutropenia were clinically asymptomatic and transient. Grade 3 sensory neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE v 2.0]) occurred more often in the *nab*-paclitaxel group compared with solvent-based paclitaxel; however, these events were manageable with therapy interruption followed by dose reduction.

A Phase 3 randomized, controlled study (Study CA031) conducted in patients with advanced NSCLC compared *nab*-paclitaxel (100 mg/m²) and carboplatin (Arm A) with Taxol (200 mg/m²) and carboplatin (Arm B). Patients in Arm A received IV *nab*-paclitaxel on Days 1, 8, and 15 of a 21-day cycle and carboplatin administered on Day 1 of each 21-day cycle. Patients in Arm B received Taxol IV over 3 hours followed by carboplatin on Day 1 of each 21-day cycle. Administration of *nab*-paclitaxel/carboplatin as a first-line therapy resulted in significantly improved overall response rates (ORR) versus Taxol/carboplatin. Statistically nonsignificant trends in favor of the *nab*-paclitaxel/carboplatin arm were observed for PFS and overall survival (OS), meeting non-inferiority criteria. The *nab*-paclitaxel/carboplatin regimen was better tolerated, with significant reduction in severe peripheral neuropathy, arthralgias, and myalgia. A higher percentage of patients in the *nab*-paclitaxel treatment arm developed anemia and thrombocytopenia. The anemia was readily corrected with a single blood transfusion in the majority of cases. The thrombocytopenia did not lead to increased rates of hemorrhages.

A Phase 3 randomized, controlled study (Study CA046) in patients with metastatic adenocarcinoma of the pancreas evaluated *nab*-paclitaxel 125 mg/m² in combination with gemcitabine 1000 mg/m² on Days 1, 8, 15, 29, 36, and 43 of a 56-day cycle in Cycle 1 only, followed by Days 1, 8, and 15 of a 28-day cycle in Cycle 2 and onwards, compared with standard therapy of gemcitabine 1000 mg/m² on Days 1, 8, 15, 22, 29, 36, and 43 of a 56-day cycle in Cycle 1 followed by Days 1, 8, and 15 of a 28-day cycle in Cycle 2 and onward. The study met its primary endpoint with an improvement in OS. Median OS was 8.5 months in the *nab*-paclitaxel/gemcitabine arm compared with 6.7 months in the gemcitabine arm. The 1-year survival rate was 35% in the *nab*-paclitaxel/gemcitabine arm compared with 22% in the gemcitabine arm. The treatment effect consistently favored the *nab*-paclitaxel/gemcitabine arm across the majority of pre-specified subgroups. Key secondary efficacy endpoints of PFS and ORR were also met. The rate of febrile neutropenia was low in the 2 treatment arms, 3% in *nab*-paclitaxel/gemcitabine arm and 1% in the gemcitabine arm. The rates of Grade 3/4 anemia and thrombocytopenia by central laboratory were comparable between the 2 treatment arms. Grade 3 or higher events of sepsis were reported for 5% of patients in the *nab*-paclitaxel/gemcitabine arm and 2% of patients in the gemcitabine arm. The most common adverse event (AE) leading to drug discontinuation in a greater percentage of patients in the combination arm was peripheral neuropathy.

Post-hoc analyses completed approximately 1 year after the final formal study analyses showed the following results: median OS increased to 8.7 months in the *nab*-paclitaxel/gemcitabine arm compared with a decrease to 6.6 months in the gemcitabine arm. The 1-year survival rate remained the same in both treatment arms. No new safety signals were observed for either treatment arm.

Pharmacokinetics

Clinical pharmacology of paclitaxel has been evaluated over the *nab*-paclitaxel dose range of 80 to 375 mg/m² in patients with solid tumors. Systemic exposure (C_{max} [maximum concentration] and AUC_∞ [area under the time curve to infinity]) of paclitaxel is approximately proportional to *nab*-paclitaxel doses from 80 to 300 mg/m²; however, at doses from 300 to 375 mg/m², the exposure appears more than dose proportional. Paclitaxel AUC in plasma was independent of the *nab*-paclitaxel infusion duration. Following *nab*-paclitaxel administration, paclitaxel is highly bound to plasma proteins (94%). However, the mean fraction unbound of paclitaxel is approximately 2.6-fold higher with *nab*-paclitaxel as compared to Taxol. The whole blood and plasma exposure levels are comparable, suggesting similar distribution between plasma and blood cells. Distribution of paclitaxel to extravascular tissue is more rapid and more extensive with *nab*-paclitaxel versus Taxol. The faster distribution to peripheral tissues, the larger volume of distribution, the 2.6-fold higher fraction of unbound drug in circulation, the higher dose, and the shorter infusion time of *nab*-paclitaxel over Taxol may all contribute to the better responses to *nab*-paclitaxel over Taxol in clinical studies.

Hepatic metabolism and biliary excretion are likely routes of paclitaxel elimination in humans. Patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x upper limit of normal [ULN]) have no clinically important changes in pharmacokinetics (PK) of paclitaxel while patients with moderate (total bilirubin > 1.5 to ≤ 3 x ULN) or severe (total bilirubin > 3 to ≤ 5 x ULN) hepatic impairment have a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function. Mild to moderate renal impairment (creatinine clearance ≥ 30 and < 90 mL/min) has no clinically important effect on the maximum elimination rate and systemic exposure (AUC and C_{max}) of paclitaxel.

In pharmacokinetic/pharmacodynamic (PK/PD) modeling, neutropenia development was driven by systemic exposure to paclitaxel, positively correlated with increasing age at a given exposure level, but was not significantly influenced by the type of solid tumors, sex, hepatic function (as indicated by albumin or total bilirubin level), and dosing schedule (every 3 weeks [q3w] versus every week [qw]).

Rationale for Starting Dose

Data suggest that weekly taxane administration improves tolerability over an every 3 week schedule, and does not appear to compromise clinical effectiveness. Taxanes have been extensively studied as weekly regimens in the breast and lung cancer literature. A phase III study compared carboplatin plus paclitaxel on a standard every three week regimen (with both drugs given on day one) to a four week cycle (with carboplatin given on day 1 and paclitaxel given weekly for weeks one to three [62]). Survival was similar between the two arms, but non-hematologic toxicity favored the weekly taxane arm. A dose finding study showed a favorable benefit to risk ratio with weekly *nab*-paclitaxel at a dose of 100mg/m² when administered in combination with carboplatin [63]. Weekly dosing of *nab*-paclitaxel administered at 100 mg/m² on days 1, 8 and 15 of a 28 day cycle was selected to coincide with q2 weekly ramucirumab

dosing.

2.3 Rationale

Ramucirumab is a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2. A recent double-blind, placebo-controlled phase III clinical trial (REVEL) evaluated the addition of ramucirumab to docetaxel compared with docetaxel and placebo in patients with Stage IV squamous and non-squamous NSCLC in the 2nd-line treatment setting (Lancet 2014;384:665-73.) This study demonstrated a superior overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) with the combination therapy compared with docetaxel with placebo. This effect was seen across histologic subtypes, in the absence of excess toxicity in patients with squamous cell histology. This finding is intriguing, as prior study of bevacizumab in patients with NSCLC of squamous cell histology was associated with excess pulmonary hemorrhage. This provides the rationale for further investigation of ramucirumab in patients with squamous histology NSCLC.

nab-Paclitaxel is a formulation of paclitaxel complexed with albumin that is readily soluble in saline and allows administration of paclitaxel without the use of lipid-based solvents and the need for corticosteroid and antihistamine premedication. *nab*-Paclitaxel was approved for the 1st line treatment of NSCLC based on a trial by Socinski et al. which demonstrated a superior ORR with the addition of nab-paclitaxel to carboplatin compared with carboplatin/paclitaxel in patients with advanced and metastatic NSCLC, as well as prolonged PFS and OS without statistical significance. The subgroup analysis by tumor histology demonstrated a statistically significant advantage for nab-paclitaxel/carboplatin in terms of best overall response rate (41% vs 24%, $p < 0.001$), and numerically better PFS and OS in squamous NSCLC. [3]

We now propose a phase II clinical trial evaluating the safety and efficacy of the addition of ramucirumab to nab-paclitaxel in patients with previously treated NSCLC, and in particularly patients with squamous cell histology. We hypothesize that the addition of ramucirumab to *nab*-paclitaxel is well-tolerated and associated with a superior PFS compared with single agent taxane-based therapy.

3. PATIENT SELECTION

3.1 Inclusion Criteria

1. Patients must have histologically or cytologically confirmed Stage IV (AJCC 7) non-small cell lung cancer.

2. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 10 for the evaluation of measurable disease.
3. Patients must have received at least one prior platinum-based chemotherapy for locally advanced or metastatic disease. Prior bevacizumab as 1st line and/or maintenance therapy is allowed. Prior nivolumab is allowed.
4. Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of ramucirumab in combination with *nab*-paclitaxel in patients < 18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
5. ECOG performance status ≤ 2 (Karnofsky $\geq 60\%$, see Appendix A).
6. Life expectancy of greater than 12 weeks.
7. Patients must have adequate liver function: total bilirubin ≤ 1.5 times the upper limit normal (ULN), AST and ALT ≤ 3.0 x ULN or 5.0 x ULN in the setting of liver metastases.
8. The patient has adequate hematologic function, as evidenced by an absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$, hemoglobin ≥ 9 g/dL (5.58 mmol/L), and platelets $\geq 100,000/\mu\text{L}$ (transfusion independent, defined as not receiving platelet transfusions within 7 days prior to laboratory sample.)
9. The patient does not have cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.
10. The patient has adequate renal function as defined by a serum creatinine ≤ 1.5 times the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥ 40 mL/minute (that is, if serum creatinine is > 1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed).
11. The patient's urinary protein is $\leq 1+$ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is $\geq 2+$, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in this protocol).
12. The patient must have adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5 , and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.

13. Patients with treated and clinically stable brain metastases are allowed.
14. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Females of child-bearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:
 - a. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption [such as use of an appropriate “double barrier” method of birth control (female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed “birth control” pills, injections, or implants], 28 days prior to starting IP therapy (including dose interruptions), and while on study medication or for a longer period if required by local regulations following the last dose of IP; and
 - b. Have a negative serum pregnancy test (β -hCG) result within 7 days of starting study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
15. Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 6 months following IP discontinuation, even if he has undergone a successful vasectomy.
16. Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE).
17. Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

1. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
2. Patients with previous intolerance to ramucirumab.

3. Patients who are receiving any other investigational agents.
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ramucirumab or *nab*-paclitaxel.
5. Patients with untreated CNS metastases. Patients with treated brain metastases are eligible if they are clinically stable with regard to neurologic function, off steroids after cranial irradiation (whole brain radiotherapy, focal radiotherapy, and stereotactic radiosurgery) ending at least 2 weeks prior to randomization, or after surgical resection performed at least 28 days prior to randomization. The patient may have no evidence of Grade ≥ 1 CNS hemorrhage based on pretreatment MRI or IV contrast CT scan (performed within 21 days before randomization).
6. The patient has significant bleeding disorders, vasculitis, or experienced Grade 3/4 gastrointestinal (GI) bleeding within 3 months prior to enrollment.
7. The patient has a history of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered “significant”) during the 3 months prior to randomization.
8. The patient has experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to enrollment.
9. The patient has a history of uncontrolled hereditary or acquired thrombotic disorder.
10. The patient has uncontrolled or poorly-controlled hypertension ($>160 / >100$ mm Hg for >4 weeks) despite standard medical management.
11. The patient has a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment.
12. The patient has undergone major surgery within 28 days prior to enrollment, or subcutaneous venous access device placement within 7 days prior to enrollment.
13. The patient is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
14. The patient has elective or planned major surgery to be performed during the course of the clinical trial.

15. Patients with hemoptysis (defined as bright red blood or $\geq 1/2$ teaspoon) within 2 months prior to enrollment, or with central or cavitating lesions, will be excluded.
16. The patient has radiologically documented evidence of major blood vessel invasion or encasement by cancer.
17. The patient has a history of GI perforation and/or fistulae within 6 months prior to enrollment, or has risk factors for perforation.
18. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
19. Pregnant women are excluded from this study because ramucirumab is pregnancy category C agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ramucirumab, breastfeeding should be discontinued if the mother is treated with ramucirumab. These potential risks may also apply to other agents used in this study.
20. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions ramucirumab. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally by the Study Coordinator.

Following registration, patients should begin protocol treatment within 5 days.

Issues that would cause treatment delays should be discussed with the Investigator. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the coordination team and the treating physician investigator, a patient will be entered on study. To register a patient, the research nurse or data manager must complete the eligibility/registration form and review the signed Informed

Consent, and HIPAA authorization form.

To complete the registration process, the research nurse or data manager will:

- Verify the eligibility
- Register the patient on study
- Assign a patient accession number

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	Premedication	Dose	Route	Schedule	Cycle Length
Ramucirumab	Diphenhydramine 50 mg IV*	8 mg/kg	IV before <i>nab</i> -paclitaxel	Day 1, 15	28 days (4 weeks)
<i>nab</i> -Paclitaxel	None*	100 mg/m ²	IV after ramucirumab	Days 1, 8, 15	
*For patients who have experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone 10 mg IV (or equivalent) and acetaminophen 500 mg po prior to each ramucirumab infusion. Additional premedications, such as antiemetics, may be used at the discretion of the treating investigator.					

5.1.1 Ramucirumab

Preparation for Administration: Inspect vial contents for particulate matter and discoloration prior to dilution. Discard the vial, if particulate matter or discolorations are identified. Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. Calculate the dose and the required volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg/10 mL or 500 mg/50 mL at a concentration of 10 mg/mL solution of ramucirumab. Withdraw the required volume of ramucirumab and further dilute with only 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. Do not use dextrose containing solutions. Gently invert the container to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications. Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]). Discard vial with any unused portion of ramucirumab.

Administration: Visually inspect the diluted solution for particulate matter and discoloration prior to administration. If particulate matter or discolorations are identified, discard the solution. Administer diluted ramucirumab infusion via infusion pump over 60 minutes, ± 5 minutes, through a separate infusion line. Use of a protein sparing 0.22 micron filter is recommended.

5.1.2 nab-Paclitaxel

nab-Paclitaxel is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling *nab*-paclitaxel. The use of gloves is recommended. If *nab*-paclitaxel (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If *nab*-paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of *nab*-paclitaxel to 30 minutes (-5 minutes or +10 minutes), as directed, reduces the likelihood of infusion-related reaction.

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration of *nab*-paclitaxel. Premedication may be needed in patients who have had prior hypersensitivity reactions to *nab*-paclitaxel. Patients who experience a severe hypersensitivity reaction to *nab*-paclitaxel should not be re-challenged with this drug.

Preparation for Administration: *nab*-paclitaxel is supplied as a sterile lyophilized powder for reconstitution before use. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides. Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: $\text{Dosing volume (mL)} = \text{Total dose (mg)} / 5 \text{ (mg/mL)}$.

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Administration: Inject the appropriate amount of reconstituted *nab*-paclitaxel into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer *nab*-paclitaxel infusions. The use of an in-line filter is not recommended. Parenteral drug products should be inspected visually for particulate matter and

discoloration prior to administration whenever solution and container permit.

nab-Paclitaxel is injected into a vein [intravenous (I.V.) infusion] over 30 minutes, -5 minutes or +10 minutes. The ideal infusion time is between 30-40 minutes, and no less than 25 minutes to avoid the safety concern of potential overdose through increase of the C_{max} by approximately 20% if infused too quickly. The use of an in-line liter is not recommended. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

5.2 General Concomitant Medication and Supportive Care Guidelines

No clinically meaningful changes in paclitaxel exposure or ramucirumab exposure were observed when ramucirumab 8 mg/kg and paclitaxel 80 mg/m² were co-administered in patients with solid tumors. No clinically meaningful changes in docetaxel exposure were observed when ramucirumab 10 mg/kg and docetaxel 75 mg/m² were co-administered in patients with solid tumors. Ramucirumab exposure appeared to be comparable regardless of concomitant docetaxel based on cross study comparisons in patients with solid tumors.

The metabolism of paclitaxel is catalyzed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, caution should be exercised when administering *nab*-paclitaxel concomitantly with medicines known to inhibit (e.g., ketoconazole, erythromycin, fluoxetine, imidazole antifungals, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

Because there is a potential for interaction of *nab*-paclitaxel with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.3 Patient Reported Outcomes for EQ-5D-5L

To ensure completion of the EQ-5D-5L questionnaires at the appropriate time-points, assigned research staff must adhere to the instructions in this section. The patient should complete the EQ-5D-5L questionnaires in clinic at the following times: at baseline, prior to the start of each cycle, and at the end of therapy.

Research staff should instruct the patient how to properly fill in the EQ-5D-5L questionnaire per

the following instructions:

- All questionnaires must be completed prior to any other study procedures (baseline following informed consent) and before discussion of current disease status to avoid biasing the patient's responses to the questions.
- Provide a private environment for the patient to answer the questions.
- Provide sufficient time for the patient to complete the questionnaire at their own pace.
- Avoid assistance from relatives, friends or clinic staff to help the patient answer the questionnaires. However, if the patient is unable to read the questionnaire (due to vision impairment such as blindness or uncorrected vision, illiteracy), the questionnaires may be read out loud by trained clinic staff and responses recorded.
- When the patient completes the questionnaire, it should be handed back to the person responsible for the questionnaires, checking for completeness prior to initiating any other procedures.
- Only one answer should be recorded for each question.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow Up

Patients will be followed via medical records review for survival for 12 months after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

At the discretion of the sponsor-investigator (or sponsor/investigator) the study may be closed prematurely.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS/TREATMENT DISCONTINUATION

All toxicities encountered during the study will be evaluated on an ongoing basis according to

the NCI Common Toxicity Criteria version 4. The following criteria should be met prior to the administration of treatment at the start of each new cycle:

- Patients must have the following clinical laboratory values:
 - a. ANC count $\geq 1,500/\mu\text{L}$.
 - b. Platelets $\geq 100,000/\mu\text{L}$.
- Evidence of adequate hepatic function :
 - a. Total Bilirubin ≤ 1.5 times the upper limit normal (ULN)
 - b. AST(SGOT)/ALT(SGPT) $\leq 3.0 \times \text{ULN}$ or $5.0 \times \text{ULN}$ in the setting of liver metastases.
- Serum creatinine ≤ 1.5 times the ULN or creatinine clearance ≥ 40 mL/minutes; if serum creatinine is >1.5 times ULN, a 24-hour urine collection to calculate creatinine clearance must be performed.

If any of the above conditions are not met, treatment will be delayed for up to 4 weeks from the planned date, to permit resolution of toxicity.

Dose modifications of ramucirumab and *nab*-paclitaxel will be based on toxicity occurring anytime between day 1 of the previous cycle and day 1 of the new cycle. Dose re-escalation is not allowed.

Ramucirumab

Permanent Dose Reductions for Hematologic and Other Adverse Drug Reactions	
Adverse Drug Reaction	Dose modification or discontinuation
Infusion-Related Reactions (IRR)	Reduce the infusion rate of ramucirumab by 50% for Grade 1 or 2 IRRs. For patients who have experienced a Grade 1 or 2 IRR, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each subsequent ramucirumab infusion
	Permanently discontinue ramucirumab for Grade 3 or 4 IRR
Hypertension	Interrupt ramucirumab for severe hypertension (180 mm Hg or greater systolic or 110 mm Hg or greater diastolic) until controlled with medical management.
	Permanently discontinue ramucirumab for severe hypertension that cannot be controlled with antihypertensive therapy.
	Patients with grade 4 hypertension must not receive further treatment with ramucirumab.
Proteinuria	Interrupt ramucirumab for urine protein levels ≥ 2 g/24 hours.

	<p>Reinitiate treatment at a reduced dose once the urine protein level returns to <2 g/24 hours as follows:</p> <p>1st Occurrence: 6 mg/kg</p> <p>2nd Occurrence: 5 mg/kg</p> <p>3rd Occurrence: Discontinue Treatment</p> <p>If the protein level does not return to <2 g/24 hours within 2 weeks: Discontinue Treatment</p>
	<p>Permanently discontinue ramucirumab for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome</p>

Other criteria for dose modification/discontinuation of ramucirumab are as follows:

- Grade 3 and 4 arterial thromboembolic events, or any pulmonary embolism/ deep vein thrombosis (PE/DVT) occurring or worsening during anticoagulant therapy, require permanent discontinuation of ramucirumab therapy. Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the SAE mechanism.
- Patients with unresected primary tumors (or local recurrence) who develop Grade 3 or 4 venous thromboembolism may also receive anticoagulation and continue ramucirumab therapy provided that the tumor does not confer an excessive bleeding risk, in the opinion of the patient's physician.
- Ramucirumab should be permanently discontinued in the event of a gastrointestinal perforation or fistula formation.
- If Reversible Posterior Leukoencephalopathy (RPLS) is diagnosed, ramucirumab must be permanently discontinued. All cases of RPLS must be reported via the SAE mechanism.
- Any patient who experiences signs of hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome must be permanently discontinued from ramucirumab therapy.
- Patients with Grade 3/4 bleeding or hemorrhagic event (any cause) must not receive further treatment with ramucirumab.

Patients who meet criteria for discontinuation of ramucirumab may continue on single agent *nab*-paclitaxel until criteria for removal from the study in Section 5.3 are met.

***nab*-Paclitaxel**

Do not administer *nab*-paclitaxel on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm³ and platelet count is at least 100,000 cells/mm³. In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute

neutrophil count of at least 1500 cells/mm³ and platelet count of at least 100,000 cells/mm³ on Day 1 or to an absolute neutrophil count of at least 500 cells/mm³ and platelet count of at least 50,000 cells/mm³ on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce *nab*-paclitaxel as outlined below. Withhold *nab*-paclitaxel for Grade 3-4 peripheral neuropathy. Resume *nab*-paclitaxel at reduced doses when peripheral neuropathy improves to Grade 1 or completely resolves (see below).

Permanent Dose Reductions for Hematologic and Neurologic Adverse Drug Reactions		
Adverse Drug Reaction	Occurrence	<i>nab</i> -Paclitaxel weekly dose (mg/m ²)
Neutropenic Fever (ANC less than 500/mm ³ with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm ³ OR ANC less than 500/mm ³ for more than 7 days	1 st	75
	2 nd	50
	3 rd	Discontinue Treatment
Platelet count less than 50,000/mm ³	1 st	75
	2 nd	50
	3 rd	Discontinue Treatment
Severe sensory Neuropathy – Grade 3 or 4	1 st	75
	2 nd	50
	3 rd	Discontinue Treatment

Hypersensitivity reactions to *nab*-paclitaxel rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, 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 *nab*-paclitaxel administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reaction to *nab*-paclitaxel should not be re-challenged.

Other dose modification and/or treatment discontinuation of either ramucirumab or *nab*-paclitaxel may be made at the discretion of the treating investigator.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Adverse Events and Risks Lists

7.1.1 Adverse Event Lists for Ramucirumab and nab-Paclitaxel

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) for each commercial agent.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. The sponsor/sponsor-investigator will routinely review any new distributions of the IB for relevant new safety information and incorporate into the informed consent form document as appropriate.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE immediately by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE report form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

Overdose, as defined for this protocol, refers to *nab*-paclitaxel dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of *nab*-paclitaxel assigned to a given patient, regardless of any associated adverse events or

sequelae.

PO any amount over the protocol-specified dose

IV 10% over the protocol-specified dose

SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase C_{max} by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

7.2 Definitions

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Life-threatening adverse event or life-threatening suspected adverse reaction is considered "life-threatening" if, in the view of the sponsor-investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction is considered "serious" if, in the view of the sponsor-investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse event or unexpected suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has

been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.3 Reporting of Suspected Adverse Reactions

In the event of a serious adverse event, the PI, the institutional review board (per institutional reporting requirements), and supporting entities per contract will be notified using the CRS Internal SAE Form. An FDA Form 3500 MedWatch report will be completed in the event FDA reporting is required.

All events meeting the definition of a serious adverse event should be recorded on the CRS Internal SAE Form and submitted to

1. PI: Liza C. Villaruz, MD
 - a. Phone: 412-648-6577
 - b. Fax: 412-648-6579
 - c. Email: villaruzl@upmc.edu
2. Clinical Research Manager: Carrie Muñiz
 - a. Phone: 412-623-6121
 - b. Fax: 412-648-6650
 - c. Email: munizca@upmc.edu
3. crssafetysubmissions@upmc.edu
4. Local Institutional Review Board per institutional reporting requirements

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Lilly in writing using the CRS Internal SAE Form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Lilly by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Lilly tracking number (I4T-US-X001) and the institutional protocol number should be included on SAE reports (or on

the fax cover letter). A copy of the fax transmission confirmation of the SAE report to Lilly should be attached to the SAE and retained with the patient records.

5. Lilly Drug Safety Contact Information:
Lilly Global Patient Safety
Fax: (866) 644-1697 or (317) 453-3402

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Section B and/or Section C – Narrative of the CRS Internal SAE Form:

- CTCAE term(s) and grade(s)
- Current status of study drug
- All interventions to address the AE (testing and result, treatment and response)
- Hospitalization and/or discharge dates
- Event relationship to study drug

Follow-up reports:

Additional information may be added to a previously submitted report by updating the original CRS Internal SAE Form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original CRS Internal SAE Form.

8. PHARMACEUTICAL INFORMATION

8.1 Ramucirumab

Ramucirumab is a recombinant human IgG1 monoclonal antibody that specifically binds to vascularendothelial growth factor receptor 2. Ramucirumab has an approximate molecular weight of 147 kDa. Ramucirumab is produced in genetically engineered mammalian NS0 cells. Ramucirumab is a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution for intravenous infusion following dilution and preparation. Ramucirumab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-dose vials. CYRAMZA is formulated in glycine (9.98 mg/mL), histidine (0.65 mg/mL), histidine monohydrochloride (1.22 mg/mL), polysorbate 80 (0.1 mg/mL), sodium chloride (4.383 mg/mL), and Water for Injection, USP, pH 6.0.

8.2 *nab*-Paclitaxel

nab-Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. *nab*-Paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel

formulated as albumin-bound particles. *nab*-Paclitaxel is free of solvents. The active agent in *nab*-paclitaxel is paclitaxel, a microtubule inhibitor. The chemical name for paclitaxel is 5 β ,20-Epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Paclitaxel is a white to off-white crystalline powder with the empirical formula C₄₇H₅₁NO₁₄ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Scans and x-rays must be done ≤ 21 days prior to enrollment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Cycle 1				Cycle 2				Cycle 3 (and subsequent 28-day cycles)				Off Study ^e
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	
Ramucirumab		A		A		A		A		A		A		
<i>nab</i> -Paclitaxel		B	B	B		B	B	B		B	B	B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X-----X												
Physical exam	X	X				X				X				X
Vital signs ^a	X	X				X				X				X
Height	X													
Weight	X	X				X				X				X
Performance status	X	X				X				X				X
CBC w/diff, plts	X	X	X	X		X	X	X		X	X	X		X
Serum chemistry ^b	X	X	X	X		X	X	X		X	X	X		X
PT/PTT/INR	X	X				X				X				X
EKG (as indicated)	X													
Adverse event evaluation		X-----X												X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation ^f	X	Radiologic measurements with CT or MRI of all sites of disease should be performed every 8 weeks.												X
B-HCG	X ^c													
Urinary protein	X ^d	X ^d				X ^d				X ^d				X ^d
EQ-5D-5L questionnaire ^g	X	X				X				X				X

A: Ramucirumab 8 mg/kg IV Day 1 and day 15 and 28 day cycle
 B: *nab*-Paclitaxel 100 mg/m² IV Day 1, 8 and 15
 a: Vital signs include pulse, breathing rate, blood pressure, and temperature
 b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. If serum creatinine is >1.5 times ULN, a 24-hour urine collection to calculate creatinine clearance must be performed – see Section 6.
 c: Serum pregnancy test (women of childbearing potential) within 7 days of starting study treatment.
 d: Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during ramucirumab treatment. The patient's urinary protein must demonstrate a urine protein level <2 g/24 hours to allow ramucirumab treatment. Perform proteinuria testing only if subject was removed from ramucirumab treatment within 30 days of end of treatment visit.
 e: Off-study evaluation completed within 30 days of being removed from treatment. Patients will be followed via medical records review for survival for 12 months after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable

- | | |
|----|---|
| | adverse event(s) will be followed until resolution or stabilization of the adverse event. |
| f. | CT or MRI scan should include at minimum chest and abdomen (including adrenals). Other scan area imaging should include all sites of disease as appropriate for each subject. |
| g. | See Appendix B [1], and section 5.3 for instructions. |

Note: There is a window of ± 1 week available for rescheduling treatment and/or procedures at the discretion of the Sub-investigator, and as discussed with the Investigator if a course is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject [i.e. non-UPMC insurance coverage] or reduce travel inconvenience, illness, transportation issues, holidays, family emergencies, etc.).

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks with CT or MRI to evaluate all sites of disease. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[64]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or as ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only

the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic 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 non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based

evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [65-67]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer[68].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- c. 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. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) 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. (Note: the appearance of one or more new lesions is also considered progressions).

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.

10.1.4.2 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 (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Investigator).

10.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment

until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Only for non-randomized trials with response as primary endpoint. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration.</i>” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
<p>* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised</p>		

10.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.1.6 Progression-Free Survival and Overall Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Overall survival is defined as the duration of time from the start of treatment to death.

11. DATA REPORTING / REGULATORY REQUIREMENTS

11.1 Data Safety Monitoring Plan

Sponsor/Investigator, Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings. See Section 12.1.1. for details of the planned interim analysis of dose delivery and adverse events.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

11.2 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and Guidelines on Good Clinical Practice compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the Education and Compliance Office – Human Subject Research, Research Conduct and Compliance Office, University of Pittsburgh.

The Investigator (i.e., the study site principal investigator) and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

11.3 Data Handling and Record-Keeping

The Investigator (i.e., the study site principal investigator) will maintain records in accordance with Good Clinical Practice.

The investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

11.4 Institutional Review Board (IRB) Approval

The investigator (i.e., the study site principal investigator) will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at [21 CFR Parts 50](#) and [21 CFR 56](#), and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice.

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of an sponsor's decision to modify the previously accepted clinical protocol, the sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of protocol changes requiring the submission of a Protocol Amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or AE; or the dropping of a test intended to monitor the safety of the investigational drug.

11.5 Ethical and Scientific Conduct of the Clinical Study

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on Guidelines on Good Clinical Practice; and relevant policies, requirements, and regulations of the University of Pittsburgh IRB, University of Pittsburgh and University of Pittsburgh Medical Center, Commonwealth of Pennsylvania, and applicable federal agencies.

11.6 Informed Consent

The investigator (i.e., the study site principal investigator) will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The

investigator, or a sub-investigator(s) designated by the sponsor, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator or sub-investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

12.1.1 Interim analysis

Enrollment will be halted for a safety review after C2D21 for the 6th patient with squamous cell histology, and separately after C2D21 for 6th patient without squamous cell histology. Patients who withdraw prior to C2D21 for reasons other than toxicity (disease progression, consent withdrawn) will not count toward these first 6 patients. Dose delivered and adverse events for those patients will be examined, and the decision to continue as planned or modify the protocol in any way will be made by the study investigators, the disease center Data and Safety Monitoring Board (DSMB), and the University of Pittsburgh Cancer Institute (UPCI) Data and Safety Monitoring Committee (DSMC).

12.1.2 Primary objective (safety)

Safety and systemic toxicity will be summarized for all patients who receive at least one dose of study drug. All adverse events that are determined to be possibly, probably or definitely related to treatment will be tabulated according to grade and type, in order of frequency, separately for patients with disease of squamous and non-squamous histology. Each adverse event will be counted only once per patient, with the highest grade recorded. Serious adverse events will also be tabulated by frequency, separately for patients with disease of squamous and non-squamous histology. Listings will be provided for all on-study deaths and adverse events that lead to withdrawal from study.

12.1.3 Primary objective (PFS)

For the unselected population (squamous and non-squamous) and for the subgroup of squamous NSCLC only, the PFS curve and a 90% confidence interval for the median PFS will be estimated by standard methods (the Kaplan-Meier method for survival, and the Greenwood variance formula applied to log-transformed survival). Sampling weights will be used to approximate PFS for the unselected population, in which about 25% of study population has disease with squamous histology [2].

12.1.4 Power calculations assume accrual of 80 patients at a uniform rate over 2 years, with 10 months of additional follow-up. A minimum of 40 patients with NSCLC of squamous cell histology will be accrued, e.g. if 40 patients with non-squamous histology are enrolled initially, the remaining patients must have squamous cell histology. Simulating data with median 5 months PFS (exponential distribution), the lower bound of the 90% confidence interval for median PFS was greater than 3 months for 93% of 10,000 simulated datasets of size $n=80$ and 75% for size $n=40$. Therefore, we conclude that with two-sided $\alpha=0.1$, the study has 93% power to conclude that the median PFS is unlikely to be 3 months or less in an unselected population, and 75% power for the squamous histology subgroup. The average width of the confidence interval for median PFS for squamous histology is expected to be about 3.8 months (ie, 90% confidence interval 3.6-7.4 months). The null rate of 3 months is from the median TTP of 2.7 months (median OS of 7 months) in previously treated advanced stage NSCLC patients treated with single agent docetaxel [4].

12.1.5 Secondary objectives

OS will be evaluated using the same methodology as for PFS. The ORR will be estimated with a 90% Wilson (Score confidence interval), for the unselected population (with sampling weights) and for the squamous histology group. Patient-reported symptoms and quality-of-life (QOL) at baseline, the end of each cycle, and at the end of therapy will be assessed using the EuroQoL Five Dimensions questionnaire[1]. Total scores and subscales will be summarized for each patient and by histology, and analyzed using standard linear mixed models methods. The primary analysis will be specified once EuroQoL results are published for the REVEL trial, which is large enough to provide precise benchmarks. In the absence of guidance from REVEL analysis, the primary analysis will summarize baseline QOL, average decreases over the first two cycles of treatment, and average QOL in survivors at approximately 6 months and 12 months.

12.2 Reporting and Exclusions

12.2.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment.

12.2.2 Evaluation of Response

All patients 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 patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B **EuroQoL EQ-5D-5L Questionnaire [[1, 69-76](#)]**

UPCI #:15-169
Version Date: 06/17/2016



Health Questionnaire

English version for the USA

Assessment Date: ___/___/___
mm/dd/yyyy

EQ-5D-5L Worksheet

Protocol: 15-169

Patient Initials: ___

Patient number: ___

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking
- I have slight problems walking
- I have moderate problems walking
- I have severe problems walking
- I am unable to walk

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

Assessment Date: ___/___/___
mm/dd/yyyy

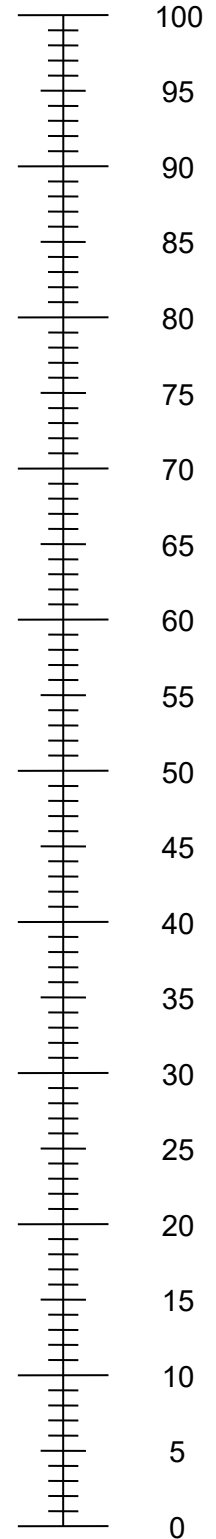
Patient Initials: ___

Patient number: ___

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine