CLINICAL PROTOCOL

Protocol No. 59R5-003

Title: A Phase 1b/2 Study of *Tarextumab (*OMP-59R5*)* in Combination with Etoposide and Platinum Therapy in Subjects with Untreated Extensive Stage Small Cell Lung Cancer

PINNACLE: **P**hase 1b/2 **IN**vestigation of anti-**N**otch **A**ntibody Therapy with Etoposide and Platinum Therapy in Small **C**ell **L**ung Carcinoma Safety and **E**fficacy

Version: 18 December 2012
Amendment 1: 09 May 2013
Amendment 2: 19 August 2013
Amendment 3: 23 October 2013
Amendment 4: 17 April 2014
Amendment 5: 10 September 2014
Amendment 6: 22 April 2016

IND Number: 106826

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CONFIDENTIAL

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INVESTIGATOR SIGNATURE PAGE

OncoMed Pharmaceuticals, Inc.

Protocol No. 59R5-003

Amendment *6: 22 April 2016*

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

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

Principal Investigator **Date**

Printed Name:

Institution:

Address:

Telephone Number:

SPONSOR SIGNATURE PAGE

OncoMed Pharmaceuticals, Inc.

Protocol No. 59R5-003

Amendment *6: 22 April 2016*

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

[redacted] 29 APR 2016

Signature of Sponsor Representative Date

[redacted]

Printed Name of Sponsor Representative

SYNOPSIS

Title of Study:

A Phase 1b/2 Study of Tarextumab in Combination with Etoposide and Platinum Therapy in Subjects with Untreated Extensive Stage Small Cell Lung Cancer

INNACLE: **P**hase 1b/2 **IN**vestigation of anti-**N**otch **A**ntibody Therapy with Etoposide and Platinum Therapy in Small Cell **L**ung Carcinoma Safety and **E**fficacy

Study Period: Approximately 36 months	**Development Phase:** Phase 1b/2

Objectives:

Primary Objectives:

- To determine the maximum tolerated dose (MTD) of tarextumab when administered on Day 1 of each 21 day cycle along with etoposide 100 mg/m^2 on Days 1, 2 and 3, and cisplatin 80 mg/m^2 or carboplatin area under the curve (AUC) of 5 mg/mL•min on Day 1 in subjects with untreated extensive stage small cell lung cancer (Phase 1b portion)
- To determine the improvement in Progression Free Survival (PFS) resulting from the addition of tarextumab to etoposide and platinum therapy (EP) in subjects receiving first-line therapy for extensive stage small cell lung cancer (Phase 2 portion)

Secondary Objectives:

- To determine the pharmacokinetics of tarextumab in combination with EP in subjects receiving first-line therapy for extensive stage small cell lung cancer (Phase 1b and *2* portion)
- To determine the immunogenicity of tarextumab in combination with EP in subjects receiving first-line therapy for extensive stage small cell lung cancer (Phase 1b and 2 portions)
- To estimate the improvement in overall survival (OS), 12 months OS, and the overall response rate (ORR) resulting from the addition of tarextumab to EP in subjects receiving first-line therapy for extensive stage small cell lung cancer (Phase 2 portion)
- *To correlate the treatment effect in PFS and OS, 12 month OS and ORR resulting from the addition of tarextumab to EP in subjects receiving first-line therapy for extensive stage small cell lung cancer in subjects with Notch3, Hes 1, Hey 2, Hey 1 and Hes 6 expression (Phase 2 portion)*
- To determine the safety and tolerability of tarextumab in combination with EP in subjects who are receiving first-line therapy for extensive stage small cell lung cancer (Phase 1b portion)
- To compare the safety and tolerability of tarextumab in combination with EP relative to EP alone in all subjects who are receiving first-line therapy for extensive stage small cell lung cancer (Phase 2 portion)

Exploratory Objective:

- To describe the changes in exploratory pharmacodynamic (PD) biomarkers, including Notch pathway related genes and proteins and circulating tumor cells following tarextumab treatment (Phase 1b and 2 portions)

Study Design:

The study consists of a Phase1b lead-in portion to determine the MTD of tarextumab in combination with EP for 6 cycles followed by treatment with tarextumab alone until unacceptable toxicity or progression of disease. The initial dose escalations of tarextumab will be conducted with etoposide and cisplatin. The dose of tarextumab will not exceed 15 mg/kg. Following the establishment of the highest tolerable dose of tarextumab in combination with etoposide and cisplatin, a cohort of 6 subjects will be treated at this dose in combination with etoposide and carboplatin. Once the safety and tolerability of tarextumab of the highest tolerable dose is confirmed with etoposide and cisplatin/carboplatin, the protocol will explore a Phase 2, multicenter, randomized, placebo-controlled portion comparing the efficacy and safety of tarextumab at this highest tolerable dose in combination with EP for 6 cycles followed by single agent tarextumab relative to EP alone for 6 cycles in subjects receiving first-line therapy for extensive stage small cell lung cancer. However, if a DLT is observed in 2 or more subjects in the cohort of 6 subjects treated with the highest tolerable dose of tarextumab with etoposide and carboplatin, a new cohort of 3 to 6 subjects will be enrolled at the next lower dose level of tarextumab with etoposide and carboplatin. The highest tarextumab dose that is tolerable with both platinum options will be used in Phase 2 portion of the study. For example: if tarextumab at 15 mg/kg is tolerable with etoposide and cisplatin, but not tolerable with etoposide and carboplatin and tarextumab at 12.5 mg/kg is tolerable with etoposide and carboplatin, then tarextumab at 12.5 mg/kg will be the dose used in Phase 2 portion of the study.

Subjects may be treated with cisplatin or carboplatin as determined by the Investigator prior to randomization. Alteration to the choice of platinum therapy is not permitted once the subject is randomized.

Etoposide 100 mg/m^2 will be administered on Days 1, 2 and 3 along with cisplatin 80 mg/m^2 or with carboplatin area under the curve (AUC) of 5 mg/mL•min on Day 1 of every 21-day cycle for 6 cycles in Phase 1b. In Phase 2 portion of the study, cisplatin dose will be 75 mg/m^2, etoposide and carboplatin dose will the same as the one used in Phase 1b. tarextumab or Placebo will be given on Day 1 of every 21-day cycle prior to the administration of EP.

Subjects may continue one of the chemotherapy drugs if the other is held or discontinued prior to completing 6 cycles of EP and prior to disease progression. Subjects should continue EP alone for a total of 6 cycles if study drug is held or discontinued prior to the completion of 6 cycles of EP. Subjects may continue study drug if one or both of the chemotherapy drugs is held or discontinued prior to completing 6 cycles of EP and prior to disease progression.

After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Study drug administration should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone ≥14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (APPENDIX A). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

Subjects who are discontinued from study treatment will be followed for survival and any subsequent anti-cancer therapies. Survival follow-up information and subsequent anti-cancer therapies, including systemic therapies, surgery (resection of metastatic disease), and radiation therapy will be collected during telephone calls, through subjects medical records, and/or clinic visits approximately every 3 months starting from the last study treatment until death, loss to follow-up, or study termination by the sponsor. The study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Additionally, subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Study Population and Number of Subjects:

Subjects must have previously untreated extensive stage small cell lung cancer proven either by histology or cytology. In addition, subjects must have Formalin-Fixed, Paraffin-Embedded (FFPE) tumor tissue, either archived or fresh biopsied for Notch3*, Hes1, Hey2, Hey1 and Hes6* analysis. In the Phase 2 portion, subjects must have measurable disease by RECIST 1.1 criteria in order to be eligible.
Approximately 30 subjects will be enrolled into Phase 1b portion of the study, the exact number will depend on the number of dose levels assessed and the toxicities observed.
For the Phase 2 portion of the trial, approximately 135 subjects will be treated with at least one dose of study drug (either tarextumab or placebo).

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria:

1. Histologically or cytologically documented extensive stage small cell lung cancer (combined small cell carcinoma is allowed); extensive stage is defined as disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases (contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited disease).
2. Adults of 18 years of age or older.
3. Performance Status (ECOG) of 0 or 1.
4. FFPE tumor tissue, either fresh core needle biopsied (two fresh cores preferred whenever possible), or archived available for Notch3*, Hes1, Hey2, Hey1 and Hes6* analysis
5. Adequate organ function:
   a. Adequate hematologic function (absolute neutrophil count [ANC] ≥ 1,500 cells/μL; hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/μL).
   b. Adequate renal function (serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 60 mL/min using Cockroft Gault formula).
   c. Adequate hepatic function (alanine aminotransferase [ALT] ≤ 3 x upper limit of normal [ULN], ALT may be ≤ 5 x ULN if due to liver metastases but cannot be associated with concurrent elevated bilirubin >1.5xULN unless it is approved by the Sponsor's Medical Monitor).
   d. Prothrombin Time (PT)/International Normalized Ration (INR) ≤1.5 × ULN, activated partial thromboplastin time (aPTT) ≤1.5 × ULN.
6. Written consent on an IRB/IEC-approved Informed Consent Form prior to any study-specific evaluation.
7. For women of child-bearing potential, negative serum pregnancy test at screening and use of physician-approved method of birth control from 30 days prior to the first study drug administration to 30 days following the last study drug administration or the last EP in the study, whichever is discontinued last.
8. Male subjects must be surgically sterile or must agree to use physician-approved contraception during the study and for 30 days following the last study drug administration or the last EP in the study, whichever is discontinued last.

Additionally, for individuals eligible to participate in Phase 2 portion of the study:

9. Subject must have evidence of measurable disease per RECIST 1.1 criteria.

Exclusion Criteria:

1. Limited stage small cell lung cancer appropriate for radical treatment with chemoradiation.
2. Prior therapy including radiation, chemotherapy or surgery for newly diagnosed extensive stage small cell lung cancer. Exceptions to this exclusion criterion include: 1) prophylactic cranial irradiation or whole brain radiation (WBRT) prior to the first administration of study drug provided that the subject has stable neurologic condition for at least 2 weeks after the completion of the radiation, adverse event that is related to the radiation has recovered to be ≤ Grade 1, and is not receiving corticosteroid of > 40 mg prednisone daily equivalent dose to control the symptoms, 2) focused radiation for symptomatic relief for isolated bone metastases; 3) bisphosphonate or denosumab therapy for bone metastasis initiated prior to study entry.
3. Presence of uncontrolled Grade ≥ 1 diarrhea within 4 weeks prior to the first study drug administration.
4. Presence of any serious or uncontrolled illness including, but not limited to: ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, uncontrolled arterial thrombosis, symptomatic pulmonary embolism, and psychiatric illness that would limit compliance with study requirement.

Diagnosis and Main Criteria for Eligibility: (Cont'd)

5. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty and/or stenting within 6 months prior to the first administration of study drug.
6. A history of malignancy with the exception of:
   a. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer
   b. Superficial bladder cancer
   c. Adequately treated stage I cancer from which the subject is currently in remission, or
   d. Any other cancer from which the subject has been disease-free for ≥ 3 years
7. Known human immunodeficiency virus (HIV) infection.
8. Females who are pregnant or breastfeeding.
9. Concurrent use of therapeutic warfarin (prophylactic low dose of warfarin, i.e., 1 mg daily for port catheter is allowed).

Additionally, individuals ineligible to participate in Phase 2 portion of the study if :

10. Subjects have relapsed after treatment for limited disease

Test Product, Dose, and Mode of Administration

Study drug will be either tarextumab or Placebo (Phase 2, only). Study drug will be given intravenously on Day 1 of every 21-day cycle. The subject should not receive two consecutive doses of study drug within 18 days.

Tarextumab is an IgG2 fully human monoclonal antibody that is directed against the Notch2/3 receptors. Tarextumab is supplied at a concentration of 10 mg/mL in 25mL single-use glass vial filled to 20 mL to deliver at total of 200 mg per vial. Tarextumab vials must be stored at 2°C–8°C. DO NOT FREEZE. DO NOT SHAKE.

Please refer to the Pharmacy Manual for the details on tarextumab preparation and administration. Placebo is a formulation of 50mM Histidine, 100mM Sodium Chloride, 45mM Sucrose and 0.01% (v/v) Polysorbate-20, pH 6.0. Placebo will be administered in the same manner as tarextumab. Please refer to the Pharmacy Manual for details regarding Placebo preparation and administration.

Etoposide will be administered by IV infusion at a dose of 100 mg/m^2 over 30 to 60 minutes on Days 1, 2 and 3 of each 21-day treatment cycle for 6 cycles in accordance with institutional standard of care. The subject should not receive two Day 1 consecutive doses of etoposide within 18 days. A one day window will be allowed for each consecutive day of etoposide dosing (e.g. Day 2 and 3 dosing may occur on Day 3 and 4, or Day 3 and 5).

Cisplatin or carboplatin will be the choice of platinum therapy. Initially, all subjects in Phase 1b will receive cisplatin until the MTD/highest tolerable dose is determined with tarextumab in combination with etoposide and cisplatin. After that, a cohort of 6 subjects will be enrolled to receive tarextumab at the MTD/highest tolerable dose with etoposide and carboplatin. Subjects in Phase 2 will receive cisplatin or carboplatin as determined by the Investigator prior to randomization.

Cisplatin will be administered by IV infusion at a dose of 80 mg/m^2 over 30 minutes to 2 hours on Day 1 of each 21-day treatment cycle for 6 cycles in accordance with institutional standard of care in Phase 1b and at a dose of 75 mg/m^2 in Phase 2 portion of the study. The subject should not receive two consecutive doses of cisplatin within 18 days.

Carboplatin will be administered by IV infusion at AUC of 5 mg/mL•min over 15 minutes or longer on Day 1 of each 21-day treatment cycle for 6 cycles in accordance with institutional standard of care. The subject should not receive two consecutive doses of carboplatin within 18 days.

On days when study drug is given together with etoposide and platinum therapy, study drug should be given prior to etoposide and platinum therapy administration. Subjects may continue one of the chemotherapy drugs if the other is held or discontinued prior to completing 6 cycles of EP and prior to disease progression. For subjects who have study drug held or discontinued for tolerability reasons, EP chemotherapy should continue to the completion of 6 cycles. Subjects may continue study drug if one or both of the chemotherapy drugs is held or discontinued prior to completing 6 cycles of EP and prior to disease progression.

Duration of Treatment:

In the absence of unacceptable study drug treatment-related toxicity or disease progression, subjects may receive study treatment for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and the Sponsor.

Safety Evaluation:

Safety will be assessed by adverse event monitoring (including attribution of adverse events and serious adverse events), physical examination, vital signs, clinical laboratory testing and anti-tarextumab testing on an ongoing basis as outlined in the Schedule of Assessments.

Efficacy Evaluation:

Subjects will be assessed for response using Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. The first response assessment will occur approximately 6 weeks/42 days (± 5 days) after the first dose of the study drug. Subsequent response assessments will occur every 6 weeks/42 days (± 5 days). Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Immunogenicity:

During Phase 1b, serum samples will be obtained for immunogenicity assessment prior to study drug administration on Day 1 of Cycle 1, every three cycles thereafter (Day 1 of Cycle 4, 7, 10, etc.), at other times as clinically indicated such as when significant toxicities occur and at the time of treatment termination for all subjects enrolled in Phase 1b. Samples that test positive will be assessed for neutralizing capability.
During Phase 2, serum samples will be obtained for immunogenicity assessment prior to study drug administration on Day 1 of Cycle 1, every other cycle thereafter (Day 1 of Cycle 3, 5, 7, etc.), at other times as clinically indicated such as when significant toxicities occur and at the time of treatment termination for all subjects enrolled in Phase 2. Samples that test positive will be assessed for neutralizing capability.

Pharmacokinetic Evaluation:

For subjects enrolled in Phase 1b portion only: Plasma samples from all subjects enrolled in Phase 1b portion will be obtained for pharmacokinetic analysis of tarextumab at pre-dose and 5 minutes post infusion on Day 1 of Cycles 1 and 3, on Days 3 and 8 of Cycles 1 and 3, at other times as clinically indicated such as when significant toxicities occur as well as at the time of treatment termination, as outlined in the Schedule of Assessments (APPENDIX B).
For subjects enrolled in Phase 2 portion only: Plasma samples from all subjects enrolled in Phase 2 portion will be obtained for pharmacokinetic analysis of tarextumab on Day 1 of Cycle*s* 1 *and 3,* at pre-dose and 5 minutes post tarextumab infusion; Day 3 of Cycle 1 and Cycle *3* prior to etoposide administration; Day 8 of Cycle 1 and Cycle 3 when blood sample is taken for biomarker evaluation; Day 1 of every other cycle starting from Cycle 5 prior to study drug administration and, at other times as clinically indicated such as when significant toxicities occur as well as at the time of treatment termination, as outlined in the Schedule of Assessments (APPENDIX C). Pharmacokinetic parameters (i.e. area under the curve [AUC], clearance, volume of distribution and apparent half life) of tarextumab will be assessed for each evaluable subject.

Biomarker Evaluation:

Samples will be obtained for biomarker evaluations as outlined in the Schedule of Assessments (APPENDIX B and APPENDIX C).

Notch3, *Hes1, Hey2, Hey1, and Hes6* expression levels (e.g., protein and/or RNA) will be assessed in FFPE tumor specimens to *correlate the treatment effect* in *relation to these gene expressions*. The expression level of additional proteins and genes may be evaluated and correlated with clinical benefit. Additionally, DNA testing may be done on subjects who consent to have the optional DNA testing on FFPE tumor specimens collected.

Exploratory pharmacodynamics assays to confirm target engagement will include assessments of hair follicles (Phase 1b portion only), plasma proteins, and blood mRNA. Circulating tumor cells (CTCs) will also be monitored to explore the effects of treatment on CTCs. In addition, a pharmacogenomic blood sample will be collected on Day 1 of Cycle 1 prior to dosing from subjects who give informed consent to assess Notch target- or pathway-related genes.

Optional tumor biopsies will be obtained to assess tumor biomarkers before and during tarextumab treatment and at the time of progression in subjects who are consented to provide pre- and post-treatment tumor biopsies, provided it is feasible.

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2.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
aPTT	activated partial thromboplastin time
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CR	complete response
CRA	clinical research associate
CRF	case report form
CT	computed tomography (scan)
CTC	circulating tumor cell
CTCAE	common toxicity criteria for adverse events (National Cancer Institute)
D5W	5% dextrose in water
dL	deciliter(s)
DLT	dose-limiting toxicity
DSMB	data safety monitoring board
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
eCRF	electronic case report form
EDC	electronic data capture
EP	etoposide and platinum therapy (cisplatin or carboplatin)
FACS	fluorescent-activated cell sorting
FFPE	formalin-fixed, paraffin-embedded
GI	gastrointestinal
GCP	good clinical practice
HIPAA	health insurance portability and accountability act OF 1996
IEC	independent ethics committee

Abbreviation or Term	Definition/Explanation
IMP	investigational medicinal product
INR	international normalized ration
IRB	institutional review board
ITT	intent-to-treat (population)
L	liter(s)
LFT(s)	liver function test(s)
IV	Intravenous
IWRS	Interactive Web-based randomization system
Kg	kilogram(s)
Kaplan-Meier	KM
LD	longest diameter (of a lesion), or limited disease
LDH	lactic dehydrogenase
MedDRA	medical dictionary for regulatory activities
Mg	milligram(s)
Min	minute(s)
mL	milliliter(s)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	national cancer institute
NE	not evaluable
NOAEL	no observed adverse effect level
ORR	overall response rate
OS	overall survival
PCI	prophylactic cranial irradiation
PD	progressive disease or pharmacodynamic
PK	pharmacokinetics
PFS	progression free survival
PR	partial response
PVC	polyvinyl chloride
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event

Abbreviation or Term	Definition/Explanation
SCLC	small cell lung cancer
SD	stable disease
SLD	sum of longest diameter
ULN	upper limit of normal
US	Ultrasound
WBRT	whole brain radiation therapy

3.0 BACKGROUND

3.1 Investigational Medicinal Product

Investigational Medicinal Product is either tarextumab or Placebo.

Tarextumab is a fully human IgG_2 monoclonal antibody that inhibits the function of both Notch2 and Notch3 receptors. Tarextumab is supplied at a concentration of 10 mg/mL in 25-mL single-use glass vial filled to 20 mL to deliver at total of 200 mg per vial. Tarextumab vials must be stored at 2°C–8°C. DO NOT FREEZE. DO NOT SHAKE.

Placebo is a formulation of 50mM Histidine, 100mM Sodium Chloride, 45mM Sucrose and 0.01% (v/v) Polysorbate-20, pH 6.0. Placebo will be handled the same way as tarextumab.

3.2 Disease Background

Small cell lung cancer (SCLC) comprises ~ 15% of the total cases of lung cancer in the US (Ref 1) and Europe. At the time of diagnosis, approximately 30% of patients with SCLC will have tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes. These patients are designated as having limited-stage disease (LD) while patients with tumors that have spread beyond the supraclavicular areas are said to have extensive-stage disease (ED). SCLC is more responsive to chemotherapy and radiation therapy than other cell types of lung cancer; however, a cure is difficult to achieve because SCLC has a greater tendency to be widely disseminated by the time of diagnosis. Chemotherapy is the main treatment for ED-SCLC. Combination therapy with EP is considered the standard first line regimen and results in a high response rate (60-70%), but tumor recurrence after therapy is very common and the five year survival rate is only ~ 5% (Ref 2). Development of new and effective therapies for this disease has been lacking, and consequently, there is a significant need to develop novel approaches for the treatment of SCLC.

3.3 Nonclinical Data

Many current cancer treatments, while producing an initial reduction in tumor burden, have not resulted in a long-term benefit. A possible explanation for this observation is the presence of cancer stem cells (Ref 3, Ref 4), which represent a small percentage of the tumor, but are the most tumorigenic component driving growth and metastasis and are more resistant to traditional cytotoxic therapy, including both radiotherapy (Ref 5) and chemotherapy (Ref 6), than the remaining bulk of the tumor. Like normal stem cells, cancer stem cells may be characterized by three properties: self-renewal, the capacity to develop into multiple lineages, and the ability to proliferate extensively (Ref 7). Cancer stem cells (CSCs) have been most extensively studied in hematologic malignancy, but have now also been identified in many solid tumors, including breast, colon, lung, head and neck, glioblastoma, and pancreatic cancers. CSCs rely on the activation of developmental pathways including the Notch pathway and several new therapies, including tarextumab, are being developed to target these pathways (Ref 8).

SCLC is characterized by expression of Notch receptors and Notch target genes indicating that the pathway is likely to be activated in this disease. OncoMed Pharmaceuticals has established a collection of patient derived xenografts, including several from small cell lung cancer patients, that retain much of the cellular heterogeneity of the patient's tumor and which enable the pre-clinical study of potential therapeutics in models that better represent the clinical setting than traditional xenografts from cell lines that have passaged in tissue culture (Ref 9). We have found that these xenograft models express various levels of Notch1, Notch2 or Notch3 as shown by immunohistochemistry. In addition, we have also shown elevated expression of various Notch target genes in SCLC including PBX1, HEYL, HEY2, and HES6 (data not shown).

Additionally, we have tested the effects of anti-Notch2/3 (tarextumab) in eight SCLC patient derived models and tarextumab was found to be active in seven of these models (Table 1)

Table 1: Summary of the Activity of Tarextumab in SCLC Xenografts

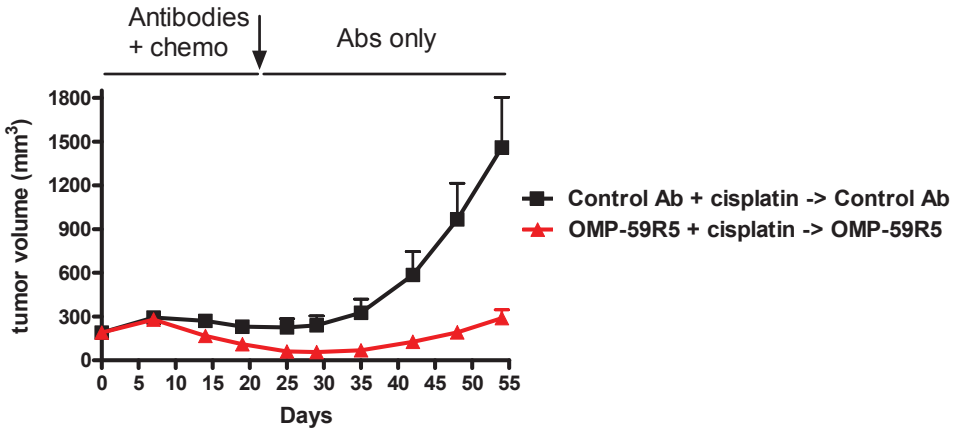
SCLC Tumor	Efficacy
Lu40	+
Lu61	+
Lu65	+
Lu66	+
Lu67	-
Lu68	+
Lu87	+
Lu90	+

SCLC patient derived xenografts were tested with tarextumab in combination with chemotherapeutic treatment. A "+" indicates a reduction in tumor volume by tarextumab plus chemotherapy ($p < 0.05$) relative to the group treated with chemotherapy alone. The asterisk indicates that tarextumab also exhibited single agent activity in Lu61.

We also tested the activity of tarextumab in SCLC in a tumor recurrence experiment that was meant to recapitulate some of the clinical features of the response of SCLC to chemotherapeutic treatment. Our initial tumor recurrence experiment was carried out in OMP-Lu68 tumors, a patient derived SCLC tumor which expresses Notch3 and Notch2, the targets of tarextumab. The experiment had two treatments phases – an "induction phase" where tumor bearing mice were treated with a high dose of chemotherapy with or without tarextumab and a "maintenance phase" where either tarextumab or control antibody treatments were continued. Established Lu68 lung tumors were treated with cisplatin or cisplatin plus tarextumab and it was observed that co-administration of tarextumab with cisplatin led to an increased rate of tumor regression relative to cisplatin alone (Figure 1). Continued treatment with tarextumab during the maintenance phase significantly delayed the rate of tumor recurrence (Figure1).

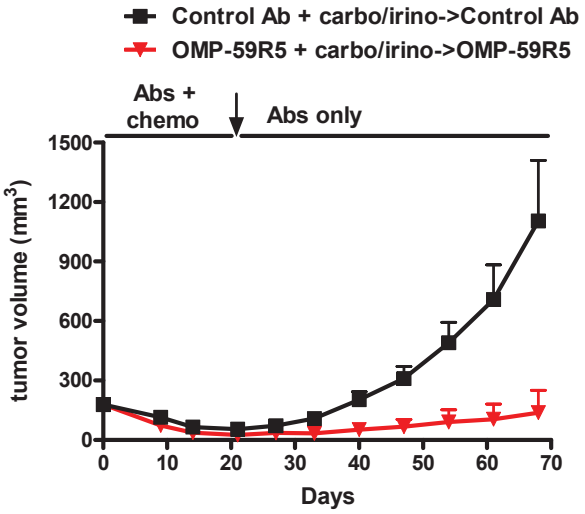
A similar experiment was carried on the Lu87 SCLC xenograft model. In this case we used carboplatin plus irinotecan as the chemotherapeutic regimen. We found that tarextumab treatment led to a significant delay in tumor regrowth after the initial response to chemotherapeutic treatment Figure 2. The design of these pre-clinical tumor recurrence experiments was intended to model the PINNACLE trial design - combination of tarextumab plus chemotherapy followed by tarextumab only in the maintenance phase. Irinotecan was chosen as a chemotherapeutic agent for these pre-clinical studies because both irinotecan and etoposide are topoisomerase inhibitors and irinotecan is much better tolerated in mice than etoposide. Similarly, we have found that carboplatin is generally better tolerated than cisplatin in our pre-clinical studies. These data in Lu87 establish that tarextumab can be efficacious in combination with chemotherapeutic regimens that include carboplatin. Additional studies in several other SCLC tumors also showed that tarextumab was efficacious in combination with carboplatin (data not shown). In addition to these tumor recurrence experiments, we also found that tarextumab inhibited tumor growth in combination with Taxol in Lu40 SCLC tumors (Figure 3) and as a single agent in Lu61 SCLC tumors (Figure 4).

Figure 1: Activity of Tarextumab in Lu68 SCLC Tumor Recurrence Model



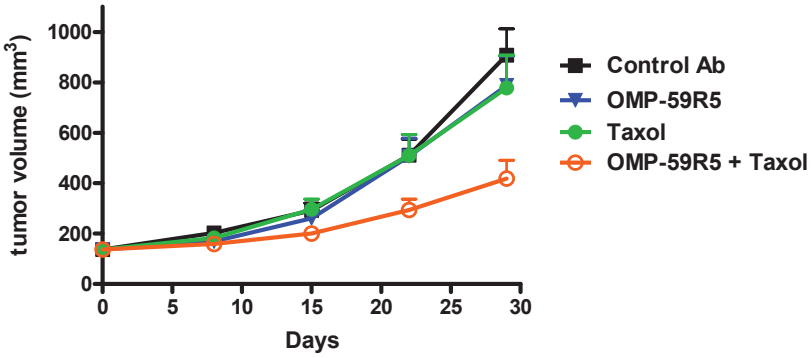
Legend: Lu68 tumor cells were implanted in Nod-Scid mice and allowed to grow until the average tumor volume was ~ 250 mm^3. Tumor bearing mice were randomized into two groups and treated with either cisplatin plus control antibody or cisplatin plus tarextumab. After three weeks, the cisplatin treatments were discontinued and the antibody treatment schedule was maintained. tarextumab was dosed at 40 mg/kg every two weeks and cisplatin was dosed at 2.5 mg/kg twice per week. There were 10 animals per group. The mean + SEM for each group is shown.

Figure 2: Activity of Tarextumab in 87 SCLC Tumor Recurrence Model in Combination with Carboplatin plus Irinotecan



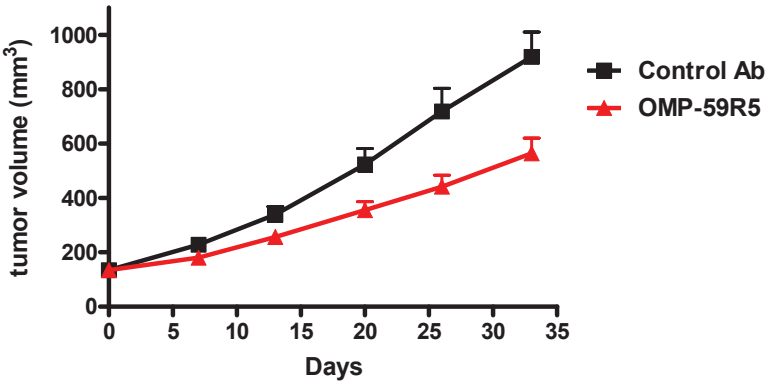
Legend: Lu87 tumor cells were implanted in Nod-Scid mice and allowed to grow until the average tumor volume was ~ 180 mm^3. Tumor bearing mice were randomized into two groups and treated with either carboplatin and irinoecan plus control antibody or carboplatin and irinotecan plus tarextumab. After three weeks, the carboplatin and irinotecan treatments were discontinued and the antibody treatment schedule was maintained. Tarextumab was dosed at 40 mg/kg every two weeks. Carboplatin and irinotecan were dosed at 20 mg/kg once per week for the first two week and 10 mg/kg once per week for the third dose. There were 8 animals per in control group and seven animals in the 59R5. The mean + SEM for each group is shown.

Figure 3: Tarextumab Inhibits Growth of Lu40 SCLC Tumors in Combination with Taxol



Legend: Lu40 tumor cells were implanted in Nod-Scid mice and allowed to grow until the average tumor volume was ~ 150 mm^3. Tumor bearing mice were randomized into four groups (n = 10 per group) and treated with either Control Ab, tarextumab, Taxol, or the combination of tarextumab and Taxol. Tarextumab was dosed at 40 mg/kg every two weeks and Taxol was dosed at 10 mg/kg once per week. Tumor measurements were taken on the indicated days and the mean + SEM for each group is shown.

Figure 4: Tarextumab Inhibits Growth of Lu61 SCLC Tumors



Legend: Lu61 SCLC tumor cells were implanted in Nod-Scid mice and allowed to grow until the average tumor volume was ~ 150 mm^3. Tumor bearing mice were randomized into two groups (n = 10 per group) and treated with either Control Ab or tarextumab. Tarextumab was dosed at 40 mg/kg every two weeks. Tumor measurements were taken on the indicated days and the mean + SEM for each group is shown.

Summary

Collectively, our data show that inhibiting Notch signaling with tarextumab results in anti-tumor activity in several SCLC xenografts. Importantly, tarextumab treatment can increase response to chemotherapy treatment and delay tumor re-growth after initial tumor shrinkage in response to chemotherapy. Given the urgent need for new therapeutic options for treatment of SCLC, we plan to explore the utility of this antibody in clinical testing in SCLC in combination with chemotherapy.

3.4 Clinical Background

The first-in-human clinical trial of tarextumab (Study 59R5-001) began with a single-agent multiple dose escalation study in subjects with solid tumors. Subjects were treated in escalating dose cohorts of 0.5, 1, 2.5, and 5 mg/kg administered IV weekly. Additionally, escalating dose cohorts of 5, 7.5, and 10mg/kg administered IV every other week, and 7.5mg/kg every three weeks were tested as well.

As of April 25, 2013, a total of forty-two subjects have been treated in Study 59R5-001: three at 0.5 mg/kg weekly, three at 1 mg/kg weekly, six at 2.5 mg/kg weekly, nine at 5 mg/kg weekly, six at 5 mg/kg every other week, six at 7.5mg/kg every other week, three at 10 mg/kg every other week, and six at 7.5mg/kg every three weeks.

Two DLTs occurred in two of nine subjects treated at 5 mg/kg weekly: one Grade 3 hypokalemia secondary to Grade 3 diarrhea in one subject and one Grade 3 diarrhea in another subject, which led to the MTD for weekly dosing schedule to be 2.5 mg/kg. No DLTs occurred in 6 subjects treated at 7.5 mg/kg every three weeks that led to the MTD for every three week schedule to be 7.5 mg/kg. Two DLTs both Grade 3 diarrhea, occurred in two of three subjects treated with a single dose of tarextumab at 10 mg/kg every other week and no DLTs occurred in 6 subjects treated at 7.5 mg/kg every other week, which led to the MTD for every other week schedule to be 7.5 mg/kg every other week.

Toxicities observed to date have been mostly Grades 1 and 2, and were manageable with supportive care and/or interruption or dose reduction of tarextumab. There were no AEs of a Grade 4 severity reported. AEs with a severity of Grade 3 were uncommon and have been primarily diarrhea.

Diarrhea has been the most common adverse event, occurring in 81% (34 of 42) of subjects treated on the study regardless of schedule, which was expected based on the observance of diarrhea in the cynomolgus monkey toxicology study. Diarrhea was observed at 2.5 mg/kg weekly and above dose cohorts, and was dose dependent. Table 2 below tabulates the incidence and worse severity of diarrhea occurred while receiving tarextumab among dose levels according NCI-CTCAE criteria v4.02.

Table 2: Study 59R5-001: Worse Grade Treatment Related Diarrhea (N=34/42)

Diarrhea Grade	0.5 mg/kg QW (n=2/3)	1 mg/kg QW (n=0/3)	2.5 mg/kg QW (n=6/6)	5 mg/kg QW (n=8/9)	5 mg/kg QoW (n=4/6)	10 mg/kg QoW (n=3/3)	7.5 mg/kg Q3W (n=5/6)	7.5 mg/kg QoW (n=6/6)
1	1	-	3	4	3	-	4	3
2	1	-	3	2	-	-	1	3
3	-	-	-	2	1	3	-	

Additional common treatment-related adverse events included (as of November 17, 2012 data cutoff with 39 subjects treated) fatigue (30.8%), nausea (28.2%), decreased appetite (17.9%), vomiting (15.4%), increased alanine transaminase (ALT) (10.3%), hypokalemia (15.4 and dizziness (10.3%).

Table 2 and Table 3 summarize all treatment related CTC Grade 3 adverse events that occurred in Study 59R5-001 by body system as of November 17, 2012; there were no Grade 4 or 5 events on study.

Table 3: Study 59R5-001: Grade 3 Treatment Related Adverse Events by Body System (N=39)

Body System	Preferred Term	Number of Subjects
Gastrointestinal Disorders	Diarrhea	6 (15.4%)
Blood and Lymphatic System Disorders	Anemia	2 (5.1%)
Investigations	Alanine Aminotransferase Increased	1 (2.6%)
	Aspartate Aminotransferase Increase	1 (2.6%)
Metabolism and Nutrition Disorders	Hypokalaemia	2 (5.1%)
General Disorders and Administration Site Conditions	Fatigue	1 (2.6%)

No RECIST complete or partial responses have been noted on this Phase 1 study. However, six subjects have had RECIST stable disease (SD) lasting greater than 56 days (ranging from 61 days to 165 days, all of them have come off the study).

As of *November 17*, *2015*, twenty *seven* subjects have been treated in the current study (Study 59R5-003): three, three, six, three and *six* each at 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 12.5 mg/kg and 15 mg/kg dose cohort*s* respectively with etoposide and cisplatin; one DLT of Grade 3 nausea was reported from a subject at 10 mg/kg dose cohort that lasted more than 48 hours despite daily IV fluids and antiemetics. The dose cohort of 10 mg/kg was expanded to enroll a total of 6 subjects. *15 mg/kg of tarextumab was the highest dose tested in Phase 1b and was selected for the Phase 2 portion of the study. To establish the safety and tolerability of this selected dose, tarextumab 15 mg/kg was administered in combination with etoposide and cisplatin to a cohort of 6 subjects. An additional 6 subjects were treated with tarextumab 15 mg/kg in combination with etoposide and carboplatin. As of April 19, 2016 a total of 119 subjects have been treated in Study 59R5-003 Phase 2 portion. 4 of these subjects have been treated with tarextumab 15 mg/kg or placebo in combination with etoposide and cisplatin and 115 subjects have been treated with tarextumab 15 mg/kg or placebo in combination with etoposide and carboplatin.*

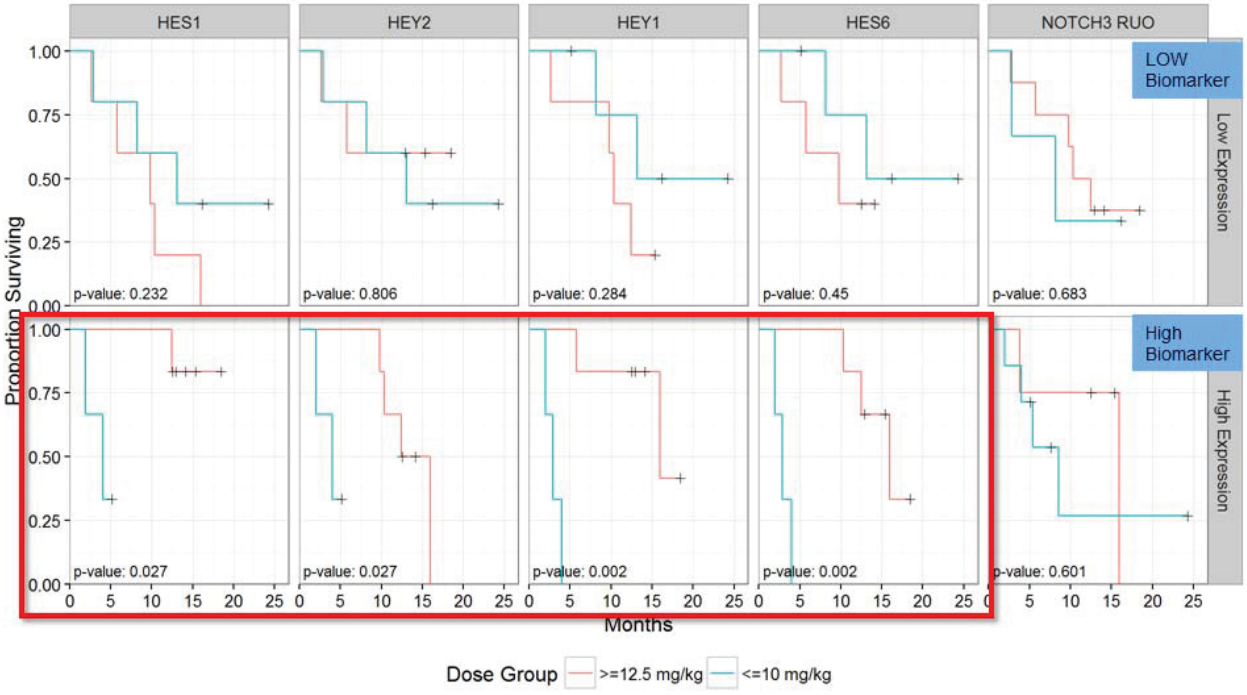
Tarextumab *has* be*en* studied in a Phase 1b/2 study in combination with nab-paclitaxel and gemcitabine in subjects with previously untreated stage IV pancreatic cancer (Study 59R5-002, ALPINE). The study was initially conducted in combination with gemcitabine alone and was amended to incorporate nab-paclitaxel into the chemotherapy backbone in response to the changes in standard of care in this disease population. As of *November 17, 2015,* forty subjects have been treated in Phase 1b of Study 59R5-002: five and four at 2.5 mg/kg and 5.0 mg/kg respectively every other week in combination with gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, four*,* six*,* six, three and twelve at 5 mg/kg, 7.5 mg/kg*,* 10 mg/kg*,* 12.5 mg/kg and 15 mg/kg respectively every other week in combination with nab-paclitaxel at 125 mg/m^2 and gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle. No DLTs have been reported in the first 35 subjects. Dose escalation stopped at tarextumab 15 mg/kg as the highest dose tested in Phase 1b portion of the study. Tarextumab 15 mg/kg dose cohort was then expanded with 5 additional subjects treated, one of which had Grade 3 diarrhea that lasted for 5 days during the first cycle. Overall, tarextumab in combination with nab-paclitaxel and gemcitabine continued to be well tolerated up to 15 mg/kg. 15 mg/kg has been selected as the Phase 2 dose in ALPINE study. *As of November 17, 2015, 177 subjects have been randomized with 172 subjects treated in Phase 2 portion of Alpine study.*

To date, tarextumab has been well tolerated up to 15 mg/kg. Among the 356 subjects treated through 17 November 2015, 23 (6.5%) subjects discontinued tarextumab/placebo treatment due to AEs, regardless of relationship. Toxicities observed to date have been mostly Grades 1 and 2, and manageable with supportive care and/or interruption or dose reduction of tarextumab. The most common (occurring in ≥25% of subjects) treatment emergent events are diarrhea (62.6%), nausea (49.2%), thrombocytopenia (45.2%), neutropenia (26.7%), anemia (48%), vomiting (31.5%), fatigue (57.0%) and decreased appetite (28.7%). The most common (occurring in ≥ 25% of subjects) treatment related events are diarrhea (53.1%), fatigue (41.6%), thrombocytopenia (26.7%) and nausea (27.2%). Adverse events with a severity of Grade 3 that were considered related were uncommon and have been primarily diarrhea (9.6%), anemia (12.1%), thrombocytopenia (10.1%), neutropenia (7.6%) and fatigue (7.6%). Please refer to the updated Investigator Brochure for more details.

Exploratory Phase 1b Biomarker Data

Exploratory biomarker data from the phase1b portion of the PINNACLE study shows a trend of improved outcome in patients with high Notch target genes i.e. Hes1, Hey2, Hey1 and Hes6 in the 12.5 mg/kg and 15 mg/kg cohorts.

Figure 5: ***Notch Genes and Overall Survival***



Legend: Notch genes and overall survival. Expression of Notch3 gene levels and Notch target genes (Hes1, Hey2, Hey1, Hes6) was measured in FFPE tissues from 19 patients in the Phase1b portion of the trial. Biomarker high vs. low was set at a 50th percentile. Red lines include patients in the 5, 7.5, and 10 mg/kg cohorts and blue lines indicate patient in the 12.5 and 15 mg/kg cohorts.

3.5 Dose Rationale

Treatment with EP is the standard of care for subjects with untreated extended stage small cell lung cancer. The most common AE of tarextumab is diarrhea, whereas cytopenia and nephrotoxicity (with cisplatin) are the most common adverse event with EP administration. Therefore, the most common AEs of tarextumab and EP do not overlap, providing the justification for investigating this combination in the study. The initial dose escalations of tarextumab will be conducted with etoposide and cisplatin. Subjects enrolled in this study will receive a starting dose of 5 mg/kg of tarextumab once every three weeks, which is one dose below the MTD of 7.5 mg/kg every three weeks in Study 59R5-001. Dose escalation will be 2.5 mg/kg per increment and will not exceed an tarextumab dose of 15 mg/kg. 15 mg/kg is twice of the single agent MTD of 7.5 mg/kg every three weeks established in Study 59R5-001 and pharmacodynamics modulation of the notch pathway was seen at 1 mg/kg above in tumor biopsies and surrogate tissues in Study 59R5-001, and at 7.5 mg/kg above in hair follicles in Study 59R5-002(Investigator Brochure Edition 04 dated January 15, 2014).

Following the establishment of the highest tolerable dose of tarextumab in combination with etoposide and cisplatin, a cohort of 6 subjects will be treated at this highest tolerable dose in combination with etoposide and carboplatin. Once the safety and tolerability of tarextumab at this dose is confirmed with etoposide and cisplatin/carboplatin, the protocol will explore a Phase 2, multicenter, randomized, placebo-controlled portion comparing the efficacy and safety of tarextumab at the highest tolerable dose in combination with EP for *6* cycles followed by single agent tarextumab relative to EP alone for 6 cycles in subjects receiving first-line therapy for extensive stage small cell lung cancer. However, if a DLT is observed in 2 or more subjects in the cohort of 6 subjects treated with the highest tolerable dose of tarextumab with etoposide and carboplatin, a new cohort of 3 to 6 subjects will be enrolled at the next lower dose level of tarextumab with etoposide and carboplatin. The highest tarextumab dose that is tolerable with both platinum options will be used in Phase 2 portion of the study. For example: if tarextumab at 15 mg/kg is tolerable with etoposide and cisplatin, but not tolerable with etoposide and carboplatin and tarextumab at 12.5 mg/kg is tolerable with etoposide and carboplatin, then tarextumab at 12.5 mg/kg will be the dose used in Phase 2 portion of the study. In Phase 2 portion of the study, Subjects may be treated with cisplatin or carboplatin as determined by the Investigator prior to randomization. Alteration to the choice of platinum therapy is not permitted once the subject is randomized. Etoposide will be administered by IV infusion at a dose of 100 mg/m^2 on Days 1, 2, and 3 of every 21-day cycle. Cisplatin will be administered by IV infusion at a dose of 80 mg/m^2 in Phase 1b and 75 mg/m^2 in Phase 2 portion of the study or carboplatin at AUC of 5 mg/mL•min on Day 1 of every 21-day cycle. This is the dose regimen for etoposide and platinum therapy commonly used in first line treatment for extensive stage small cell lung cancer. tarextumab has an estimated apparent half-life of 2 to 3 days at 7.5 mg/kg in Study 59R5-001, subjects will not receive PCI within 2 weeks of study drug administration and will not receive tarextumab during the radiation to alleviate any potential interaction between the study drug and the radiation. Therefore, risks and potential benefits of participation have been appropriately mitigated for this patient population.

3.6 Study Conduct

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

3.7 Subject Population

Subjects must be at least 18 years of age, have adequate organ and marrow function, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, have untreated extensive stage small cell lung cancer, and FFPE tumor tissue, either archived or fresh core

needle biopsied for Notch3*, Hes1, Hey2, Hey1 and Hes6* analysis. Additionally for the Phase 2 portion of the study, subjects must have evidence of measurable disease by RECIST 1.1 criteria.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

Primary Objectives:

- To determine the maximum tolerated dose (MTD) of tarextumab when administered on Day 1 of each 21 day cycle along with etoposide 100 mg/m^2 on Days 1, 2 and 3 and cisplatin 80 mg/m^2 or carboplatin AUC of 5 mg/mL•min on Day 1 in subjects with untreated extensive stage small cell lung cancer (Phase 1b portion)

- To determine the improvement in Progression Free Survival (PFS) resulting from the addition of tarextumab to etoposide and platinum therapy (EP) in subjects receiving first-line therapy for extensive stage small cell lung cancer (Phase 2 portion)

Secondary Objectives:

- To determine the pharmacokinetics of tarextumab in combination with EP in subjects receiving first-line therapy for extensive stage small cell lung cancer (Phase 1b and 2 portions)
- To determine the immunogenicity of tarextumab in combination with EP in subjects receiving first-line therapy for extensive stage small cell lung cancer (Phase 1b and 2 portions)
- To estimate the improvement in overall survival (OS), 12 months OS, and the overall response rate (ORR) resulting from the addition of tarextumab to EP in subjects receiving first-line therapy for extensive stage small cell lung cancer (Phase 2 portion)
- *To correlate the treatment effect in PFS, OS, 12 month OS and the ORR resulting from the addition of tarextumab to EP in subjects with Notch 3, Hey2, Hes1, Hey1 and Hes6 expression (Phase 2 portion)*
- To determine the safety and tolerability of tarextumab in combination with EP in subjects who are receiving first-line therapy for extensive stage small cell lung cancer (Phase 1b portion)
- To compare the safety and tolerability of tarextumab in combination with EP relative to EP alone in all subjects who are receiving first-line therapy for extensive stage small cell lung cancer with Phase 2 portion)

Exploratory Objective:

- To describe the changes in exploratory pharmacodynamic (PD) biomarkers, including Notch pathway related genes and proteins and circulating tumor cells following tarextumab treatment. (Phase 1b and 2 portions)

5.0 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

The study consists of a Phase1b lead-in portion to determine the MTD of tarextumab in combination with EP for 6 cycles followed by treatment with tarextumab alone until unacceptable toxicity or progression of disease. The initial dose escalations of tarextumab will be conducted with etoposide and cisplatin. The dose of tarextumab will not exceed 15 mg/kg. Following the establishment of the highest tolerable dose of tarextumab in combination with etoposide and cisplatin, a cohort of 6 subjects will be treated at this dose in combination with etoposide and carboplatin. Once the safety and tolerability of tarextumab at this dose is also confirmed with etoposide and carboplatin, the protocol will explore a Phase 2, multicenter, randomized, Placebo-controlled portion comparing the efficacy and safety of tarextumab at the highest tolerable dose in combination with EP for 6 cycles followed by single agent tarextumab relative to EP alone for 6 cycles in subjects receiving first-line therapy for extensive stage small cell lung cancer. However, if a DLT is observed in 2 or more subjects in the cohort of 6 subjects treated with the highest tolerable dose of tarextumab with etoposide and carboplatin, a new cohort of 3 to 6 subjects will be enrolled at the next lower dose level of tarextumab with etoposide and carboplatin. The highest tarextumab dose that is tolerable with both platinum options will be used in Phase 2 portion of the study.

In Phase 2 portion of the study, Subjects may be treated with cisplatin or carboplatin as determined by the Investigator prior to randomization. Alteration to the choice of platinum therapy is not permitted once the subject is randomized.

Etoposide 100 mg/m^2 will be administered on Days 1, 2 and 3 along with cisplatin 80 mg/m^2 for Phase 1 b and 75 mg/m^2 for Phase 2 portion of the study or carboplatin at AUC of 5 mg/mL•min on Day 1 of every 21-day cycle for 6 cycles, tarextumab or Placebo will be given on Day 1 of every 21-day cycle prior to the administration of EP.

Subjects may continue one of the chemotherapy drugs if the other is held or discontinued prior to completing 6 cycles of EP and prior to disease progression. Subjects should continue EP alone for a total of 6 cycles if tarextumab is held or discontinued prior to the completion of 6 cycles of EP. Subjects may continue study drug if one or both of the chemotherapy drugs is held or discontinued prior to completing 6 cycles of EP and prior to disease progression.

5.1 Phase 1b Portion

The Phase 1b portion is to determine the MTD of tarextumab in combination with etoposide and cisplatin/carboplatin in subjects with previously untreated extensive stage small cell lung cancer. Initially, cohorts of 3 to 6 subjects with previously untreated extensive stage small cell lung cancer will be enrolled sequentially into successively higher tarextumab dose level in combination with etoposide 100 mg/m^2 on Days 1, 2 and 3 and cisplatin 80 mg/m^2 on Day 1 of every 21-day cycle for 6 cycles. The starting dose of OMP59R5 is 5 mg/kg. Dose escalation will be 2.5 mg/kg per increment and will not exceed an tarextumab dose of 15 mg/kg. Subjects at each dose level will be treated and observed for DLT through the end of the first cycle (21 days). Each subject will participate in only 1 cohort. Once the highest tolerable dose is determined with tarextumab in combination with etoposide and cisplatin, a cohort of 6 subjects will be treated at this dose with etoposide and carboplatin to confirm the safety and tolerability of this dose with etoposide and carboplatin. Carboplatin will be given at AUC of 5 mg/mL•min on Day 1 of every 21- day cycle for 6 cycles in combination with etoposide 100 mg/m^2 on Days 1, 2, and 3. If a DLT is observed in 2 or more subjects in the cohort of 6 subjects treated with the highest tolerable dose of tarextumab with etoposide and carboplatin, a new cohort of 3 to 6 subjects will be enrolled at the next lower dose level of tarextumab with etoposide and carboplatin. Subjects may continue one of the chemotherapy drugs if the other is held or discontinued prior to completing 6 cycles of EP and prior to disease progression. For subjects who have tarextumab held or discontinued for tolerability reasons, EP chemotherapy should continue to the completion of 6 cycles. Subjects may continue study drug if one or both of the chemotherapy drugs is held or discontinued prior to completing 6 cycles of EP and prior to disease progression.

After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Tarextumab administration should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume tarextumab alone ≥14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (Appendix A). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

Approximately 30 subjects will be enrolled into Phase 1b portion of the study, the exact number will depend on the number of dose levels assessed and the toxicities observed.

5.2 Dose Limiting Toxicity

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.02 (see Study Reference Binder). Doselimiting- toxicity (DLT) is defined as either of the following tarextumab treatment-related toxicities occurring within the first 21 days (Cycle 1):

- ≥ Grade 3 non-hematologic toxicity except for Grade 3 electrolyte disturbances that respond to correction within 24 hours, or Grade 3 rash, diarrhea, nausea, vomiting, and mucositis that responds to standard medical supportive care within 48 hours;
- Grade 3 thrombocytopenia associated with Grade ≥2 hemorrhage or any Grade 4 thrombocytopenia;
- Grade 4 neutropenia lasting >7 days
- Grade 3 or 4 neutropenia of any duration associated with fever ≥ 38.3°C (101°F);
- Grade 4 anemia;
- Any clinically significant toxicity that occurs during the first 21 days or beyond Day 21 that in the judgment of the Investigators and Sponsor is dose-limiting.

5.3 Dose Escalation Plan

Initially, cohorts of 3 to 6 evaluable subjects with previously untreated extensive stage small cell lung cancer will be enrolled sequentially into successively higher tarextumab dose level in combination with etoposide 100 mg/m^2 on Days 1, 2 and 3, and cisplatin 80 mg/m^2 on Day 1 of every 21-day cycle for 6 cycles. Subjects at each dose level will be treated and observed for DLT through the end of the first cycle (21 days) to be considered evaluable for DLT determination. Each subject will participate in only 1 cohort.

The starting dose of tarextumab is 5 mg/kg on Day 1 of each 21-day cycle. The subsequent dose level will be increased in 2.5 mg/kg increments (i.e., 7.5 mg/kg, 10 mg/kg, etc) until the MTD is reached but will not exceed an tarextumab dose of 15 mg/kg. Dose escalation will only proceed if no DLT is observed in a cohort of at least 3 subjects after discussion and agreement between the participating Investigators and Sponsor's Medical Monitor.

If a DLT is observed in only 1 subject in a cohort of 3 subjects, an additional 3 subjects may be enrolled up to a total of 6 subjects at this dose level. Dose escalation will then proceed only if no more than 1 subject in the cohort of six subjects has experienced a DLT during the first cycle of treatment and after discussion and agreement between the participating Investigators and Sponsor's Medical Monitor.

If a DLT is observed in 2 or more subjects in a cohort of 3 or 6 subjects, an additional 3 subjects will be enrolled for a total of 6 subjects at the previous lower dose level, if only 3 subjects were treated at that lower dose level. The Investigators and Sponsor, after their safety review, may elect to study a dose level that is intermediate to the current dose level and the next lower dose level previously studied, e.g. 6 mg/kg as an intermediate dose between 5 mg/kg and 7.5mg/kg. The level of dose de-escalation and a decision to go to an intermediate dose level will be determined after discussion between the participating Investigators and Sponsor's Medical Monitor prior to dose escalation. If a DLT is observed in 2 or more subjects in a cohort of 3 to 6 subjects treated with the starting dose of 5 mg/kg, a new cohort of 3 to 6 subjects will be enrolled at either 2.5 mg/kg or an intermediate dose level between 2.5 mg/kg and 5 mg/kg. Table 4 below provides a summary of the dose escalation decision rules for determination of the MTD.

5.4 Maximum Tolerated Dose

The MTD is defined as the highest dose level of tarextumab at which no more than 1 out of 6 subjects experiences DLT during the first cycle (21 days) of therapy with etoposide and cisplatin. Dose escalation will not continue beyond 15 mg/kg of tarextumab. Table 4 provides a summary of the dose escalation decision rules for determination of the MTD.

Table 4: Maximum Tolerated Dose Determination and Cohort Expansion

Number of Subjects per Cohort With a DLT During Cycle 1 (Days 1 to 21)	Dose Escalation Decision Rule
0 out of 3	Enter at least 3 subjects at the next dose level.
1 out of 3	Enter up to 3 more subjects at this dose level. If none of the 3 additional subjects has a DLT, proceed to the next dose level. If 1 or more of the 3 additional subjects has a DLT, then dose escalation will be stopped, and the MTD will have been exceeded. Up to 3 additional subjects may be entered at a lower dose level if only 3 subjects were treated previously at that dose or a new cohort of 3 subjects at an intermediate dose level may be evaluated.
≥2	Dose escalation will be stopped, and the MTD will have been exceeded. Up to 3 additional subjects may be entered at a lower dose level if only 3 subjects were treated previously at that dose or a new cohort of 3 subjects at an intermediate dose level may be evaluated.
≤1 out of 6 at the highest dose evaluated.	This is generally the MTD.

Abbreviations: DLT = dose limiting toxicity; MTD = maximum tolerated dose.

All participating sites are required to send in DLT Notification Forms within 24 hours of learning of the event. Participating investigators and the Sponsor's Medical Monitor will review study drug-related toxicities from the current dose before escalating to the next dose.

Once the highest tolerable dose is determined with tarextumab in combination with etoposide and cisplatin with 15 mg/kg as the highest dose of tarextumab being tested, a cohort of 6 subjects will be treated at this dose with etoposide and carboplatin (AUC 5 mg/mL•min on on Day 1 of every 21-day cycle for 6 cycles) to confirm the safety and tolerability of this dose with etoposide and carboplatin before commencing the Phase 2 portion of the study. However, if a DLT is observed in 2 or more subjects in the cohort of 6 subjects treated with the highest tolerable dose of tarextumab with etoposide and carboplatin, a new cohort of 3 to 6 subjects will be enrolled at the next lower dose level of tarextumab with etoposide and carboplatin. The highest tarextumab dose that is tolerable with both platinum options will be used in Phase 2 portion of the study. For example: if tarextumab at 15 mg/kg is tolerable with etoposide and cisplatin, but not tolerable with etoposide and carboplatin and tarextumab at 12.5 mg/kg is tolerable with etoposide and carboplatin, then tarextumab at 12.5 mg/kg will be the dose used in Phase 2 portion of the study.

5.4.1 Follow-Up

Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Additionally, subjects who are discontinued from study treatment will be followed for survival and any subsequent anti-cancer therapies. Survival follow-up information and subsequent anti-cancer therapies, including systemic therapies, surgery (resection of metastatic disease), and radiation therapy will be collected during telephone calls, through subjects medical records, and/or clinic visits every 3 months starting from the last study treatment until death, loss to follow-up, or study termination by the sponsor. The study staff may use a public information source (e.g., county records) to obtain information about survival status only.

5.5 Phase 2 Portion

Phase 2 portion may commence after the safety and tolerability of the highest tolerable dose of OMP 59R5 has been confirmed in both cohorts of subjects with etoposide and cisplatin/carboplatin during Phase 1b. The highest tarextumab dose that is tolerable with both platinum options will be used in the Phase 2 portion of the study. For example: if tarextumab at 15 mg/kg is tolerable with etoposide and cisplatin, but not tolerable with etoposide and carboplatin and tarextumab at 12.5 mg/kg is tolerable with etoposide and carboplatin, then tarextumab at 12.5 mg/kg will be the dose used in Phase 2 portion of the study. The Phase 2 portion includes a blinded treatment phase and follow-up phase. It is a multicenter, randomized, placebo-controlled portion evaluating the efficacy and safety of tarextumab in combination with etoposide and platinum therapy in subjects with previously untreated extensive stage small cell lung cancer. Subjects may be treated with cisplatin or carboplatin as determined by the Investigator prior to randomization. Alteration to the choice of platinum therapy is not permitted once the subject is randomized.

Approximately 135 evaluable subjects will be enrolled to the Phase 2 portion of the study. Evaluable subjects are those who received at least one dose of study drug (either tarextumab or Placebo).

5.5.1 Blinded Treatment Phase

Subjects who qualify for enrollment into the Phase 2 portion of the study will be randomized in a 1:1 ratio to receive study treatment of EP with Placebo or EP with tarextumab. The randomization will be balanced on the choice of platinum therapy (cisplatin versus carboplatin) and the prior use of whole brain radiation or prophylactic cranial irradiation). Alteration to the choice of platinum therapy is not permitted once the subject is randomized. Treatment for each subject will begin on Study Day 1 (the first dosing day). Etoposide 100 mg/m^2 will be given on Days 1, 2 and 3 and cisplatin 75 mg/m^2 or carboplatin AUC of 5 mg/mL•min will be given on Day 1 of every 21-day cycle for 6 cycles. Subjects may remain in the Blinded Treatment Phase to continue one of the chemotherapy drugs if the other is held or discontinued prior to completing 6 cycles of EP and prior to disease progression. For subjects who have study drug held or discontinued for tolerability reasons, EP chemotherapy should continue to the completion of 6 cycles. Subjects may continue study drug if one or both of the chemotherapy drugs is held or discontinued prior to completing 6 cycles of EP and prior to disease progression.

After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Study drug (tarextumab or Placebo) administration should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone ≥ 14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (Appendix A). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

5.5.2 Follow-up

Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner. Additionally, subjects who are discontinued from study treatment will be followed for survival and any subsequent anti-cancer therapies. Survival follow-up information and subsequent anti-cancer therapies, including systemic therapies, surgery (resection of metastatic disease), and radiation therapy will be collected during telephone calls, through subjects medical records, and/or clinic visits every 3 months starting from the last study treatment until death, loss to follow-up, or study termination by the sponsor. The study staff may use a public information source (e.g., county records) to obtain information about survival status only.

6.0 SELECTION OF STUDY POPULATION

6.1 Inclusion Criteria

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

1. Histologically or cytologically documented extensive stage small cell lung cancer (combined small cell carcinoma is allowed); extensive stage is defined as disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases (contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited disease).
2. Adults of 18 years of age or older.
3. Performance Status (ECOG) of 0 or 1.

4. FFPE tumor tissue, either fresh core needle biopsied (two fresh cores preferred whenever possible), or archived available for Notch3, *Hes1, Hey2, Hey1 and Hes6* analysis.
5. Adequate organ function:
   a. Adequate hematologic function (absolute neutrophil count [ANC] ≥ 1,500 cells/μL; hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/μL).
   b. Adequate renal function (serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 60 mL/min using Cockroft Gault formula).
   c. Adequate hepatic function (alanine aminotransferase [ALT] ≤ 3 x upper limit of normal [ULN], ALT may be ≤ 5 x ULN if due to liver metastases but cannot be associated with concurrent elevated bilirubin > 1.5xULN unless it is approved by the Sponsor's Medical Monitor).
   d. Prothrombin Time (PT)/International Normalized Ration (INR) ≤ 1.5 × ULN, activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN.
6. Written consent on an IRB/IEC-approved Informed Consent Form prior to any study-specific evaluation.
7. For women of child-bearing potential, negative serum pregnancy test at screening and use of physician-approved method of birth control from 30 days prior to the first study drug administration to 30 days following the last study drug administration or the last EP in the study, whichever is discontinued last.
8. Male subjects must be surgically sterile or must agree to use physician-approved contraception during the study and for 30 days following the last study drug administration or the last EP in the study, whichever is discontinued last.

Additionally, for individuals eligible to participate in Phase 2 portion of the study:

9. Subject must have evidence of measurable disease per RECIST 1.1 criteria.

6.2 Exclusion Criteria

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

1. Limited stage small cell lung cancer appropriate for radical treatment with chemoradiation.

2. Prior therapy including radiation, chemotherapy or surgery for newly diagnosed extensive stage small cell lung cancer. Exceptions to this exclusion criterion include: 1) prophylactic cranial irradiation or whole brain radiation (WBRT) prior to the first administration of study drug provided that the subject has stable neurologic condition for at least 2 weeks after the completion of the radiation, adverse event that is related to the radiation has recovered to be ≤ Grade 1, and is not requiring corticosteroid of > 40 mg prednisone daily equivalent dose to control the symptoms, 2) focused radiation for symptomatic relief for isolated bone metastases; *3*) bisphosphonate or denosumab therapy for bone metastasis initiated prior to study entry.
3. Presence of uncontrolled Grade ≥ 1 diarrhea within 4 weeks prior to the first study drug administration.
4. Presence of any serious or uncontrolled illness including, but not limited to: ongoing or active infection, symptomatic congestive heart failure unstable angina pectoris, uncontrolled cardiac arrhythmia, uncontrolled arterial thrombosis, symptomatic pulmonary embolism, and psychiatric illness that would limit compliance with study requirement.
5. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty and/or stenting within 6 months prior to the first administration of study drug.
6. A history of malignancy with the exception of:
   a. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer
   b. Superficial bladder cancer
   c. Adequately treated stage I cancer from which the subject is currently in remission, or
   d. Any other cancer from which the subject has been disease-free for ≥ 3 years
7. Known human immunodeficiency virus (HIV) infection.
8. Females who are pregnant or breastfeeding.
9. Concurrent use of therapeutic warfarin (prophylactic low dose of warfarin, i.e., 1 mg daily for port catheter is allowed)

Additionally, individuals ineligible to participate in Phase 2 portion of the study if:

10. Subjects have relapsed after treatment for limited disease

6.3 Removal of Subjects from Study Treatment

Each subject has the right to withdraw from the study at any time without prejudice to further treatment. The Investigator must withdraw from the study any subjects who request to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment. When possible, tests and evaluations listed for the treatment termination visit should be carried out approximately 4 weeks after the last administration of tarextumab or Placebo, etoposide, or platinum therapy, whichever is discontinued last, but before the initiation of new anti-cancer therapy. The sponsor must be notified of all subjects' withdrawals as soon as possible. The sponsor also reserves the right to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after 2 attempts, a certified letter should be send to the subjects requesting contact with the Investigator. This information should be recorded in the study records.

Prior to enrollment into the study, the Investigator or designee must explain to each subject, that the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and IRB/EC in order to analyze and evaluate study results. It is the Investigator's responsibility to obtain written permission to use protected health information per country-specific regulations. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

Subjects may terminate study treatment due to:

- Disease progression
- Initiation of new anti-cancer therapy including surgical resection of tumor, palliative radiation (prophylactic cranial irradiation, according to standard of care, is permitted for subjects who are without progression following 6 cycles of etoposide and cisplatin treatment; subjects may have prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry) and/or a new systemic anti-cancer therapy.
- Initiation of a new intravenous bisphosphonate or denosumab more than 30 days after the first administration of study drug
- Development of toxicity that, in the Investigator's judgment, precludes further study participation
- Significant protocol violations or noncompliance on the part of the subject or Investigator
- Discontinuation is in the subject's best interest and/or in the judgment of the Investigator
- Lost to follow-up
- Pregnancy

6.4 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier. This unique identifier will be on all electronic case report form (eCRF) pages. In Phase 1b, subjects who withdraw from the study prior to completing Day 21 of Cycle 1 for reasons other than study drug-related toxicities will be replaced. In Phase 2, subjects who are randomized, but not dosed, will not be replaced. However, enrollment in the study will continue until 135 subjects are randomized and treated.

7.0 TREATMENT OF SUBJECTS

Subjects will be given study drug in combination with EP.

Study drug will be tarextumab in the Phase 1b portion, and either tarextumab or Placebo in the Phase 2 portion. Study drug will be administered by IV infusion on Day 1 of every 21-day cycle. The subject should not take two consecutive doses of study drug within 18 days.

Etoposide will be administered by IV infusion at a dose of 100 mg/m^2 over 30 to 60 minutes on Days 1, 2 and 3 of each 21-day treatment cycle for 6 cycles in accordance with institutional standard of care. The subject should not receive two Day 1 consecutive doses of etoposide within 18 days. A one day window will be allowed for each consecutive day of etoposide dosing (e.g. Day 2 and 3 dosing may occur on Day 3 and 4, or Day 3 and 5).

Cisplatin or carboplatin will be the choice of platinum therapy. Initially, all subjects in Phase 1b will receive cisplatin until the MTD/highest tolerable dose is determined with tarextumab in combination with etoposide and cisplatin. After that, a cohort of 6 subjects will be enrolled to receive tarextumab at the MTD/highest tolerable dose with etoposide and carboplatin. Subjects in Phase 2 will receive cisplatin or carboplatin as determined by the Investigator prior to randomization.

Cisplatin will be administered by IV infusion at a dose of 80 mg/m^2 over 30 minutes to 2 hours on Days 1 of each 21-day treatment cycle for 6 cycles in accordance with institutional standard of care in Phase 1b and at 75 mg/m^2 in Phase 2 portion of the study. The subject should not receive two cisplatin doses within 18 days.

Carboplatin will be administered by IV infusion at a dose of AUC of 5 mg/mL•min over 15 minutes or longer on Days 1 of each 21-day treatment cycle for 6 cycles in accordance with institutional standard of care. The subject should not receive two carboplatin doses within 18 days.

On days when study drug is given together with etoposide and cisplatin/carboplatin, study drug should be given prior to etoposide and cisplatin/carboplatin administration. Subjects may continue one of the chemotherapy drugs if the other is held or discontinued prior to completing 6 cycles of EP and prior to disease progression. If tarextumab held or discontinued, subjects will continue to receive etoposide on days 1, 2, and 3, and platinum therapy on day 1 of each 21-day cycle for a total of 6 cycles. Subjects may continue study drug if one or both of the chemotherapy drugs is held or discontinued prior to completing 6 cycles of EP and prior to disease progression.

After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Study drug (tarextumab or Placebo) administration should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone ≥ 14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (Appendix A). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

The baseline weight should be used to calculate the total dose (mg) of the study drug, etoposide, and cisplatin throughout the study, unless the weight changes by ≥10%, in which case the current weight should be used to calculate the dose.

In the absence of subjects meeting any of the withdrawal criteria (see Section 6.3), they may receive study treatment for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and the Sponsor.

7.1 Study Drug (tarextumab or Placebo)

7.1.1 Study Drug Administration

Please refer to the Pharmacy Manual for the details on tarextumab or Placebo preparation and administration.

There is no provision for intra-subject dose escalation of study drug. Weight-based doses will not be recalculated unless there is a weight change ≥10%. Carboplatin dose needs to be recalculated in subjects who have ≥ 10% weight change from baseline. If a semipermanent peripheral or central line is used to administer the drug, the catheter should be flushed per institutional standard procedures prior to and at the end of each infusion and the line should NOT be used for blood draws when there is a post-dose PK sampling. On days when study drug is given together with etoposide and platinum therapy, study drug should be given prior to etoposide and platinum therapy administration.

7.1.2 Study Drug Description

Tarextumab is an IgG2 fully human monoclonal antibody that is directed against the Notch2/3 receptors.

Tarextumab is a clear to opalescent, colorless to slightly yellow liquid and is supplied at a concentration of 10 mg/mL in 25-mL single-use glass vial filled to 20 mL to deliver at total of 200 mg per vial.

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

7.1.3 Study Drug Packaging

Labeling of the study drug vials and cartons will comply with all applicable regulations.

7.1.4 Study Drug Ordering, Storage, and Accountability

The instructions for drug ordering are provided in the Pharmacy Binder. The study drug vials must be stored at 2°C–8°C. DO NOT FREEZE. DO NOT SHAKE. An accurate study drug accountability log must be maintained and kept up to date at all times.

7.1.5 Study Drug Preparation

Please refer to the Pharmacy Manual for details on study drug preparation.

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

7.2 Etoposide

7.2.1 Administration

Etoposide must be administered after the administration of the study drug, and prior to cisplatin on Day 1. Etoposide should be administered by IV infusion at a dose of 100 mg/m^2 over 30 to 60 minutes on Days 1, 2, and 3 of every 21-day cycle.

7.2.2 Description

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. The chemical name for etoposide is 4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D-glucopyranoside], 4'-(dihydrogen phosphate).

7.2.3 Storage

Etoposide should be stored in a controlled setting according to the instructions of the package insert.

7.2.4 Packaging

The labeling of etoposide will comply with all applicable regulations.

7.3 Cisplatin

7.3.1 Administration

Cisplatin must be administered after the administration of the study drug and etoposide on Day 1. Cisplatin should be administered by IV infusion at a dose of 80 mg/m^2 over 30 minutes to 2 hours on Day 1 of every 21-day cycle for Phase 1b and 75 mg/m^2 for Phase 2 portion of the study.

7.3.2 Description

Cisplatin is a platinum containing anti-cancer drug used mainly in solid malignancies. The chemical name for cisplatin is (SP-4-2)-diamminedichloridoplatinum.

7.3.3 Storage

Cisplatin must be stored at 15°C–25°C (59°F–77°F) in a controlled setting. Do not refrigerate. Protect the contents from light.

7.3.4 Packaging

The labeling of cisplatin will comply with all applicable regulations.

7.4 Carboplatin

7.4.1 Administration

Carboplatin must be administered after the administration of the study drug and etoposide on Day 1. Carboplatin should be administered by IV infusion at a dose of AUC of 5 mg/mL•min over 15 minutes or longer on Day 1 of every 21-day cycle per package insert. Using Calvert formula for carboplatin dosing, the total carboplatin is calculated in mg, total dose (mg) = target AUC of 5 x (GFR+25).

7.4.2 Description

Carboplatin is a platinum containing anti-cancer drug used mainly in solid malignancies. The chemical name for Carboplatin is platinum, diammine[1,1-cyclobutanedicarboxylato(2-)-O,O']-, (SP-4-2).

7.4.3 Storage

Carboplatin must be stored at 15°C–30°C (59°F–86°F) in a controlled setting. Do not refrigerate. Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.

7.4.4 Packaging

The labeling of carboplatin will comply with all applicable regulations.

7.5 Dose Modifications or Delay for Treatment-Related Toxicities

The Investigator should try his/her best to assess whether an adverse event is possibly related to study drug only, etoposide only, cisplatin or carboplatin only, or a combination of the drugs, and treat the subject accordingly. This section and Table 5 provides suggested guidelines for the management of various study drug related toxicities in subjects receiving study drug, etoposide, and cisplatin or carboplatin.

Etoposide dosing should be withheld for ≥ Grade 2 etoposide-related toxicities and resumed at the same dose or at a 25% dose reduction, which refers to a decrease of 25 mg/m^2 depending on the timing of recovery and number of episodes occurred (see Table 5). If etoposide dosing is delayed for > 21 consecutive days despite supportive treatment per standard clinical practice or more than 2 dose reductions of etoposide (≤ 50 mg/m^2) is required, stop etoposide therapy or call the Sponsor's Medical Monitor to discuss resuming etoposide treatment after more than 21 consecutive days interruption or further dose reduction beyond 50 mg/m^2 if clinically indicated. Study drug and platinum therapy may continue as scheduled in the event of delay or discontinuation of etoposide.

Cisplatin dosing should be withheld for ≥Grade 2 cisplatin-related toxicities (except for peripheral neuropathy that cisplatin dosing should be held for ≥ Grade 3), and resumed at the same dose or at a 25% dose reduction, depending on the timing of recovery and number of episodes occurred (see Table 5). If cisplatin dosing is delayed for > 21 consecutive days despite supportive treatment per standard clinical practice or more than 2 dose reductions of cisplatin (≤ *35* mg/m^2) is required, stop cisplatin therapy, or call the Sponsor's Medical Monitor to discuss resuming cisplatin treatment after more than 21 consecutive days interruption or further dose reduction beyond 35 mg/m^2 if clinically indicated. Study drug and etoposide may continue as scheduled in the event of delay or discontinuation of cisplatin.

Carboplatin dosing should be withheld for ≥Grade 2 carboplatin-related toxicities, and resumed at the same dose or at reduced to AUC of 4 mg/mL•min, depending on the timing of recovery and number of episodes occurred (see Table 5). If carboplatin dosing is delayed for >21 consecutive days despite supportive treatment per standard clinical practice or carboplatin-related toxicities recurred after the dose has been reduced to AUC of 4 mg/mL•min, stop carboplatin therapy or call the Sponsor's Medical Monitor to discuss resuming carboplatin treatment after more than 21 consecutive days interruption or further dose reduction beyond AUC of 4 mg/mL•min if clinically indicated. Study drug and etoposide may continue as scheduled in the event of delay or discontinuation of carboplatin.

The Investigator should hold tarextumab/Placebo for treatment related toxicity according to suggested guideline in Table 5, along with his/her best judgment. Subjects with a starting dose of 5 mg/kg study drug will have dose reduced to ≥2.5 mg/kg if dose reduction is required. Study drug will be discontinued permanently if study drug dosing is delayed for >21 consecutive days due to treatment –related toxicity (this is not applicable when PCI is administered as study drug will be held for >21 consecutive days during PCI administration and will resume ≥14 days after the completion of PCI) despite supportive treatment, or if more than 2 dose reductions of study drug are required or dose reduction to <2.5 mg/kg is required *or* the Investigator should call the Sponsor's Medical Monitor to discuss to resume study drug after > 21 days consecutive days interruption or further dose reduction if clinically indicated. Subjects continuing EP after discontinuing study drug will continue to receive etoposide on days 1, 2, and 3, and platinum therapy on day 1 of each 21-day cycle for the completion of planned cycles. Special attention should be paid to diarrhea as this is an expected adverse event of tarextumab and Section 7.5 describes the recommended diarrhea management approach in this study.

Table 5: Suggested Guidelines for Study Drug and Etoposide-Platinum Therapy Dose Modification and Delay

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay	Carboplatin Dose Reduction and/or Delay
Absolute Neutrophil Count (ANC)				
≥1000/mm^3	No change.	No change. Continue supportive care according to institution's standard	No change. Continue supportive care according to institution's standard	No change. Continue supportive care according to institution's standard
500 -999/mm^3 without fever	No change	Hold etoposide till ANC ≥ 1000/ mm^3. Resume etoposide based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, no change. Consider prophylactic myeloid growth factor according to institution's standard • 2nd episode: reduce etoposide dose by 25% from starting dose for all subsequent administration • 3rd episode, reduce etoposide dose by 50% from starting dose for all subsequent administration • 4th episode, discontinue etoposide treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ > 3 consecutive weeks of interruption, discontinue etoposide permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of etoposide if clinically indicated Continue supportive care according to institution's standard	Hold cisplatin till ANC ≥ 1000/ mm^3. Resume cisplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, no change. Consider prophylactic myeloid growth factor according to institution's standard • 2nd episode: reduce cisplatin dose by 25% for all subsequent administration • 3rd episode, reduce cisplatin dose by 50% from starting dose for all subsequent administration • 4th episode, discontinue cisplatin treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ > 3 consecutive weeks of interruption, discontinue cisplatin permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of cisplatin if clinically indicated Continue supportive care according to institution's standard	Hold carboplatin till ANC ≥ 1000/ mm^3. Resume carboplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, no change. Consider prophylactic myeloid growth factor according to institution's standard • 2nd episode: reduce carboplatin dose to AUC of 4 mg/mL•min for all subsequent administration • 3rd episode: discontinue carboplatin treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated. ➢ > 3 consecutive weeks of interruption, discontinue carboplatin or call the Sponsor's Medical Monitor to discuss resuming the treatment of carboplatin if clinically indicated Continue supportive care according to institution's standard

Table 5: Suggested Guidelines for Study Drug and Etoposide-Platinum Therapy Dose Modification and Delay (Cont'd)

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay	Carboplatin Dose Reduction and/or Delay
Fever ≥ 38.3^{0}C (101^{0}F) with either 500 -999/mm^3 or < 500/mm^3 OR < 500/mm^3 without fever	No change.	Hold etoposide till ANC ≥ 1000/ mm^3 Resume etoposide based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce etoposide dose by 25% from starting dose for all subsequent administration • 2nd episode, reduce etoposide dose by 50% from starting dose for all subsequent administration • 3rd episode, discontinue etoposide treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ > 3 consecutive weeks of interruption, discontinue etoposide permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of etoposide if clinically indicated Continue supportive care according to institution's standard	Hold cisplatin till ANC ≥ 1000/ mm^3. Resume cisplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce cisplatin dose by 25% for all subsequent administration • 2nd episode, reduce cisplatin dose by 50% from starting dose for all subsequent administration • 3rd episode, discontinue cisplatin treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ > 3 consecutive weeks of interruption, discontinue cisplatin permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of cisplatin if clinically indicated Continue supportive care according to institution's standard	Hold carboplatin till ANC ≥ 1000/ mm^3. Resume carbplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce carboplatin dose to be AUC of 4 mg/mL•min for all subsequent administration • 2nd episode, discontinue carboplatin treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ >3 consecutive weeks of interruption, discontinue carboplatin permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of carboplatin if clinically indicated Continue supportive care according to institution's standard
Thrombocytopenia				
≥75,000/mm3	No change.	No change.	No change.	No change

Table 5: Suggested Guidelines for Study Drug and Etoposide-Platinum Therapy Dose Modification and Delay (Cont'd)

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay	Carboplatin Dose Reduction and/or Delay
Thrombocytopenia (Cont'd)				
50,000-74,999/mm^3, or 25,000-49,999/mm^3	No change.	Consider to hold etoposide till platelet count ≥ 75,000/ mm^3 Resume etoposide based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, no change to etoposide dose • 2nd episode, reduce etoposide dose by 25% from starting dose for all subsequent administration • 3rd episode, reduce etoposide dose by 50% from starting dose for all subsequent administration • 4th episode, discontinue etoposide treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ > 3 Consecutive weeks of interruption, discontinue etoposide permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of etoposide if clinically indicated	Consider to hold cisplatin till platelet count ≥ 75,000/ mm^3 Resume cisplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, no change to cisplatin dose • 2nd episode, reduce cisplatin dose by 25% from starting dose for all subsequent administration • 3rd episode, reduce cisplatin dose by 50% from starting dose for all subsequent administration • 4th episode, discontinue cisplatin treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated. ➢ > 3 Consecutive weeks of interruption, discontinue cisplatin permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of cisplatin if clinically indicated	Consider to hold carboplatin till platelet count ≥ 75,000/ mm^3 Resume carboplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, no change to carboplatin dose • 2nd episode, reduce carboplatin dose to AUC of 4 mg/mL•min for all subsequent administration • 3rd episode, discontinue carboplatin treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated. ➢ > 3 Consecutive weeks of interruption, discontinue cisplatin permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of carboplatin if clinically indicated

Table 5: Suggested Guidelines for Study Drug and Etoposide-Platinum Therapy Dose Modification and Delay (Cont'd)

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay	Carboplatin Dose Reduction and/or Delay
Thrombocytopenia (Cont'd)				
<25,000/mm^3	No change	Hold etoposide till platelet count ≥ 75,000/ mm^3. Resume etoposide based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce etoposide dose by 25% from starting dose for all subsequent administration • 2nd episode, reduce etoposide by 50% from the starting dose for all subsequent cycles • 3rd episode, discontinue etoposide treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ > 3 Consecutive weeks of interruption, discontinue etoposide permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of etoposide if clinically indicated Platelet transfusions should be administered prophylactically if platelets ≤10,000/mm^3 or as clinically indicated if there is bleeding.	Hold cisplatin till platelet count ≥ 75,000/ mm^3. Resume cisplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce cisplatin dose by 25% from starting dose for all subsequent administration • 2nd episode, reduce cisplatin dose by 50% from starting dose for all subsequent administration • 3rd episode, discontinue cisplatin treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ > 3 Consecutive weeks of interruption, discontinue cisplatin permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of cisplatin if clinically indicated Platelet transfusions should be administered prophylactically if platelets ≤10,000/mm^3 or as clinically indicated if there is bleeding.	Hold carboplatin till platelet count ≥ 75,000/ mm^3 Resume carboplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce carboplatin dose to AUC of 4 mg/mL•min for all subsequent administration • 2nd episode, discontinue carboplatin treatment or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated ➢ > 3 Consecutive weeks of interruption, discontinue carboplatin permanently or call the Sponsor's Medical Monitor to discuss resuming the treatment of carboplatin if clinically indicated Platelet transfusions should be administered prophylactically if platelets ≤10,000/mm^3 or as clinically indicated if there is bleeding.

Table 5: Suggested Guidelines for Study Drug and Etoposide-Platinum Therapy Dose Modification and Delay (Cont'd)

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay	Carboplatin Dose Reduction and/or Delay
Renal (creatinine)				
Grade 1 (> ULN-1.5x ULN or > 1-1.5 x baseline)	No change	No change	Monitor renal function and consider IV hydration	Monitor renal function and consider IV hydration
Grade 2 (>1.5-3x ULN or >1.5-3.0 x baseline)	No change.	No change	Consider to hold cisplatin until creatinine returns to Grade ≤ 1. Resume cisplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce cisplatin dose by 25% from starting dose for all subsequent administration • 2nd episode, reduce cisplatin dose by 50% from starting dose for all subsequent administration • 3rd episode, discontinue cisplatin administration ➢ > 3 consecutive weeks of interruption, discontinue cisplatin permanently Consider increasing the duration of cisplatin infusion and other supportive cares	Recalculate carboplatin dose with the creatinine and GFR to have the AUC of 5 mg/mL•min

Table 5: Suggested Guidelines for Study Drug and Etoposide-Platinum Therapy Dose Modification and Delay (Cont'd)

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay	Carboplatin Dose Reduction and/or Delay
Renal (creatinine) Cont'd				
Grade ≥ 3 (>3-6x ULN/>3 baseline or >6 ULN)	No change if creatinine returns to Grade ≤ 1 before the next study drug administration after withholding cisplatin or etoposide for one cycle. Hold study drug if creatinine does not return to Grade ≤1 after holding cisplatin or etoposide for one cycle. Resume study drug if creatinine returns to Grade ≤1 within 3 weeks. ➢ ≤ 3 consecutive weeks of interruption • Resume study drug at the next lower dose ➢ > 3 Consecutive weeks of interruption, discontinue or call the Sponsor's Medical Monitor to resume the treatment if clinically indicated	No change if creatinine returns to Grade ≤1 before the next scheduled etoposide administration after withholding one dose of cisplatin or reduced carboplatin dose. Hold etoposide until creatinine returns to Grade ≤1. Resume etoposide based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce etoposide dose by 25% from starting dose for all subsequent administration • 2nd episode, reduce etoposide dose by 50% from starting dose for all subsequent administration • 3rd episode, discontinue etoposide treatment ➢ > 3 Consecutive weeks of interruption, discontinue etoposide permanently or call the Sponsor's Medical Monitor to resume the treatment if clinically indicated Consider supportive care according to institution's standard	Hold cisplatin until creatinine returns to Grade ≤ 1. Resume cisplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce cisplatin dose by 25% from starting dose for all subsequent administration • 2rd episode, reduce cisplatin dose by 50% from starting dose for all subsequent administration • 3rd episode, discontinue cisplatin treatment ➢ > 3 Consecutive weeks of interruption, discontinue cisplatin permanently Consider supportive care according to institution's standard, and decrease the infusion rate	Hold carboplatin until creatinine returns to Grade ≤ 1 Resume carboplatin based on timing of recovery and number of previous episodes ➢ ≤ 3 consecutive weeks of interruption • 1st episode, reduce carboplatin dose to AUC of 4 mg/mL•min for all subsequent administration • 2nd episode, discontinue carboplatin treatment ➢ > 3 Consecutive weeks of interruption, discontinue carboplatin permanently

Table 5: Suggested Guidelines for Study Drug and Etoposide-Platinum Therapy Dose Modification and Delay (Cont'd)

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay	Carboplatin Dose Reduction and/or Delay
Diarrhea				
≤Grade 2	No change. Supportive care according to standard practice and diarrhea management described in the protocol (Section 7.5 below)	No change. Supportive care according to standard practice	No change. Supportive care according to standard practice	No change. Supportive care according to standard practice
≥Grade 3	Hold study drug, supportive care according to standard practice. Resume study drug according to the number of episodes that resolved to ≤Grade 1 within 3 weeks of treatment interruption: • 1st episode: resume at the next lower dose (reduce by 2.5 mg/kg or to discuss the increment of dose reduction with the Sponsor's Medical Monitor) • 2rd episode: reduce by 5 mg/kg from starting dose or to discuss alternative increment of dose reduction with the Sponsor's Medical Monitor • 3rd episode: discontinue study drug permanently or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated diarrhea management described in the protocol (Section 7.5 below)	Hold etoposide if diarrhea does not improve to ≤Grade 1 after withholding study drug for one cycle. Resume etoposide according to the number of episodes that resolved to ≤Grade 1 within 3 weeks of study drug interruption: • 1st episode: resume at the same dose • 2rd episode: reduce etoposide dose by 25% from starting dose for all subsequent administration • 3rd episode: reduce etoposide dose by 50% from starting dose for all subsequent administration • 4th episode: discontinue etoposide permanently or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated	Hold cisplatin if diarrhea does not improve to ≤Grade 1 after withholding study drug for three weeks. Resume cisplatin according to the number of episodes that resolved to ≤Grade 1 within 3 weeks of study drug interruption: • 1st episode: resume at the same dose • 2rd episode: reduce cisplatin dose by 25% from starting dose for all subsequent administration • 3rd episode: reduce cisplatin dose by 50% from starting dose for all subsequent administration • 4th episode: discontinue cisplatin permanently or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated	Hold carboplatin if diarrhea does not improve to ≤Grade 1 after withholding study drug for three weeks. Resume carboplatin according to the number of episodes that resolved to ≤Grade 1 within 3 weeks of study drug interruption: • 1st episode: resume at the same dose • 2rd episode: reduce carboplatin dose to AUC of 4 mg/mL•min for all subsequent administration • 3rd episode: discontinue carboplatin permanently or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated

Table 5: Suggested Guidelines for Study Drug and Etoposide-Platinum Therapy Dose Modification and Delay (Cont'd)

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay	Carboplatin Dose Reduction and/or Delay
Peripheral Neuropathy				
Grade ≤ 2	No change	No change	No change	No change
Grade ≥ 3	No change	No change	Hold cisplatin for one cycle to see if peripheral neuropathy improves to Grade ≤2. Resume cisplatin according to the number of episodes that improved to Grade ≤2 within 3 weeks of study drug interruption: • 1st episode: Reduce cisplatin dose by 25% from starting dose for all subsequent cycles • 2rd episode: reduce cisplatin dose by 50% from starting dose for all subsequent administration. • 3rd episode: discontinue cisplatin permanently or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated Call the Sponsor's Medical Monitor to discuss resume cisplatin if the event does not recover to Grade ≤ 2 after one cycle of cisplatin interruption.	Hold carboplatin for one cycle to see if peripheral neuropathy improves to Grade ≤2. Resume carboplatin according to the number of episodes that improved to Grade ≤2 within 3 weeks of study drug interruption: • 1st episode: Reduce carboplatin dose to AUC of 4 mg/mL•min for all subsequent cycles • 2rd episode: discontinue carboplatin permanently or call the Sponsor's Medical Monitor to discuss further dose reduction if clinically indicated Call the Sponsor's Medical Monitor to discuss resume carboplatin if the event does not recover to Grade ≤ 2 after one cycle of carboplatin interruption.

7.5.1 Infusion Reaction Management

The administration of monoclonal antibodies may result in an infusion reaction that may consist of a symptom complex characterized by fever, chills, nausea, vomiting, headache, dizziness, bronchospasm, dyspnea, hypotension, and/or rash including urticaria. If an infusion reaction occurs, the infusion should be stopped and any appropriate medical care should be administered. For subjects whose infusion-associated events were either Grade 1 or 2, and completely resolved on the day of the infusion, the infusion may be resumed at the discretion of the Investigator at a rate that is slower than the initial rate of infusion. *If a Grade 1 or 2 reaction occurs during the first cycle (also with complete resolution of symptoms), the infusion may be resumed at either a slower rate or at the initial rate of infusion (i.e. over 180 minutes).* Please refer to the Pharmacy Manual for details on study drug administration. All subsequent infusions for that subject should then be administered at the reduced rate of infusion.

Subjects experiencing a Grade 2 infusion reaction should be premedicated prior to subsequent infusions. Premedications may include medications such as corticosteroids, diphenhydramine, and/or bronchodilators as indicated. If the Grade 2 infusion reaction recurs during subsequent infusions despite the premedications, the subject should be removed from treatment. In addition, permanently discontinue the study drug therapy in any subject who experiences a Grade 3 or 4 infusion reaction or acute allergic reaction (e.g., symptomatic bronchospasm with or without urticaria, edema, angioedema, or hypotension). Grade 3 or 4 acute allergic reactions should be medically managed as appropriate and treatment may include the administration of epinephrine, corticosteroids, diphenhydramine, bronchodilators, and/or oxygen as indicated.

7.6 Anti-Emetics, Anti-diarrhea and Hematopoietic Supportive Care

Antiemetic therapy and anti-diarrheal medications may be administered at the discretion of the Investigator. However, since diarrhea is the main adverse event associated with tarextumab as a single agent it is recommended that the Investigator follow diarrhea management guidelines below.

It is recommended that all subjects enrolled on the study are to be given a prescription for loperamide at study entry with instructions to take an initial 4 mg dose following the first loose stool, followed by 2 mg after every unformed stool with a maximum of 16 mg per day. Loperamide should be continued until the subject was diarrhea-free for 12 hours. If Grade 3 diarrhea develops, loperamide should be discontinued and the subject would be started on second-line therapy (i.e., Lomotil 2 tablets 4 times daily and/or octreotide 100-150 µg SC three times daily up to a maximum 500 µg 3 times daily).

Hematopoietic growth factors, transfusion of blood and blood products should not be used prophylactically prior to the dosing of the study drug and EP on Day 1 of Cycle 1, but may be administered per standard clinical practice during the course of the study as needed.

7.7 Concomitant and Prohibited Therapy

All concomitant medication administered within 28 days prior to the first administration of study drug through 30 days following the administration of the last dose of study drug will be recorded on the Concomitant Medication eCRF. Investigational medicinal products, therapeutic warfarin (prophylactic low dose of warfarin, i.e., 1 mg daily is allowed for port catheter) and anticancer agents (e.g., cytotoxic agents and biologics with known activity against small cell lung cancer) may not be administered from enrollment through the first line therapy.

Subjects planning to initiate intravenous bisphosphonate or denosumab therapy after study entry must begin within the first 30 days of the first administration of study drug. Oral bisphosphonate may be initiated at any point in the study for the treatment of osteoporosis. Subjects can switch intravenous bisphosphonate to denosumab or vice versa during the study, but the initiation of a new intravenous bisphosphonate or denosumab therapy beyond 30 days after the first administration of study drug is prohibited.

After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Study drug administration should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone ≥ 14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (Appendix A). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

7.8 Treatment Compliance

Tarextumab, Placebo, etoposide and cisplatin or carboplatin will be administered IV by study site personnel. Thus, compliance with each infusion will be documented in the subject's medical records and then recorded on the appropriate electronic data capture (EDC) screen. In addition, drug accountability will be performed.

8.0 SAFETY ASSESSMENTS

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

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

8.1 Adverse Events Definitions and Reporting Procedures

All Adverse Events from the time of the first administration of study drug through 30 days after the last dose of study drug or EP whichever is discontinued last **must** be documented in the medical record and reported on the AE Case Report Form (CRF).

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). The grading of the adverse events will be done using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.02 (see Study Reference Binder).

8.1.1 Definition of Adverse Event

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any medical condition or clinically significant laboratory abnormality with an onset date before the first administration of study drug is a pre-existing condition that must be listed on the Medical History CRF and should not be considered an adverse event unless the condition worsens in intensity or frequency after enrollment (e.g., Grade 2 nausea prior to the first administration of study drug becomes Grade 3 nausea after the first administration of study drug).

8.1.2 Adverse Event -Causality rating

The causality of each adverse event should be assessed and classified by the Investigator as "related" or "not related". An event is considered related if the administration of study drug and the occurrence of the AE are reasonably related in time AND the event could not be explained equally well by factors or causes other than exposure to study drug. An event is considered unrelated if the administration of study drug and the occurrence of the AE are not reasonably related in time AND the event is likely to be related to an etiology other than the use of study drug; that is, there are facts, evidence or arguments to suggest a causal relationship to study drug.

8.1.3 Definition of Serious Adverse Event

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

- death
- life-threatening condition (places the subject at immediate risk of death)
- subject hospitalization or prolongation of existing hospitalization
- persistent or significant disability/incapacity
- congenital anomaly/birth defect, or any other adverse event that, based upon the Investigators medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse)

8.1.3.1 Disease Progression and Death

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

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

8.1.4 Serious Adverse Event Reporting Procedures

SAEs that occur during the study must be clearly documented in the medical record. In addition, the SAE form must be completed for each event and promptly submitted to OncoMed designated fax number. Details of SAE reporting procedures will be available in Study Reference Manual.

The Investigator is encouraged to discuss with the Medical Monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the Medical Monitor is as follows:

Primary: [redacted]

Backup: [redacted]
OncoMed Pharmaceuticals, Inc.
800 Chesapeake Drive
Redwood City, CA 94063

The reporting period for SAEs is the period from the first administration of the study drug through 30 days after the last administration of study drug or EP whichever is discontinued last. SAEs reported to the Investigator outside of this reporting period will be reported to OncoMed or its designee if in the judgment of the *I*nvestigator there is "a reasonable possibility" that the event may have been caused by the product.

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

8.2 Clinical Laboratory Assessments

8.2.1 Hematology

Hematology includes complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count. Coagulation test of PT/INR and aPTT will be obtained on Day 1 of each treatment cycle. The results need to be reviewed by the *I*nvestigator prior to each study drug administration.

8.2.2 Chemistry

For Phase 1b, Serum Chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, albumin, calcium, phosphorus, and magnesium. The results for BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium need to be reviewed by the Investigator prior to each study drug administration.

For Phase 2, Chemistry (Serum or Plasma) includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, albumin, calcium, phosphorus, and magnesium. The results for BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium need to be reviewed by the Investigator prior to each study drug administration.

8.2.3 Urinalysis

For Phase 1b, Urinalysis (dip stick is sufficient) includes color, appearance, pH, ketones, specific gravity, bilirubin, protein, blood, glucose and urobilinogen.

For Phase 2, Urinalysis (dip stick is sufficient) includes pH, ketones, specific gravity, bilirubin, protein, blood and glucose.

8.3 Vital Signs and Other Physical Findings

A full physical examination will be done at screening, clinically indicated during the study and treatment termination. Targeted physical examinations will be done at all other times, *with areas of the body to be examined* at the Investigator's discretion.

Vitals signs (blood pressure, pulse, respiratory rate, and temperature) will be done at screening and during study visits as specified in the Schedule of Assessments (Appendix B and Appendix C).

8.4 Cardiac Studies

Twelve-lead electrocardiograms (ECGs) with assessment of PR interval, QRS duration, and QTc interval will be obtained at Screening and during study visits as specified in the Schedule of Assessments (APPENDIX B and APPENDIX C).

8.5 Immunogenicity Assessments

During Phase 1b, serum samples will be obtained for immunogenicity assessment (Anti-tarextumab) prior to study drug administration on Day 1 of Cycle 1, every three cycles thereafter (Day 1 of Cycle 4, 7, 10, etc.), at other times as clinically indicated such as when significant toxicities occur and at the time of treatment termination for all subjects enrolled in Phase 1b. Samples that test positive will be assessed for neutralizing capability.

During Phase 2, serum samples will be obtained for immunogenicity assessment (Anti-tarextumab) prior to study drug administration on Day 1 of Cycle 1, every other cycle thereafter (Day 1 of Cycle 3, 5, 7, etc.), at other times as clinically indicated such as when significant toxicities occur and at the time of treatment termination for all subjects enrolled in Phase 2. Samples that test positive will be assessed for neutralizing capability.

Instructions for sample collection, handling, storage, and shipping can be found in the Study Reference Binder.

8.6 Pharmacokinetic Assessments

For subjects enrolled in Phase 1b portion only: Plasma samples from all subjects enrolled in Phase 1b portion will be obtained for pharmacokinetic analysis of tarextumab at pre-dose and 5 minutes post tarextumab infusion on Day1 of Cycles 1 and 3, on Days 3 and 8 of Cycles 1 and 3, at other times as clinically indicated such as when significant toxicities occur as well as at the time of treatment termination, as outlined in the Schedule of Assessments (Appendix B).

For subjects enrolled in Phase 2 portion only: Plasma samples from all subjects enrolled in Phase 2 portion will be obtained for pharmacokinetic analysis of tarextumab on Day 1 of Cycles 1 and 3, at pre-dose and 5 minutes post tarextumab infusion Day 3 of Cycle 1 and Cycle 3 prior to etoposide administration; Day 8 of Cycle 1 and Cycle 3 when blood sample is taken for biomarker evaluation; Day 1 of every other cycle staring from Cycle 5 prior to study drug infusion and, at other times as clinically indicated such as when significant toxicities occur as well as at the time of treatment termination, as outlined in the Schedule of Assessments (Appendix C).

Pharmacokinetic parameters (i.e. area under the curve [AUC], clearance, volume of distribution and apparent half life) of tarextumab will be assessed for each evaluable subject. Instructions for sample collection, handling, storage, and shipping can be found in the Study Reference Binder.

9.0 EFFICACY ASSESSMENTS

Subjects will be assessed for response using Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. The first response assessment will occur approximately 6 weeks/42 days (± 5 days) after the first dose of the study drug. Subsequent response assessments will occur every 6 weeks/42 days (± 5 days). Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

10.0 BIOMARKERS AND EXPLORATORY ASSESSMENTS

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

Notch Expression: Notch3*, Hes1, Hey2, Hey1 and Hes6* expression levels will be assessed in FFPE tumor specimens, either archived or fresh core needle biopsied at study entry (two fresh cores preferred whenever possible). FFPE samples must be obtained during screening for Notch3*, Hes1, Hey2, Hey1 and Hes6* levels to be measured by immunohistochemistry and/or gene expression assay*s*. Notch 2 and other Notch-related genes and proteins may also be measured.

In addition, DNA testing may be performed on the FFPE tumor specimens for subjects who sign the optional FFPE Informed Consent for DNA testing. Exploratory analysis of these tumors may help to identify biomarkers that could be used in the future to predict which subjects are more likely to respond to tarextumab treatment. Analysis of candidate genes relevant to the Notch pathway may be performed (e.g. Notch2, Notch3, etc.).

Blood Biomarkers: A pre-dose sample of a total of 19 mL of blood will be drawn during study visits according to Schedule of Assessments (Appendix B and Appendix C) to evaluate changes in plasma proteins by immunochemistry (e.g., EGFR, PLGF, ENA-78, etc.), circulating tumor cells(CTCs), and Notch-related gene expression of mRNA, e.g., Affymetrix microarrays, quantitative PCR. Plasma microRNAs may also be evaluated by microRNA expression profiling. A sample will also be obtained at the time of treatment termination unless one has been obtained during the prior 14 days. A pre-dose blood sample will also be obtained on Day 1 of Cycles 4 and 5 to explore effects of treatment on CTCs.

CTCs will be enumerated in blood and correlation with response to EP plus tarextumab will be assessed. Biomarker proteins and mRNA expression in the CTCs (e.g., Notch3, Notch2, CD44, ALDH1, etc.) may also be evaluated. Circulating endothelial cells may also be evaluated.

Hair Follicle mRNA Expression for subjects in Phase 1b only: Predose hair samples (6 hairs) will be collected during study visits according to Schedule of Assessments (Appendix B) for gene expression RT-PCR analysis of Notch-pathway related mRNA expression, e.g., heyl, hey2, etc. RNA extracted from hair samples may be analyzed on microarrays, e.g., Affymetrix platform to measure tarextumab–affected gene expression changes in samples.

Pharmacogenomics: A blood sample (10 mL) will be collected on Day 1 of Cycle 1. Pharmacogenomic analysis of candidate genes relevant to tarextumab may influence safety, tolerability, or pharmacodynamic effects of tarextumab for the treatment of extensive stage small cell lung cancer. Analysis of genes relevant to Notch/DLL4 target or pathway genes or disease genes may be performed (e.g., Notch 2, Notch3, FBW7 and PTEN). Pharmacogenomic samples will be destroyed after 10 years.

Optional Tumor Biomarkers: Optional tumor specimens will be collected during study visits and at the time of treatment termination, if feasible according to Schedule of Assessments (Appendix B and Appendix C) from subjects who are consented and who have tumor lesions that are amenable to core biopsies. Tumor samples will be analyzed for treatment-induced changes in Notch-related gene expression (i.e., mRNA) and/or protein markers and cancer stem cell–related gene expression.

11.0 STUDY VISIT SCHEDULE AND ASSESSMENTS

Subjects must sign and date the Informed Consent Form that has been approved by the IEC/IRB prior to undergoing any study-related procedures.

The enrollment and cohort assignment will be centrally managed by OncoMed and its designee. When a treatment cohort is open for enrollment during Phase 1b portion, the site will fax in a Subject Registration Form along with subject eligibility supporting documents for each potential subject to OncoMed and its designee after the subject's screening process has been completed. OncoMed and its designee will assign a subject number and treatment cohort for each subject that is accepted into the study. Sites cannot enroll or start dosing a subject without receiving the assigned subject number and treatment cohort from OncoMed or its designee during Phase 1b portion. During Phase 2 portion, the Investigator/study coordinator will use a randomization method that is detailed in the Study Reference Manual to enroll the subject after OncoMed or its representative has signed and approved the enrollment form. Study drug must be administered within 4 days from the date of enrollment/randomization. The following study evaluations must be performed at the indicated timepoints.

11.1 Screening

The following evaluations and procedures will be performed within 28 days prior to the first study drug administration (Cycle 1 Day 1):

- Informed Consent **(must be obtained before any study specific procedures are performed)**
- Medical and oncology history including demographics
- Radiographic evaluation: CT with contrast, or MRI of the chest, abdomen, pelvis, and brain, and bone scan performed as outlined by the RECIST criteria 1.1 (see Appendix E). Note: PET/CT can be used in lieu of bone scan to identify and follow up bone lesions. The same method (CT or MRI, bone scan or PET/CT for bone lesions) must be used consistently throughout the study to follow the same anatomical location.
- FFPE tumor tissues, either archived or fresh core needle biopsied available for Notch*3, Hes1, Hey1, Hey2, and Hes6* analysis (two fresh cores preferred whenever possible). In addition, DNA testing may be performed on the FFPE tumor specimens for subjects who sign the optional Pharmacogenomics/DNA Testing Informed Consent form. Details of the requirement of tissue specimen will be provided in the Study Reference Manual
- Tumor core biopsy (**Optional and only if subject has signed the optional tumor core biopsy consent)**
- Concomitant medications

The following evaluations and procedures will be performed within 14 days prior to the first administration of study drug (Cycle 1 Day 1):

- Physical examination
- Vital signs
- Height
- Weight
- ECOG performance status
- Hematology
- *C*hemistry
- Coagulation
- Serum pregnancy test for all females of childbearing potential (a negative result must be obtained prior to enrollment)
- Urinalysis (dip stick is sufficient)
- Electrocardiogram (ECG) including PR interval, RR interval, QRS duration, and QTc interval
- Concomitant medications

11.2 Treatment Visits – Phase 1b

If the subject meets all inclusion/exclusion criteria after the screening visit(s), the site will complete an enrollment form and submit it to OncoMed along with supporting source documents for approval. Once OncoMed or its representative has approved the enrollment form, the Investigator/study coordinator will receive a subject number and dose cohort assignment from OncoMed and its designees to enroll a subject into Phase 1b portion of the study.

The subject will start treatment of study drug on Day 1 in combination with etoposide 100 mg/m^2 on Days 1, 2, and 3, and cisplatin 80 mg/m^2 for Phase 1b or carboplatin at AUC of 5 mg/mL•min on Day 1 of every 21-day cycle. On days when study drug is given together with etoposide and platinum therapy, study drug should be given prior to etoposide and platinum therapy administration. Hematology, BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium lab results must be available and reviewed by the Investigator prior to each study drug dosing. For subjects who have study drug held or discontinued for tolerability reasons, EP chemotherapy should continue to the completion of 6 cycles.

After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Study drug administration (tarextumab or Placebo) should continue at every 21-day (± 1 day) cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone (tarextumab or Placebo) ≥ 14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent. Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

11.2.1 Cycle 1

11.2.1.1 Cycle 1 Day 1

The following assessments will be completed prior to study drug infusion. These assessments will be repeated if they were done more than 7 days prior to Cycle 1 Day 1.

- Physical examination
- ECOG performance status
- Hematology
- Serum chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)
- Electrocardiogram (ECG) including PR interval, RR interval, QRS duration, and QTc interval

The following assessments will be done prior to study drug infusion on Cycle 1 Day 1:

- Weight
- Serum sample for anti-tarextumab antibody on all subjects
- Blood sample for biomarker
- Plasma sample for tarextumab PK from all subjects
- Hair follicle samples (6 hairs)

- Blood sample for pharmaco-genomics **(Optional and only if subject has signed the separate pharmacogenomics Informed Consent Form)**
- Concomitant medications
- Vital Signs

Administration of study drug, etoposide, and cisplatin or carboplatin:

Hematology, BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium lab results must be reviewed by the Investigator prior to study drug dosing. Study drug will be administered first, followed by etoposide infusion, and then cisplatin or carboplatin infusion.

The following procedures will be completed after administration of study drug:

- Plasma samples for tarextumab PK only from all subjects: 5 (±2) minutes after the end of tarextumab infusion, but prior to EP administration.
- Adverse event recording

11.2.1.2 Cycle 1 Day 2

The following assessments will be completed prior to etoposide infusion:

- Vital signs
- Weight
- Concomitant medications
- Adverse event recording

Administration of etoposide:

Etoposide dosing will be given.

11.2.1.3 Cycle 1 Day 3

The following assessments will be completed prior to etoposide infusion:

- Vital signs
- Weight
- Plasma sample for tarextumab PK from all subjects enrolled
- Concomitant medications
- Adverse event reporting

Administration of etoposide:

Etoposide dosing will be given.

- Adverse event recording

11.2.1.4 Cycle 1 Day 8

- Blood sample for biomarker
- Plasma sample for tarextumab PK from all subjects
- Hematology
- Concomitant medications
- Adverse event recording

11.2.2 Cycles 2-6

11.2.2.1 Day 1 (± 1 day) of Cycles 2-6

The following assessments will be completed prior to study drug infusion (laboratory assessments can be performed up to 3 days prior to Day 1 of Cycles 2-6):

- Targeted physical examination at the Investigator's discretion
- Vital signs
- Weight
- ECOG performance status
- Hematology
- Serum chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)
- Electrocardiogram (ECG) including PR interval, RR interval, QRS duration, and QTc interval
- Concomitant medications
- Serum sample for anti-tarextumab antibody on all subjects **(Collect at Cycle 4, only)**
- Blood sample for CTCs (collect at Cycles 4 and 5 only)
- Plasma sample for tarextumab PK from all subjects enrolled **Collect at Cycle 3 only**

- Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, and pelvis will be done every 6 weeks±5 days after Day 1 of Cycle 1 (Day 1 of Cycle 3 and every 6 weeks±5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. Bone scan will be only performed at the investigator's discretion if clinically indicated

Administration of study drug, etoposide, and cisplatin or carboplatin:

Hematology, BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium lab results must be reviewed by the Investigator prior to study drug dosing. Study drug will be administered first, followed by etoposide infusion, and then cisplatin or carboplatin infusion.

- Adverse event recording

The following procedures will be completed after administration of study drug at Cycle 3 only for all subjects and for subjects enrolled in Phase *2* portion:

- Plasma samples for tarextumab PK at Cycle 3 only: 5 (±2) minutes after the end of tarextumab infusion, but prior to EP administration.

11.2.2.2 Day 2 of Cycles 2-6

The following assessments will be completed prior to etoposide infusion:

- Vital signs
- Weight
- Blood sample for biomarker (**Collect at Cycles 2 and 3 only**)
- Concomitant medications
- Adverse event recording

Administration of etoposide:

Etoposide dosing will be given.

11.2.2.3 Day 3 of Cycles 2-6

The following assessments will be completed prior to etoposide infusion:

- Vital signs
- Weight
- Plasma sample for tarextumab PK **at Cycle 3 only**
- Concomitant medications
- Adverse event reporting

Administration of etoposide:

Etoposide dosing will be given.

11.2.2.4 Day 8 of Cycles 2 and 3 Only

- Plasma sample for tarextumab PK from all subjects **(Collect at Cycle 3 only)**
- Blood sample for biomarker
- Hematology
- Hair follicle samples (6 hairs) **(Collect at Cycle 2 only.)**
- Tumor core biopsy (**Optional and only if subject has signed the optional tumor core biopsy consent; collect at Cycle 2 only).** The site can call the Sponsor's medical monitor to discuss an alternative timepoint if it is not feasible to collect the optional tumor biopsy on Day 8 (±2) of Cycle 2.
- Concomitant medications
- Adverse event recording

11.2.3 After Cycle 6 of etoposide and cisplatin/carboplatin with tarextumab

After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. tarextumab administration should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone ≥14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (Appendix A Study Schema). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

11.2.4 Cycle 7 and every cycle thereafter

11.2.4.1 Day 1 (± 1 day) of Cycle 7 and every cycle thereafter

After the subject completes 6 cycles of EP, only tarextumab will be given on Day 1 of subsequent cycles.

The first dose of tarextumab after the completion of prophylactic cranial irradiation (PCI) should be given ≥ 14 days after the last dose of radiation.

The following assessments will be completed prior to study drug infusion (laboratory assessments can be done up to 3 days prior to Day 1 of each cycle):

- Targeted physical examination at the Investigator's discretion
- Vital signs
- Weight
- ECOG performance status
- Hematology
- Serum chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)

- Concomitant medications
- Serum sample for anti-tarextumab antibody on all subjects **(Phase 1b Subjects: collect at Cycle 7, 10 and every 3rd cycle thereafter, only)**
- Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, pelvis, will be done every 6 weeks ±5 days after Day 1 of Cycle 1 (Day 1 of Cycle 7 and every 6 weeks ±5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. Bone scan will be only performed at the investigator's discretion if clinically indicated

Administration of study drug:

Hematology, BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium lab results must be reviewed by the Investigator prior to study drug dosing. Only study drug will be given on day 1 of each cycle beginning at Cycle 7.

- Adverse event recording

11.3 Treatment Visits – Phase 2

If the subject meets all inclusion/exclusion criteria after the screening visit(s), the site will complete an enrollment form and submit it to OncoMed along with supporting source documents for approval. Once OncoMed or its representative has approved the enrollment form, OncoMed will use a randomization system to enroll a subject into Phase 2 portion of the study.

The subject will start treatment of study drug on Day 1 in combination with etoposide 100 mg/m^2 on Days 1, 2, and 3, and cisplatin 75 mg/m^2 or carboplatin at AUC of 5 mg/mL•min on Day 1 of every 21-day cycle. On days when study drug is given together with etoposide and platinum therapy, study drug should be given prior to etoposide and platinum therapy administration. Hematology, BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium lab results must be available and reviewed by the Investigator prior to each study drug dosing. For subjects who have study drug held or discontinued for tolerability reasons, EP chemotherapy should continue to the completion of 6 cycles.

After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Study drug administration (tarextumab or Placebo) should continue at every 21-day (± 1 day) cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone (tarextumab or Placebo) ≥ 14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (Appendix A Study Schema). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

11.3.1 Cycle 1

11.3.1.1 Cycle 1 Day 1

The following assessments will be completed prior to study drug infusion. These assessments will be repeated if they were done more than 7 days prior to Cycle 1 Day 1.

- Physical examination
- ECOG performance status
- Hematology
- Chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)
- Electrocardiogram (ECG) including PR interval, RR interval, QRS duration, and QTc interval

The following assessments will be done prior to study drug infusion on Cycle 1 Day 1:

- Weight
- Serum sample for anti-tarextumab antibody on all subjects
- Blood sample for biomarker
- Plasma sample for tarextumab PK
- Blood sample for pharmaco-genomics **(Optional and only if subject has signed the separate pharmacogenomics Informed Consent Form)**
- Concomitant medications
- Vital Signs

Administration of study drug, etoposide, and cisplatin or carboplatin:

Hematology, BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium lab results must be reviewed by the Investigator prior to study drug dosing. Study drug will be administered first, followed by etoposide infusion, and then cisplatin or carboplatin infusion.

The following procedures will be completed after administration of study drug:

- Plasma samples for tarextumab PK: 5 (±2) minutes after the end of study drug infusion, but prior to EP administration.
- Adverse event recording

11.3.1.2 Cycle 1 Day 2

The following assessments will be completed prior to etoposide infusion:

- Vital signs
- Weight
- Concomitant medications
- Adverse event recording

Administration of etoposide:

Etoposide dosing will be given.

11.3.1.3 Cycle 1 Day 3

The following assessments will be completed prior to etoposide infusion:

- Vital signs
- Weight
- Plasma sample for tarextumab PK
- Concomitant medications
- Adverse event reporting

Administration of etoposide:

Etoposide dosing will be given.

- Adverse event recording

11.3.1.4 Cycle 1 Day 8

- Blood sample for biomarker
- Plasma sample for tarextumab PK
- Hematology
- Concomitant medications
- Adverse event recording

11.3.2 Cycles 2-6

11.3.2.1 Day 1 (± 1 day) of Cycles 2-6

The following assessments will be completed prior to study drug infusion (laboratory assessments can be performed up to 3 days prior to Day 1 of Cycles 2-6):

- Targeted physical examination with areas of the body to be examined at the Investigator's discretion
- Vital signs
- Weight
- ECOG performance status
- Hematology
- Chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)

- Electrocardiogram (ECG) including PR interval, RR interval, QRS duration, and QTc interval
- Concomitant medications
- Serum sample for anti-tarextumab antibody on all subjects **(Collect at Cycles 3 and 5 only)**
- Blood sample for CTCs **(Collect at Cycles 4 and 5 only)**
- Plasma sample for tarextumab PK (**Collect at Cycles 3 and 5 only)**
- Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, and pelvis will be done every 6 weeks±5 days after Day 1 of Cycle 1 (Day 1 of Cycle 3 and every 6 weeks±5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. Bone scan will be only performed at the investigator's discretion if clinically indicated

Administration of study drug, etoposide, and cisplatin or carboplatin:

Hematology, BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium lab results must be reviewed by the Investigator prior to study drug dosing. Study drug will be administered first, followed by etoposide infusion, and then cisplatin or carboplatin infusion.

- Adverse event recording

The following procedures will be completed after administration of study drug at Cycle 3 only:

- Plasma samples for tarextumab PK: 5 (±2) minutes after the end of study drug infusion, but prior to EP administration.

11.3.2.2 Day 2 of Cycles 2-6

The following assessments will be completed prior to etoposide infusion:

- Vital signs
- Weight
- Blood sample for biomarker (**Collect at Cycles 2 and 3 only**)
- Concomitant medications
- Adverse event recording

Administration of etoposide:

Etoposide dosing will be given.

11.3.2.3 Day 3 of Cycles 2-6

The following assessments will be completed prior to etoposide infusion:

- Vital signs
- Weight
- Plasma sample for tarextumab PK **at Cycles 3 and 5**
- Concomitant medications
- Adverse event reporting

Administration of etoposide:

Etoposide dosing will be given.

11.3.2.4 Day 8 of Cycles 2 and 3 Only

- Plasma sample for tarextumab PK **(Collect at Cycle 3 only)**
- Blood sample for biomarker
- Hematology
- Tumor core biopsy (**Optional and only if subject has signed the optional tumor core biopsy consent; collect at Cycle 2 only).** The site can call the Sponsor's medical monitor to discuss an alternative timepoint if it is not feasible to collect the optional tumor biopsy on Day 8 (±2) of Cycle 2.
- Concomitant medications
- Adverse event recording

11.3.3 After Cycle 6 - Planned EP Treatment cycles

After the completion of 6 planned cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Study drug (tarextumab or Placebo) administration should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone ≥14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (Appendix A). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

11.3.4 Subsequent Cycles After Cycle 6

11.3.4.1 Day 1 (± 1 day) of Subsequent Cycles After Completion of Planned EP Cycles

After the subject completes the 6 planned cycles of EP, only study drug will be given on Day 1 of subsequent cycles.

The first dose of study drug after the completion of prophylactic cranial irradiation (PCI) should be given ≥ 14 days after the last dose of radiation.

The following assessments will be completed prior to study drug infusion (laboratory assessments can be done up to 3 days prior to Day 1 of each cycle):

- Targeted physical examination at the Investigator's discretion
- Vital signs
- Weight
- ECOG performance status
- Hematology
- Chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)
- Concomitant medications

- Serum sample for anti-tarextumab antibody on all subjects **(Collect at Cycle 7, 9 and every other cycle thereafter, only)**
- Plasma sample for tarextumab PK **(collect at Cycle 7, 9 and every other cycle thereafter only)**
- Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, pelvis, will be done every 6 weeks ±5 days after Day 1 of Cycle 1 (Day 1 of Cycle 7 and every 6 weeks ±5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. Bone scan will be only performed at the investigator's discretion if clinically indicated

Administration of study drug:

Hematology, BUN, bicarbonate, creatinine, glucose, chloride, potassium, and sodium lab results must be reviewed by the Investigator prior to study drug dosing. Only study drug will be given on day 1 of each cycle after Cycle 4.

- Adverse event recording

11.4 Treatment Termination

Subjects who have agreed to the optional tumor core biopsy in the Informed Consent and have pre and post-treatment optional tumor biopsy collected, will have tumor core biopsy at the time of treatment termination visit, if feasible.

The following assessments must be performed approximately 4 weeks after the last dose of study drug, etoposide, or cisplatin or carboplatin, whichever is discontinued last, but prior to the initiation of a new anti-cancer therapy:

- Physical examination
- Vital signs
- Weight
- ECOG performance status
- Hematology
- Chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)
- Electrocardiogram (ECG) including PR interval, RR interval, QRS duration, and QTc interval

- Serum sample for anti-tarextumab antibody on all subjects
- Blood sample for biomarker **(unless done within the last 14 days)**
- Plasma sample for tarextumab PK from all subjects enrolled.
- Tumor assessment with CT (with contract) or MRI scan of chest, abdomen, and pelvis for subjects who have not previously demonstrated disease progression within the previous 4 weeks.
- Concomitant medications
- Adverse event recording

11.5 Follow up

Subjects who are discontinued from study treatment will be followed for survival and any subsequent anti-cancer therapies. Survival follow-up information and subsequent anti-cancer therapies, including systemic therapies, surgery (resection of metastatic disease), and radiation therapy will be collected during telephone calls, through subjects medical records, and/or clinic visits every 3 months until death, loss to follow-up, or study termination by the sponsor. The study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Additionally, subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) and bone scan every 12 weeks (+/- 5 days) during the Follow-up Period until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

12.0 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures. Site initiation visits will be conducted separately at each clinical site. Clinical Research Associates (CRAs) will monitor the study and verify that the data are accurate. OncoMed Pharmaceuticals, Inc. has contracted with a contract research organization (CRO) to perform the data management of this trial. The data will be captured using a validated EDC system. The medical monitors, CRAs, and site personnel will be trained in the use of the EDC system. The clinical data and the site-specific laboratory data will be entered by site personal into the EDC system. System backups for data stored at OncoMed Pharmaceuticals, Inc. and at all CROs, and records retention for the study data will be consistent with the standard procedures for these organizations.

13.0 STATISTICAL PLAN

13.1 Power and Sample Size

13.1.1 Phase 1b

The Phase 1b portion of the trial is a 3+3 dose escalation design. Table 6 shows the probability of declaring a dose as exceeding the MTD for a variety of underlying toxicity rates. For example there is an 83 percent probability to declare a dose with an incidence of dose limiting toxicity of 50 percent as exceeding the MTD. This compares with a probability of 29 percent for a dose with an incidence of dose limiting toxicity of 20 percent.

Table 6: Power to Declare a Dose as Exceeding the MTD for Various Incidence Rates

Incidence of Toxicity	Probability of more than 1 out of 3 subjects with Toxicity in first group of three	Probability of 1 subject with Toxicity in first group of 3 then at least 1 subject with toxicity in second group of 3	Probability of Stopping Dose Escalation
0.05	0.007	0.019	0.027
0.10	0.028	0.066	0.094
0.15	0.061	0.125	0.186
0.20	0.104	0.187	0.291
0.25	0.156	0.244	0.400
0.30	0.216	0.290	0.506
0.35	0.282	0.322	0.604
0.40	0.352	0.339	0.691
0.45	0.425	0.340	0.766
0.50	0.500	0.328	0.828

13.1.2 Sample Size Justification – Phase 2

At the final analysis we will evaluate the effect of tarextumab on PFS *in* subjects in the intention to treat population. The final analysis will take place when *91* progression events have been observed or 10 months after the completion of enrollment whichever occurs first.

Lets denote the treatment effect *in terms of the log of the hazard ratio* by θ_1:

We can write the null hypotheses *for this test in the ITT group of subjects* as.

$H_1 : \theta_1 = 0$

and the alternative as

$H_A : \theta_1 < 0$

The power and type 1 error for the log rank test of this hypothesis is presented in Table 7. .

Table 7: PFS: Power for H1

	Analysis 1	***Analysis 2***	***Final Analysis***
Total Number of Events	*61*	*76*	*91*
Z-Statistic (reject the null) (1)	*3.168*	*2.301*	*1.036*
p-value (1 sided)	*0.00077*	*0.011*	*0.15*
Z statistic (reject the Alt) (2)	*-1.773*	*-1.486*	*-1.079*
p-value (1 sided)	*0.038*	*0.069*	*0.14*
Cumulative Type 1 Error (1-sided)	*8e-04*	*0.0107*	*0.1501*
Cumulative Power			
HR=0.75	*0.0204*	*0.1479*	*0.6318*
HR=0.67	*0.0543*	*0.2897*	*0.809*
HR=0.65	*0.0687*	*0.3365*	*0.846*
HR=0.60	*0.1204*	*0.4709*	*0.9194*
HR=0.50	*0.3223*	*0.7647*	*0.9884*
Cumulative Prob of Stopping for Harm			
Alt	*4e-04*	*8e-04*	*0.0018*
Null	*0.0381*	*0.0762*	*0.1501*
HR=1/0.75=1.33	*0.258*	*0.4246*	*0.6275*
HR=1/0.67=1.49	*0.4172*	*0.617*	*0.8052*
HR=1/0.50=2.0	*0.8248*	*0.9412*	*0.9877*

1) The boundary for rejecting the null hypothesis for efficacy is obtained from the gamma(-16) alpha spending function

2) The boundary for rejecting the null hypothesis for harm is obtained from the gamma(-4) alpha spending function

With 91 events at the final analysis, there is 80 percent power with 0.15 type 1 error to detect a hazard ratio of 0.67. There is a 7.6 percent chance of stopping early for Harm under the null, 42.5 percent chance of stopping early for Harm if the hazard ratio is 1/.75 = 1.33, 61.7 percent chance of stopping early for harm if the hazard ratio is 1/.67 = 1.49, and a 94.1 percent chance of stopping early for harm if the hr = 1/.5 = 2.0.

Analyses 1 and 2 will take place at the last two quarterly safety review meeting of the DSMB. The estimated number of events at those times are presented in Table 7. If the number of events differs from what is presented in the table, the efficacy and safety boundaries will be recalculated using the spending functions which are footnoted in Table 7.

Survival is a secondary endpoint in this study. *An* analysis of overall survival will take place at *the time of each analysis for PFS as well as at* the time that the final analysis of PFS takes place. *Further the final analysis of survival will take place when there are 98 events* or *6 months after the final analysis for PFS whichever occurs first*. Figure 10 and Table *10* present enrollment, PFS events and Deaths over time. The calculations in Figure 9 and Table *10* take into account

non constant hazard as described in Table 8 *and* 9. The basis for the estimates of non constant hazard are presented in Figure 6- 9 which are Kaplan -Meier (KM) curves for PFS and Survival in (Ref 10, and Ref 14). Regarding enrollment it *was initially* assumed that there is a ramp up time of 5 months with a starting enrollment of 4 subjects per months and that the maximum enrollment rate is 6 subjects per month. *The enrollment in Table 10 and Figure 10 represents the observed enrollment up to January 2016 and the remaining enrollment is assumed to be 15 subjects per month.*

The censoring rate *was initially* assumed to be 40 percent of the rate at which events accrue in the control arm and 60 percent of the rate at which events accrue in the tarextumab arm. *When* 79 PFS event accrued in the study*, we observed* 39 censors for a censoring rate of 39/(39+*79)*=33 percent. This information w*as* used to recalibrate the total number of events at the final analysis, the type 1 error and the power.

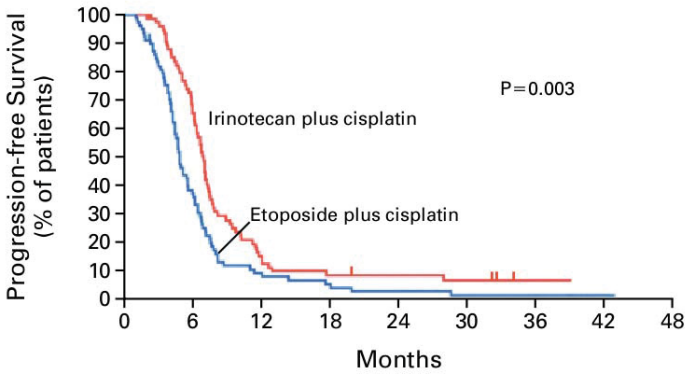
Table 8: Hazards for Piece-Wise Exponential Model of Progression Free Survival

Period	0-5 months	5-7 months	7-8 months	>8 months
Percent Change in Proportion without an event (Change in PFS)	0.50 (1.00 to 0.50)	0.50 (0.50 to 0.25)	0.50 (0.25 to 0.125)	0.50 (0.125 to 0.0625) from 8 to 18 months (Noda) 0.50 (0.125 to 0.0625) from 8 to 11 months (Hanna)
Hazard Control	0.1386	0.3466	0.6931	0.0693, 0.2310
Hazard Treatment	0.0901	0.2253	0.4505	0.0451, 0.1502
Hazard Ratio	0.65	0.65	0.65	0.65

Table 9: Hazards for Piece-wise *E*xponential *M*odel of Survival

Period	0-9 months	9-15 months	15-18 months	>18 months
Percent Change in Proportion without an event	0.50 (1.00 to 0.50)	0.50 (0.50 to 0.25)	0.60 (0.25 to 0.10)	0.467 (.15 to 0.080 from 18 to 24 months Hanna)
Hazard Control	0.07702	0.1155	0.1703	0.127
Hazard Treatment	0.05006	0.07509	0.1107	0.0825
Hazard Ratio	0.65	0.65	0.65	0.65

Figure 6: PFS in Subjects Treated with Etoposide plus Cisplatin. from Noda et al



NO. AT RISK

Irinotecan plus cisplatin	77	47	9	9
Etoposide plus cisplatin	77	27	6	2

Figure 2. Progression-free Survival of Patients with Extensive Small-Cell Lung Cancer Who Were Assigned to Treatment with Irinotecan plus Cisplatin or Etoposide plus Cisplatin.
The tick marks indicate patients whose data were censored.

Figure 7: PFS in Subjects Treated with Etoposide plus Cisplatin - Hanna

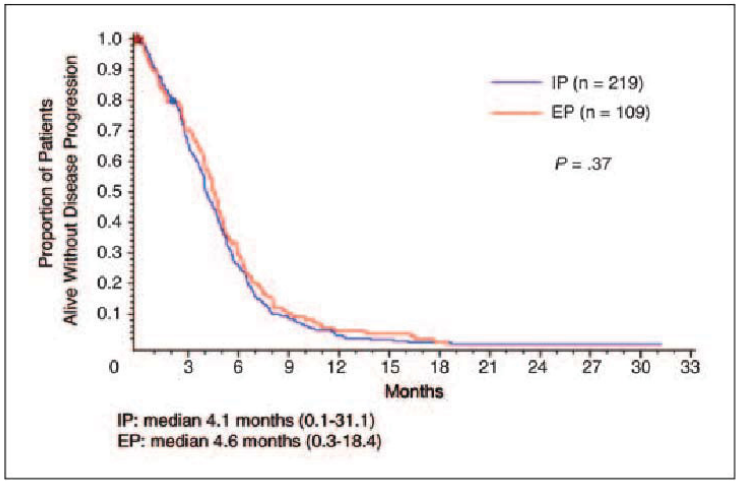
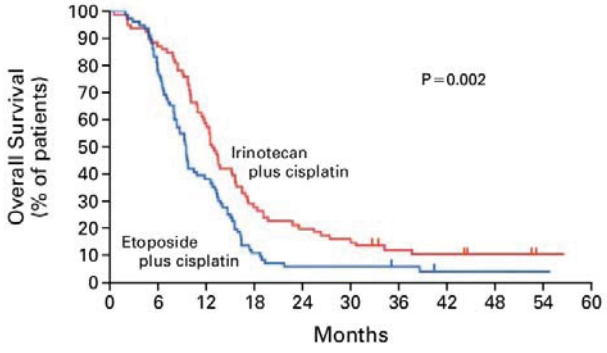


Fig 1. Time to disease progression. IP, irinotecan/cisplatin; EP, etoposide/cisplatin.

Figure 8: Survival in Subjects Treated with Etoposide plus Cisplatin(from Noda et al.)



NO. AT RISK

Irinotecan plus cisplatin	77	67	45	21	15	11	7
Etoposide plus cisplatin	77	60	29	8	4	4	3

Figure 1. Overall Survival of Patients with Extensive Small-Cell Lung Cancer Who Were Assigned to Treatment with Irinotecan plus Cisplatin or Etoposide plus Cisplatin.
The tick marks indicate patients whose data were censored.

Figure 9: Survival in Subjects Treated with Etoposide plus Cisplatin (from Hanna et al.)

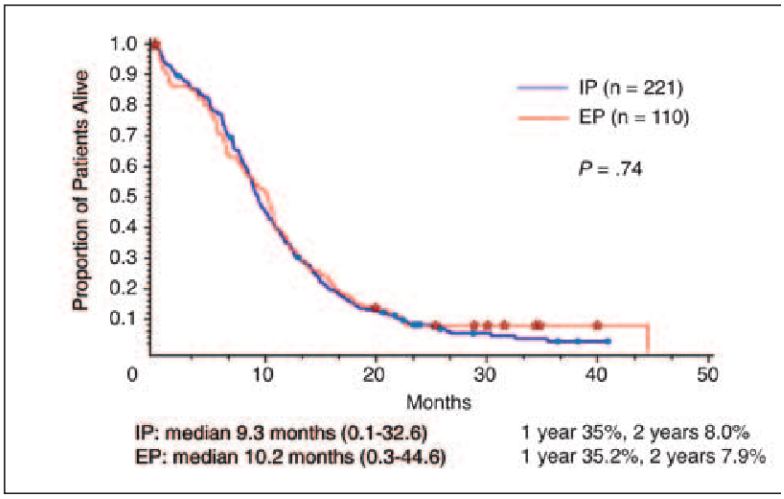


Fig 2. Overall survival. IP, irinotecan/cisplatin; EP, etoposide/cisplatin.

Figure 10: Enrollment, Progressions and Deaths over Time – Control Hazard of Progression of 0.1386 Beyond 9 months

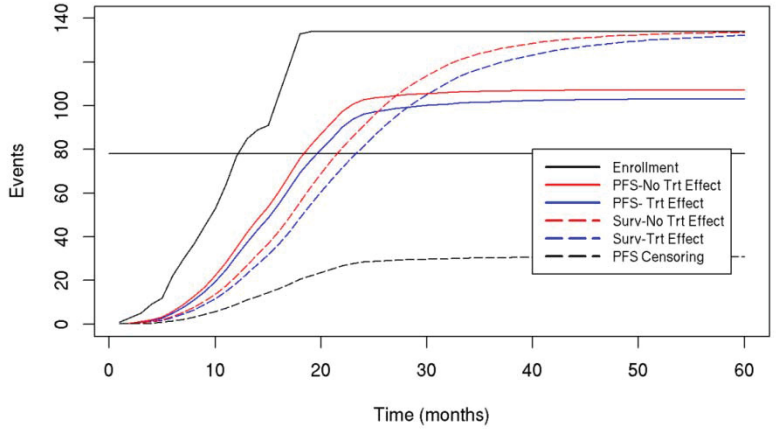


Table 10: Enrollment, Progressions and Deaths over Time – Control Hazard of Progression of 0.1386 beyond 9 months

Study Time (months)	*6*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*
Cum Enrollment	*22*	*77*	*85*	*89*	*91*	*105*	*119*	*133*	*134*	*134*	*134*	*134*	*134*	*134*	*134*	*134*	*134*	*134*	*134*	*134*
Total PFS Events	*5*	*31*	*38*	*43*	*49*	*55*	*62*	*69*	*75*	*80*	*85*	*90*	*94*	*96*	*97*	*98*	*99*	*99*	*100*	*100*
Total PFS Events2	*6*	*35*	*42*	*48*	*54*	*61*	*68*	*76*	*82*	*87*	*92*	*98*	*101*	*103*	*104*	*104*	*105*	*105*	*105*	*106*
Total Deaths	*3*	*19*	*23*	*27*	*32*	*37*	*42*	*49*	*55*	*61*	*66*	*72*	*77*	*81*	*86*	*91*	*95*	*99*	*102*	*105*
Total Deaths2	*4*	*22*	*27*	*32*	*37*	*42*	*49*	*56*	*63*	*69*	*75*	*81*	*86*	*91*	*96*	*100*	*104*	*108*	*111*	*114*
PFS Censor(Trt)	*1*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*15*	*16*	*16*	*16*	*16*	*16*	*16*	*17*
PFS Censor(Ctl)	*1*	*4*	*5*	*6*	*7*	*8*	*9*	*9*	*10*	*11*	*12*	*12*	*13*	*13*	*13*	*13*	*13*	*13*	*13*	*13*

Total PFS Events 2 and Total Deaths 2 refer to the number of progressions and deaths observed when tarextumab does not prolong progression nor death.

We see from *Table 10* that approximately 70 percent of the 98 deaths required for the final analysis of survival will be observed at the time of the final analysis for PFS. Table *11* presents the power to detect a survival benefit for several hazard ratios assuming that type 1 error is controlled *at the 0.15 level and additional analyses* take place at *approximately 50, 67, 83* percent of full information. *These additional analyses will take place at the quarterly DSMB review meetings. If the actual number of events at the review meetings differs from what is presented in the table, the efficacy and safety boundaries will be recalculated using the spending functions footnoted in Table 11.*

Table 11: Power for OS

	Analysis 1	***Analysis 2***	***Analysis 3***	***Final Analysis***
Total Number of Events	*49*	*66*	*81*	*98*
Z-Statistic (reject the null)1	*3.889*	*3.174*	*2.333*	*1.036*
p-value (1-sided)	*0.000050*	*0.00075*	*0.0098*	*0.15*
Z statistic (reject the Alt) 2	*-2.1*	*-1.848*	*-1.511*	*-1.082*
p-value (1-sided)	*0.018*	*0.032*	*0.0658*	*0.139*
Cumulative Type 1 Error (1-sided)	*1e-04*	*8e-04*	*0.0099*	*0.1501*
Cumulative Power				
HR=0.75	*0.002*	*0.0226*	*0.1499*	*0.6511*
HR=0.682	*0.0054*	*0.053*	*0.2711*	*0.8047*
HR=0.60	*0.0178*	*0.1365*	*0.4869*	*0.9324*
HR=0.65	*0.0086*	*0.0777*	*0.3471*	*0.8637*
HR=0.50	*0.0717*	*0.361*	*0.7846*	*0.9918*
Cumulative Probability of Stopping for Harm				
Alt	*3e-04*	*5e-04*	*9e-04*	*0.0019*
Null	*0.0179*	*0.0381*	*0.0744*	*0.1501*
HR=1/0.75 = 1.33	*0.1372*	*0.266*	*0.4332*	*0.647*
HR=1/0.682=1.47	*0.2235*	*0.4037*	*0.6007*	*0.80*
HR=1/0.50 =2.00	*0.6278*	*0.8426*	*0.9496*	*0.9911*

[1]*The boundary for rejecting the null hypothesis for efficacy is obtained from the gamma(-16) alpha spending function*

[2]*The boundary for rejecting the null hypothesis for harm is obtained from the gamma(-4) alpha spending function*

With 98 deaths at the final analysis there is 80 percent power with 0.15 type 1 error to detect a hazard ratio of 0.682. There is a 7.4 percent chance of stopping early for Harm under the null, 43.3 percent chance of stopping early for Harm if the hazard ratio is 1/.75 = 1.33, 60.1 percent chance of stopping early for harm if the hazard ratio is 1/.682 = 1.47, and a 95.0 percent chance of stopping early for harm if the hr = 1/.5 = 2.0.

13.1.3 Randomization and Blinding

For the purpose of randomizing subjects to treatment, each subject's platinum based therapy as well as the the prior use of whole brain radiation or PCI will be collected at screening. A dynamic randomization system will assign subjects to treatment in a way that balances the assignments to tarextumab + Chemo versus Chemo + placebo alone among all subjects in the trial, among all subjects receiving the same platinum based therapy (Carboplatin or Cisplatin), and among subjects who received as well as those who did not receive prior whole brain radiation or PCI.

Investigators, site personnel, subjects, and the sponsor will remain blinded to treatment assignment for the duration of the study until the final analysis of overall survival is completed.

13.1.4 Procedures for Unblinding

All requests for urgent safety unblinding require the approval of the Medical Monitor and may be made by calling either the Medical Monitor directly during business hours or the 24-hour randomization support staff after business hours (contact information will be provided in the Study Reference Manual). The randomization support staff will forward the request to the Medical Monitor. Upon OncoMed's approval, the randomization system will provide the site with the study treatment assignment. No treatment cross-over will be permitted in the study.

13.2 Phase 1b

All reported adverse events will be mapped to standard coding terms using the Medical Dictionary for Regulatory Activities (MedDRA), grouped by system organ class and preferred terms and tabulated by dose groups. The incidence of adverse events at each dose will be tabulated by grade and relationship to study drug. Vital signs and Laboratory markers will also be summarized by dose of study drug using mean changes from baseline. Shift tables for lab markers will be provided for each dose of study drug.

Tumor response will be presented in a subject listing sorted by dose group. Information included in the listing will be Best tumor response, time to progression or death, best percent decrease in sum of longest diameter (SLD) from baseline, and duration of response.

Tumor response in the expansion cohort will also be summarized. Time to Progression or Death and duration of response will be summarized with a Kaplan Meier Curve and related statistics. Best tumor response will be summarized with simple descriptive statistics. The largest percent decrease in SLD will be summarized with a waterfall plot and simple descriptive statistics.

13.3 Phase 2

13.3.1 Subject Populations for Analysis

The Intent-to-Treat (ITT) Population is comprised of all randomized subjects. All baseline characteristics, demographic *and* efficacy data will be analyzed using the ITT Population.

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

The Safety Population is comprised of all subjects who receive at least one partial dose of tarextumab or Placebo and who have at least one post-dosing safety evaluation (labs, vital signs or adverse events). All safety endpoints will be summarized using the Safety Population.

The Pharmacokinetic Population is comprised of all subjects who had at least one follow-up tarextumab blood sample obtained.

The Immunogenicity Population is comprised of all subjects who had a baseline and at least one follow-up anti-*tarextumab* sample obtained.

13.3.2 Analysis Set

The Analysis set for the Phase 2 portion of the study will include all subjects who were randomized in the Phase 2 portion of the trial to receive either tarextumab or control. The Analysis set will not include data from subjects who were enrolled in the Phase 1b portion of the trial. The data cut for the formal final analysis of the study will take place at the point where *91* progression events have occurred or 10 months after the completion of enrollment, whichever occurs first. Note that the analysis time may be extended beyond 10 months for reasons concerning study conduct (e.g. subjects who are randomized and not treated). This will ensure that the study will have *81* percent power to detect a hazard ratio of 0.6*7* (improvement in median PFS from 4.8 months to 7.*2* months) with an associated total one sided type 1 error of *0.15*. The data cut for the final analysis of survival will be 6 months after the data cut for the formal final analysis of the study or when 98 deaths have been observed, whichever occurs first. Once again, the time for the final analysis may be extended beyond 6 months for reasons of study conduct.

13.4 Endpoints

13.4.1 Efficacy Endpoints

Efficacy endpoints will include Investigator-assessed progression-free survival, continuous variable assessment of tumor length, best response, response rate defined as rate of confirmed complete response (CR) + rate of confirmed partial response (PR), duration of response, sites of progression, Land mark survival at 6, 12, 18 and 24 months and overall survival. Efficacy

endpoints will be analyzed using the ITT Population and are described in more detail in the Statistical Methods (Section 13.6).

13.4.2 Safety Endpoints

Safety endpoints will include AEs, SAEs, clinical laboratory assessments, and anti-tarextumab antibody testing. Safety endpoints will be analyzed using the Safety Population for both treatment groups. The purpose of these analyses will be to provide a thorough evaluation of potential safety issues.

Adverse Events

All reported adverse events will be mapped to standard coding terms using the Medical Dictionary for Regulatory Activities (MedDRA), grouped by system organ class and preferred terms and tabulated by treatment groups. The incidence of adverse events in each treatment group will be tabulated by NCI-CTCAE v 4.0.2 grade and relationship to study drug. Adverse events that led to withdrawal and adverse events that were considered serious will be tabulated separately.

Clinical Laboratory Assessments and Vital Signs

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

ECOG

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

13.4.3 Immunogenicity Endpoints

Immunogenicity endpoints will be analyzed using the Immunogenicity Population. The incidence of anti-tarextumab antibody development in each treatment group will be compared with simple proportions. For subjects with a positive result for anti-tarextumab antibody, the incidence of neutralizing capability development will further be summarized by standard quantitative methods. In addition, the impact on safety and efficacy of detectable anti-tarextumab antibodies and neutralizing anti-tarextumab antibodies will be assessed by summarizing PFS and Response rate in the subgroups of subjects with and without these anti tarextumab antibodies. These analyses may not be carried out if the number of subjects with anti-59R5 antibodies does not permit a reasonable estimate of PFS and Response rate.

13.4.4 Pharmacokinetic Endpoints

For subjects enrolled in the Phase *1b* portion of the trial, AUC, clearance, volume of distribution and apparent half life) of tarextumab will be summarized by dose group with descriptive statistics including the mean, variance, median and range.

Pharmacokinetic data obtained from the Phase 1b and Phase 2 portions of the study will be pooled with data from the Phase 1a study (Study 59R5-001) to conduct population PK analysis. Population mean and inter-individual variability of the PK parameters will be reported. Individual PK parameter and exposure will be reported.

13.4.5 Exploratory Endpoints

Changes from baseline in exploratory pharmacodynamic biomarkers, including Notch pathway related genes and proteins and circulating tumor cells following tarextumab treatment will be summarized with simple descriptive statistics. Tests to compare the changes in these variables between the 59R5 arm and the control arm may be undertaken as well on an informal descriptive basis. Surrogacy of changes in these exploratory biomarkers will be evaluated in models for time to progression and response that include these exploratory variables and the randomized treatment assignment. These models may also account for the level of Notch 3 expression.

13.5 Statistical Methods

Other than for the primary efficacy endpoint of PFS, and overall survival, no adjustment will be made for multiplicity. The methods of analyses listed below are described for the intention to treat group of subjects.

13.5.1 Progression-Free Survival

The primary endpoint PFS, based on the Investigator-assessments of tumor response, is defined as the number of days from randomization until death or disease progression as defined by RECIST criteria for the ITT Population. The Kaplan-Meier method will be used to estimate the proportion of subjects without progression or death overtime and the median progression-free survival time. The 95% confidence intervals for median progression-free survival time will also be calculated for each treatment arm. The p-value for treatment effect will be generated using a stratified Log-Rank test. The stratification factors will be platinum choice (cisplatin versus carboplatin) and the prior use of whole brain radiation or PCI. . Subjects who have not experienced death or progression by their last contact will be censored at the time of their last radiographic response assessment and the number and percentage of these subjects will be displayed. In addition subjects who receive non protocol anti-cancer therapy will be censored at the time they start this treatment. Surgical resection of tumor, palliative radiation (prophylactic cranial irradiation, according to standard of care, is permitted for subjects who are without progression following 6 cycles of EP treatment, subjects may have prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry) and/or a new systemic anti-cancer therapy will be considered non protocol therapy. Initiation of a new intravenous bisphosphonate or denosumab more than 30 days after the first administration of study drug will be also considered non protocol therapy.

Formal testing for determining whether tarextumab has an impact of PFS will be carried out as described in *Table 7*. If there is a disparity in discontinuation rates between treatment arms or in the types of censoring or in the use of non protocol therapy, sensitivity analyses will be performed to assess the impact.

In addition, for subjects who died or progressed after an extended lost-to-follow-up period (greater than 17 weeks from the previous assessment), PFS will be right censored at the date of the last adequate assessment prior to the lost to follow-up period. Subjects who do not have any tumor assessments will be treated as censored at Day 1.

PFS will also be summarized for the subset of subjects who received cisplatin and separately for the subset of subjects who received carboplatin.

Continuous Variable Assessment of Tumor Length

The tumor length will be calculated as the sum of the longest diameters for the target lesions (as defined by RECIST 1.1 criteria). The data will be displayed graphically with waterfall plots. Summary statistics including mean, standard deviation, median, minimum, and maximum for tumor length will be presented for baseline, 6 weeks post-baseline, and 12 weeks post-baseline. These summary statistics will also be presented for differences from baseline at 6 and 12 weeks post-baseline for each arm of the study. Along with the summary statistics, the 95% confidence intervals of the mean tumor length for each treatment arm at each of the three timepoints will also be displayed. An ANCOVA model will be used to test the hypothesis that there is no

difference between treatment arms with regard to changes from baseline tumor length at scheduled tumor assessments. Choice of platinum therapy (cisplatin versus carboplatin) and prior use of WBRT or PCI will be factors in the model and baseline tumor length will be used as a covariate. Missing values will not be imputed.

In the event that the parametric assumptions are not met, the p-value will be generated using a nonparametric test utilizing ranks. This nonparametric test will be performed at scheduled tumor assessments, using the log of (tumor length at week t divided by tumor length at baseline) as the endpoint. In the case of complete response when the outcome variable is undefined, the best possible rank will be assigned. In the case of death or withdrawal due to adverse event, the worst possible rank will be assigned.

The rate of change in tumor volume at progression (SLD at progression – SLD at nadir)/SLD at nadir will be compared between the two arms of the study. The rate of change in tumor burden has been shown to be predictive of survival (Ref 15, and Ref 16). In addition the rate of change in tumor volume from baseline to the first tumor assessment (SLD first scheduled post baseline tumor assessment – SLD baseline)/(SLD baseline) will be compared between the two arms of the study. The comparison will be made to test the difference in the growth rate in the tarextumab arm versus control arm.

13.5.2 Response Rate (Best Overall Response)

The best overall response is defined as the best Investigator-assessed response recorded from the start of the treatment until disease progression in the following order of importance:

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

The number and proportion of subjects achieving each of these categories of response will be summarized for each dose group. The best overall response rate is the number of subjects whose best response is either a CR or PR divided by the number of subjects randomized to the respective arms. The confirmed response rate is the number of subjects per treatment arm who have either a confirmed CR or confirmed PR (according to RECIST criteria) divided by the number of subjects randomized to the respective arms. These proportions and their 95% confidence intervals will be displayed. The p-value for equality between treatment arms will be calculated for the two groups using a logistic regression model with treatment, type of platinum based therapy, and prior use of WBRT or PCI as factors in the model. Subjects without any tumor assessments will be counted as a non responder.

13.5.3 Duration of Response

The Investigator-assessed duration of response is defined as the time from the first partial or complete response to the time of death or disease progression for subjects with a confirmed response. The Kaplan-Meier method will be used to estimate the duration of response. The 95% confidence intervals for duration of response will also be calculated for each treatment arm. The p-value for treatment effect will be generated using a Cox proportional hazards model. Subjects who have not experienced death or progression by their last contact will be censored at the time of their last radiographic response assessment. If the number of responses is not sufficient to produce interpretable KM curves, the analysis of duration of response may not be undertaken.

Sites of Progression

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

13.5.4 Overall Survival

A comparison of the overall survival for the two groups will be performed. Overall survival is defined as the number of days from randomization until death occurs. No treatment cross-over is permitted in the study. The Kaplan-Meier method will be used to estimate both the survival curves and the median survival time. The 95% confidence intervals for median survival times will also be calculated. A p-value for treatment effect will also be generated using a stratified Cox proportional hazards model. The stratification factors will be type of platinum based therapy and the prior use of whole brain radiation or PCI. Subjects who have not experienced death by their last contact date will be censored at that time and the number and percentage of these subjects will be displayed. Subjects will not be censored for OS if they start non-protocol therapy. If there is a disparity in discontinuation rates between treatment arms, a sensitivity analysis will be performed to assess the impact.

Survival will also be summarized for the subset of subjects who received cisplatin and separately for the subset of subjects who received carboplatin.

13.5.5 Landmark Survival

The Kaplan Meier estimates of survival at 6, 12, 18 and 24 months will be compared between the two arms using a simple Z test.

13.5.6 Correlation of Biomarkers with Efficacy Endpoints

The impact of the biomarkers Notch3, Hes1, Hey2, Hey1 and Hes6 on the treatment effect as measured by PFS and OS will be evaluated with a Cox Proportional Hazards regression model with treatment, biomarker and treatment by biomarker interaction included in the model as independent variables. The impact of these biomarkers will also be assessed on the treatment effect for 12 month OS and ORR using a logistic regression model with treatment, biomarker and treatment by biomarker interaction included in the model.

13.6 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be analyzed using the Intent-to-Treat Population for both treatment arms. Quantitative and/or categorical summaries will be presented for demographics and other baseline characteristics. For continuous variables, data will be summarized by sample size, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized as frequency counts and percentages.

13.7 Treatment Exposure

Treatment exposure will be summarized as duration on treatment and extent of exposure to Cisplatin, Carboplatin, Etoposide, tarextumab, and Placebo by treatment arm. Duration on treatment will be summarized quantitatively by number of doses and duration in days using mean, standard deviation, median, minimum, and maximum.

Measures of extent of exposure include the cumulative dose per subject, dose intensity and compliance. Dose intensity is defined as the total dose the subject actually received divided by the total dose the subject would have received had there been no dose delays and no dose reductions. Compliance will be summarized as the number of subjects who had dose(s) withheld or delayed. A table summarizing the number of subjects with 0%, 20%, 40%, 60%, 80%, and 100% compliance will also be presented. The reasons for dose(s) withheld or delayed will also be summarized.

13.8 Termination Criteria

Enrollment will terminate when approximately 135 subjects have been randomized. All ongoing subjects will continue to be dosed until disease progression, unacceptable toxicity, subject withdrawal, or the Investigator withdraws subjects from the study.

13.9 Deviation Reporting

The following protocol deviations will be recorded and summarized by treatment arm in the final report:

1. enrollment violations
2. dosing violations
3. concomitant therapy violations
4. continuation of therapy when treatment should have been discontinued

13.10 Data Safety Monitory Board

A Data Safety Monitoring Board (DSMB) will review data on an ongoing basis in Phase 2 portion of the study to ensure subject safety. Specifically, they will review partially blinded demographic, dosing and safety data at the following timepoints: 1) after 10 subjects have been randomized and all subjects have received at least *2* doses of tarextumab or Placebo, 2) after 25 subjects have been randomized and all subjects have received *2* doses of tarextumab or Placebo, and 3) quarterly thereafter. The DSMB will consist of at least two Oncologists and a statistician who are not otherwise participating in the conduct of the trial. A separate unblinded and independent statistician designated by OncoMed will prepare summary tables and listings summarizing results for all subjects.. The rules/details of presentations to the DSMB will be summarized in the DSMB Charter.

13.11 Analysis of PFS and OS Prior to the Final Analysis

Two analyses for PFS are planned beyond the DSMB Safety Reviews detailed in Section 13.10. These analyses will take place at the quarterly meetings of the DSMB and be initiated in May 2016. As noted above in Table 7 and Table 11, a gamma(-12)spending function will be used to control the type 1 error for the assessment of efficacy and a gamma(-4) spending function will be used to control the type 1 error for the assessment of harm arising from the multiple analysis over time of PFS and overall survival. The final analysis for pfs will occur when 91 progression events have occurred while the final analysis for OS will occur when 98 deaths have been observed

13.12 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

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

14.0 ETHICAL CONSIDERATIONS

This study will be conducted according to international standards of Good Clinical Practice (ICH guidance E6), all federal, state, and local regulations as well as with the requirements of the appropriate Institutional Review Board or Ethics Committee and any other institutional requirements.

15.0 INVESTIGATOR REQUIREMENTS

15.1 Informed Consent

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

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

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

15.2 Institutional Review Board/Ethics Committee Approval

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

The Principal Investigator is responsible for keeping the IRB or IEC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate. The IRB or IEC must be updated at least once a year or in accordance with local requirements. The Principal Investigator must also inform the IRB or IEC of any significant adverse events.

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

15.3 Study Monitoring

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

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

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

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

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

15.4 Auditing Procedures

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

15.5 Data Collection

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

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

15.6 Investigational Medicinal Product Accountability

The tarextumab and Placebo required for completion of this study will be provided by OncoMed or its agent. The recipient will acknowledge receipt of this IMP by completing the Drug Request/ Acknowledgment of Receipt Form and faxing it to OncoMed or its representative in Phase 1b portion of the study and by completing the corresponding information in Interactive Web-based randomization system (IWRS) *in Phase 2 portion of the study.* Damaged supplies will be replaced.

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

Sites will destroy all used and/or partially used vials. If the site does not have the capacity to destroy IMP, the used/partially used vials should be returned to the drug distribution center for destruction along with a completed Drug Return Form.

Sites will destroy all unopened, unused, and expired vials per the site's institutional guidelines after approval by OncoMed or designee. Site may also return the remaining IMP to the drug distribution center along with a completed Drug Return Form.

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

15.7 Disclosure of Data and Publication

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

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

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

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

15.8 Retention of Records

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

16.0 REFERENCES

1. D'Angelo SP, Pietanza MC. The molecular pathogenesis of small cell lung cancer. Cancer Biology & Therapy 2010;10 (1):1-10.

2. Puglisi M, Dolly S, Faria A, Myerson JS, Popat S, O'Brien MER. Treatment options for small cell lung cancer – do we have more choice? British Journal of Cancer 2010;102:629-638.

3. Clarke MF, Fuller M. Stem Cells and Cancer: Two Faces of Eve. Cell 2006;124:1111-1115.

4. Wicha MS, Liu S, Dontu G. Cancer Stem Cells: An Old Idea – A Paradigm Shift. Cancer Research 2006;66:1883-1890.

5. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 2006; 444:756-760.

6. Dylla SJ, Beviglia L, Park IK, Chartier C, Raval J, Ngan L, et al. Colorectal Cancer Stem Cells Are Enriched in Xenogeneic Tumors Following Chemotherapy. PloS ONE 2008;3(6):1-13.

7. Rosen JM, Jordan CT. The Increasing Complexity of the Cancer Stem Cell Paradigm. Science 2009;324:1670-1673.

8. Takebe N, Harris PJ, Warren RQ, Ivy SP. Targeting cancer stem cells by inhibiting Wnt, Notch, and Hedgehog pathways. Nature Clinical Oncology 2011; 8:97-106.

9. Daniel VC, Marchionni L, Hierman JS, Rhodes JT, Devereux WL, Rudin CM, et al.A Primary Xenograft Model of Small_Cell Lung Cancer Reveals Irreversible Changes in Gene Expression Imposed by Culture In vitro. Cancer Research 2009;69(8):3364-3373.

10. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. New England Journal of Medicine 2002;346(2): 85-91.

11. Foster N, Mandrekar S, Schild S, Nelson G, Rowland K, et al. Prognostic Factors Differ by Tumor Stage for Small Cell Lung Cancer. Cancer 2009;115:2721-31.

12. Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

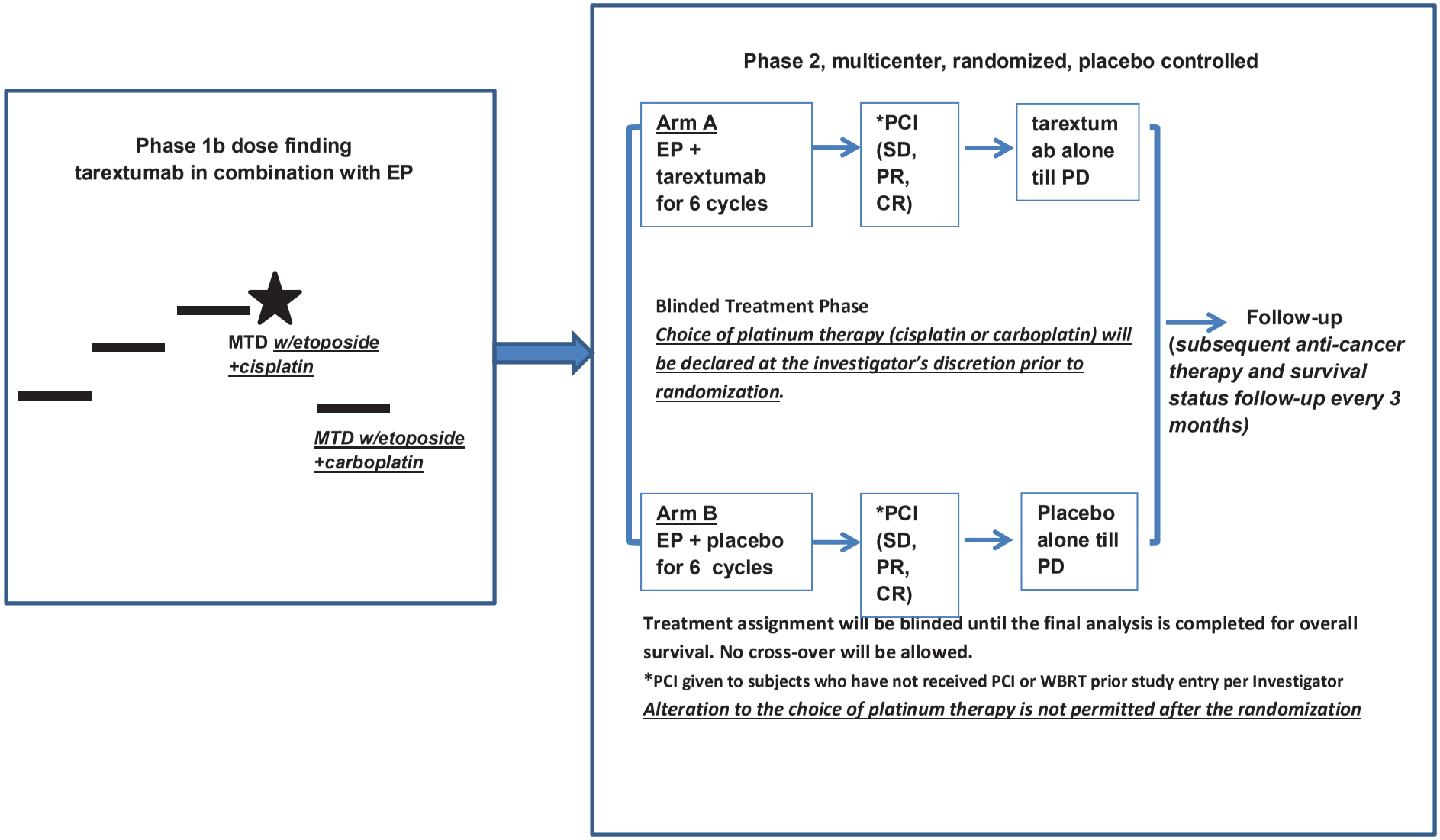
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009:45:228–47.

14. Hanna N, Bunn PA Jr., Langer C, Einhorn L, Guthrie T Jr., Beck T, et al. Randomized Phase III Trial Comparing Irinotecan/Cisplatin With Etoposide/Cisplatin in Patients With Previously Untreated Extensive-Stage Disease Small-Cell Lung Cancer; J Clin Oncol 2006;24(13):2038-43.

15. Claret L, Girard P, Hoff PM, Van Cutsem E, Zuideveld KP, Jorga K, et al. Model-Based Prediction of Phase III Overall Survival in Colorectal Cancer on the Basis of Phase II Tumor Dynamics. J. Clin. Oncol. 27:4103-8 2009.

16. Claret L, Gupta M, Han K, Joshi A, Sarapa N, He J, et al. Evaluation of Tumor-Size Response Metrics to Predict Overall Survival in Western and Chinese Patients With First-Line Metastatic Colorectal Cancer. J. Clin. Oncol. 31:2110-14, 2013

APPENDIX A: STUDY SCHEMA



APPENDIX B: SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 1B

Procedure	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
	Day -28 to -1	Day-14 to -1	Day 1 (±1 day)	Day 2	Day 3	Day 8 (Cycles 1-3 only)	Post Cycle 6	Day 1(± 1 day)	Treatment Termination[a]	Every 3 months
Informed Consent	X									
Medical and oncology history	X									
Physical examination[c]		X	X[d]					X	X	
Weight, vital signs, height[e]		X	X	X	X			X	X	
ECOG performance status		X	X[d]					X	X	
Electrocardiogram		X	X[d]						X	
Hematology[f]		X	X[d]			X		X	X	
Serum chemistry[g]		X	X[d]					X	X	
Coagulation (PT/INR, aPTT)		X	X[d]					X	X	
Urinalysis (dip stick sufficient)		X	X[d]					X	X	
Serum pregnancy test (childbearing potential only)		X								

APPENDIX B: SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 1B (CONT'D)

Procedure	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
	Day -28 to -1	Day-14 to -1	Day 1 (±1 day)	Day 2	Day 3	Day 8 (Cycles 1-3 only)	Post Cycle 6	Day 1(± 1 day)	Treatment Termination[a]	Every 3 months
Pharmacokinetics[h]			X[h] (C1/C3)		X[h] (C1/C3)	X[h] (C1/C3)			X[h]	
Anti-tarextumab[i]			X[i] (C1/C4)					X[i]	X[i]	
Blood for biomarkers[j]			X[j] (C1)	X[j] (C2/C3)		X[j] (C1/C2/C3)			X[j]	
Hair for biomarkers[k]			X[k]			X[k] (C2)				
Blood for pharmaco-genomics			X[l]							
FFPE tissue[m]	X									
Optional tumor biopsy[n]	X					X[n] (C2)			X[n]	
Contrast CT, or MRI (chest, abdomen, and pelvis), brain MRI/CT with contrast[o]	X		X[o] (C3/C5)					X[o]	X[o]	Every 6 weeks[p]
Bone Scan	X		*As clinically indicated*							

APPENDIX B: SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 1B (CONT'D)

Procedure	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)	Treatment Termination[a]	
	Day -28 to -1	Day-14 to -1	Day 1 (±1 day)	Day 2	Day 3	Day 8 (Cycles 1-3 only)	Post Cycle 6	Day 1(± 1 day)		Every 3 months
Concomitant medications	X	X	X	X	X	X		X	X	
Adverse events			X	X	X	X		X	X	
Survival Follow-up										X
Subsequent anti-cancer therapies										X
Etoposide administration			X	X	X					
Platinum therapy administration			X							
tarextumab Infusion			X					X		
Prophylactic cranial irradiation (PCI)							X[q]			

NOTES TO APPENDIX B:

a. Approximately 4 weeks after the last study drug, or etoposide or platinum therapy, whichever is discontinued last, but before the initiation of a new anti-cancer therapy

b. All Subjects will be followed for survival and subsequent anti-cancer therapy information after the treatment termination unless a subject requests to be withdrawn from study survival follow-up. Survival follow-up and subsequent anti-cancer therapy information will be collected during telephone calls, through subjects' medical records, and/or at clinic visit every 3 months until death, loss to follow-up or study termination by the sponsor.

c. Full physical examination at screening and treatment termination only. At all other times, targeted physical examination will be done at the Investigator's discretion.

d. The assessment does not need to be repeated if it was done within 7 days prior to the first dose

e. Height required at screening only. Vital signs and weight: screening, day 1 of each cycle prior to the start of study drug dosing, days 2 and 3 prior to etoposide administration during Cycles 1 through 6 and treatment termination.

f. Hematology includes complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count. The results need to be reviewed by the Investigator prior to each study drug and EP administration. Hematology on Day 1 of each cycle starting from Cycle 2 can be performed up to 3 days prior to Day 1 dosing.

g. Full chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, albumin, calcium, phosphorus, and magnesium. Chemistry on Day 1 of each cycle starting from Cycle 2 can be performed up to 3 days prior to Day 1 dosing.

h. Plasma samples will be obtained for tarextumab pharmacokinetic analysis at pre-dose and 5 minutes (±2 minutes) after the end of tarextumab infusion and prior to the EP administration on Day 1 of Cycle 1 and Cycle 3, and on Days 3 (pre-dose) and 8 of Cycles 1 and 3, at other times as clinically indicated such as when significant toxicities occur, as well as at treatment termination. On days when tarextumab and etoposide and/or platinum therapy are given together, the plasma sample should be obtained 5 minutes (±2 minutes) after the completion of the infusion of tarextumab, but prior to EP administration.

i. Serum samples will be obtained for anti-tarextumab pre-dose on Day 1 of every three cycles starting from Cycle 1, at other times as clinically indicated such as when significant toxicities occur, and at the Treatment Termination visit.

j. A pre-dose sample of a total of 19 mL of blood will be drawn on Day 1 of Cycle 1(pre-dose), on Day 2 of Cycles 2 and 3, and on Day 8 of Cycles 1-3 for subjects continuing on tarextumab to evaluate changes in plasma proteins (4 mL) (e.g., EGFR, PLGF, ENA-78, etc.), CTCs (10 mL), and Notch-related gene expression of mRNA (5 mL) as described in Section 10.0. A sample will also be obtained at the time of treatment termination, unless one has been obtained during the prior 14 days. A pre-dose sample of blood will be drawn on Day 1 of Cycle 4 and 5 to explore effects of treatment on CTCs. Instructions for the collection, handling, storage, and shipment are provided in the Study Reference Binder.

NOTES TO APPENDIX B: (Cont'd)

k. Hair follicle mRNA expression: Predose hair samples (6 hairs) will be collected at Day 1 of Cycle 1 (pre-dose) and on Day 8 of Cycle 2 only for gene expression analysis of Notch pathway–related gene expression as described in Section 11.0. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder.

l. Only on Day 1 of Cycle 1 prior to tarextumab infusion from subjects who have signed separate pharmacogenomics Informed Consent Form.

m. FFPE tumor specimens obtained will be collected. Notch3 expression levels will be assessed in FFPE tumor specimens, either archived or fresh core needle biopsied at study entry (two FFPE cores preferred whenever possible). FFPE samples must be obtained during screening. Notch3 levels will be measured by immunohistochemistry and/or a quantitative PCR gene expression assay. Notch 2 and other Notch-related genes and proteins may also be measured. In addition, DNA testing may be performed on the FFPE tumor specimens for subjects who sign the optional FFPE Informed Consent for DNA testing. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder.

n. Optional tumor biopsy will be done at screening, on Day 8 of Cycle 2, and at the time of treatment termination, if feasible. The site can call the Sponsor's medical monitor to discuss an alternative timepoint if it is not feasible to collect the optional tumor biopsy on Day 8 (±2) of Cycle 2.

o. Contrast CT of chest, abdomen and pelvis, and brain MRI/CT with contrast will be performed at screening. Contrast CT of chest, abdomen and pelvis will be performed every 6 weeks (±5 days) after initial study drug dosing (prior to the start of Cycle 3 and every 6 weeks±5 days thereafter). MRI can be used in lieu of contrast-enhanced CT for subjects who are allergic to contrast. The same methodology should be used throughout the study to follow the same lesion.

p. Subjects who have not demonstrated disease progression will have contrast CT of chest, pelvis and abdomen (or MRI for subjects who are allergic to contrast), conducted every 6 weeks (± 5 days) after initial study drug dosing until disease progression or initiation of new anti-cancer therapy. The same methodology should be used throughout the study.

q. After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. tarextumab administration should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume tarextumab alone ≥ 14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (APPENDIX A). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

APPENDIX C SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 2

Procedure	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
	Day -28 to -1	Day-14 to -1	Day 1 (± 1 day)	Day 2	Day 3	Day 8 (Cycles 1-3 only)	Post Cycle 6	Day 1(± 1 day)	Treatment Termination[a]	Every 3 months
Informed Consent	X									
Medical and oncology history	X									
Physical examination[c]		X	X[d]					X	X	
Weight, vital signs, height[e]		X	X	X	X			X	X	
ECOG performance status		X	X[d]					X	X	
Electrocardiogram		X	X[d]						X	
Hematology[f]		X	X[d]			X		X	X	
Chemistry[g]		X	X[d]					X	X	
Coagulation (PT/INR, aPTT)		X	X[d]					X	X	
Urinalysis (dip stick sufficient)		X	X[d]					X	X	
Serum pregnancy test (childbearing potential only)		X								
Anti-tarextumab[h]			X[h] (C1/C3/C5)					X[h]	X[h]	

APPENDIX C SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 2 (CONT'D)

Procedure	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
	Day -28 to -1	Day-14 to -1	Day 1 (± 1 day)	Day 2	Day 3	Day 8 (Cycles 1-3 only)	Post Cycle 6	Day 1 (± 1 day)	Treatment Termination[a]	Every 3 months
Pharmacokinetics[l]			X[l] (C1/C3/C5)		X[l] (C1/C3/C5)	X[l] (C1/C3)		X[l]	X[l]	
Blood for biomarkers[i]			X[i] (C1)	X[i] (C2/C3)		X[i] (C1/C2/C3)			X	
Blood for pharmaco-genomics			X[j]							
FFPE tissue[k]	X									
Tumor *biomarker* testing	X									
Optional tumor biopsy[m]	X					X[m] (C2)			X	
Contrast CT or MRI (chest, abdomen, and pelvis), brain MRI/CT with contrast[n]	X		X[n] (C3/C5)					X[n]	X[n]	Every 6 weeks[o]
Bone Scan	X		as clinically indicated							
Concomitant medications	X	X	X	X	X	X		X	X	
Adverse events			X	X	X	X		X	X	
Survival Follow-up										X

APPENDIX C SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 2 (CONT'D)

Procedure	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
	Day -28 to -1	Day-14 to -1	Day 1 (± 1 day)	Day 2	Day 3	Day 8 (Cycles 1-3 only)	Post Cycle 6	Day 1 (± 1 day)	Treatment Termination[a]	Every 3 months
Subsequent anti-cancer therapies										X
Etoposide administration			X	X	X					
Platinum therapy administration			X							
Study Drug Infusion (tarextumab or Placebo)			X					X		
Prophylactic cranial irradiation (PCI)[p]							X[p]			

NOTES TO APPENDIX C:

a. Approximately 4 weeks after the last study drug, or etoposide or platinum therapy, whichever is discontinued last, but before the initiation of a new anti-cancer therapy
b. All Subjects will be followed for survival and subsequent anti-cancer therapy information after the treatment termination unless a subject requests to be withdrawn from study survival follow-up. Survival follow-up and subsequent anti-cancer therapy information will be collected during telephone calls, through subjects' medical records, and/or at clinic visit every 3 months until death, loss to follow-up or study termination by the sponsor.
c. Full physical examination at screening and treatment termination only. At all other times, targeted physical examination, at the Investigator's discretion.
d. The assessment does not need to be repeated if it was done within 7 days prior to the first dose.
e. Height required at screening only. Vital signs and weight: screening, day 1 of each cycle prior to the start of the treatment, days 2 and 3 prior to etoposide administration from Cycles 1 thru 6, and treatment termination.
f. Hematology includes complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count. The results need to be reviewed by the Investigator prior to each study drug administration. Hematology on day 1 of each cycle starting from Cycle 2 can be performed up to 3 days prior to Day 1 dosing.
g. Full chemistry (serum or plasma) includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, albumin, calcium, phosphorus, and magnesium. Chemistry on Day 1 of each cycle starting from Cycle 2 can be performed up to 3 days prior to Day 1 dosing.
h. Serum samples will be obtained for anti-tarextumab pre-dose on Day 1 of every other cycle starting from Cycle 1, at other times as clinically indicated such as when significant toxicities occur and at the Treatment Termination visit.
i. A pre-dose sample of a total of 19 mL of blood will be drawn on Day 1 of Cycle 1 (pre-dose), on Day 2 of Cycles 2 and 3, and on Day 8 of Cycles 1-3 for subjects continuing on tarextumab to evaluate changes in plasma proteins (4 mL) (e.g., EGFR, PLGF, ENA-78, etc.), CTCs (10 mL), and Notch-related gene expression of mRNA (5 mL) as described in Section 10.0. A sample will also be obtained at the time of treatment termination, unless one has been obtained during the prior 14 days. A pre-dose sample of blood will be drawn on Day 1 of Cycle 4 and 5 to explore effects of treatment on CTCs. Instructions for the collection, handling, storage, and shipment are provided in the Study Reference Binder.
j. Only on Day 1 of Cycle 1 prior to tarextumab infusion from subjects who have signed separate pharmacogenomics Informed Consent Form.
k. FFPE tumor specimens obtained will be collected. Notch3, *Hes1, Hey1, Hey2, and Hes6* expression levels will be assessed in FFPE tumor specimens, either archived or fresh core needle biopsied at study entry (two FFPE cores preferred whenever possible). FFPE samples must be obtained during screening. Notch3, *Hes1, Hey1, Hey2, and Hes6* levels will be measured by immunohistochemistry and/or a gene expression assays. Notch 2 and other Notch-related genes and proteins may also be measured. In addition, DNA testing may be performed on the FFPE tumor specimens for subjects who sign the optional FFPE Informed Consent for DNA testing. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder.
l. Plasma samples will be obtained for tarextumab pharmacokinetic analysis at on Day 1 of Cycles 1 and 3, at pre-dose and 5 minutes (±2 minutes) post tarextumab infusion; Day 3 of Cycle 1 and Cycle 3 prior to etoposide administration; Day 8 of Cycle 1 and Cycle 3 when blood sample is taken for biomarker evaluation; Day 1 of every other cycle starting from Cycle 5 prior to study drug infusion and, at other times as clinically indicated such as when significant toxicities occur as well as at the time of treatment termination. On days when tarextumab and etoposide and/or platinum therapy are given together, the plasma sample should be obtained 5 minutes (±2 minutes) after the completion of the infusion of tarextumab, but prior to EP administration.

NOTES TO APPENDIX C: (Cont'd)

m. Optional tumor biopsy will be done at screening, on Day 8 of Cycle 2, and at the time of treatment termination, if feasible. The site can call the Sponsor's medical monitor to discuss an alternative timepoint if it is not feasible to collect the optional tumor biopsy on Day 8 (±2) of Cycle 2.

n. Contrast CT of chest, abdomen and pelvis, and MRI of brain will be performed at screening. During the study, contrast CT of chest, abdomen and pelvis will be performed every 6 week s ± 5 days) after initial study drug dosing (prior to the start of Cycle 3 and every two cycles thereafter). MRI can be used in lieu of contrast-enhanced CT for subjects who are allergic to contrast. The same methodology should be used throughout the study to follow the same lesion.

o. Subjects who have not demonstrated disease progression will have contrast CT of chest, abdomen and pelvis (or MRI for subjects who are allergic to contrast), conducted every 6 weeks (±5 days) after initial study drug dosing until disease progression or initiation of new anti-cancer therapy. The same methodology should be used throughout the study.

p. After the completion of 6 cycles of EP, subjects who do not have disease progression and have not had prophylactic cranial irradiation (PCI) or whole brain radiation (WBRT) prior to study entry and are good candidates for PCI per the Investigators should receive PCI within 8 weeks after the last dose of chemotherapy at a total dose of 25 Gy in 10 fractions. If subjects discontinue EP with treatment-related toxicities prior to completing 6 cycles and are good candidates for PCI per the Investigators, PCI can be initiated at the time that is determined appropriated per the Investigator. Subjects who do not receive PCI within 8 weeks after the last dose of chemotherapy can have PCI later during the study as determined by the Investigator. Study drug administration (tarextumab or Placebo) should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI. PCI should not be initiated within 2 weeks of study drug administration and study drug will be held during the PCI treatment period. Subjects will resume study drug alone (tarextumab or Placebo) ≥ 14 days after completion of PCI, until disease progression or unacceptable treatment-related toxicities or withdrawal of consent (APPENDIX A Study Schema). Subjects will discontinue study treatment if there is evidence of central nervous system (CNS) metastasis.

APPENDIX D: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale (Ref 12)	
Grade	**Descriptions**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX E: RECIST CRITERIA 1.1

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

ELIGIBILITY

Subjects must have measurable disease at baseline to be eligible for the Phase 2 portion of the study.

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

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

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

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

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

Bone lesions:

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

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

Blastic bone lesions are non-measurable.

Cystic lesions:

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

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

Lesions with prior local treatment:

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

Measurement of Lesions

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

Methods of Measurement

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

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

- CT is currently the best currently available and reproducible method to measure target lesions selected for response assessment. The CT scan slice thickness should be 5 mm or less. When the CT scans have a slice thickness that is greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. Please see Ref 13 for more details concerning the use of CT scan and MRI.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

RESPONSE CRITERIA

Evaluation of Target Lesions

*Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph node (whether target or 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. The appearance of one or more new lesions is also considered progression.
*Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

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

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

Evaluation of Overall Response

The overall response is assessed according to the following table.

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

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Confirmation

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

REPORTING OF RESULTS

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

APPENDIX F: SAMPLE INFORMED CONSENT – PHASE 1B

PROTOCOL 59R5-003: A Phase 1b/2 Study of Taretumab (OMP-59R5) in Combination with Etoposide and Platinum Therapy in Subjects with Untreated Extensive Stage Small Cell Lung Cancer

Principal Investigator: _____

Before you decide whether or not to take part in this research study, it is important for you to understand the purpose of the study, what risks may be involved, and what is expected of you during the study. Your participation in this study is entirely voluntary. If you have any questions that are not answered or if there are words that you do not understand in this consent form, your study doctor will give you more information. Once you understand the purpose of this study, and if you decide to volunteer to participate in the study, you will be asked to sign this consent form. Once you sign the consent form, you will be referred to as a "subject".

PURPOSE AND BACKGROUND

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

The study drug, tarextumab (OMP-59R5), used in this study is experimental. That means the United States Food and Drug Administration (FDA) has not approved it for use by the general public. Tarextumab is a humanized monoclonal antibody and was developed to target cancer stem cells. Tarextumab may block the growth of cancer stem cells, the remaining tumor cells. The sponsor for this study is OncoMed Pharmaceuticals.

The research study consists of two portions and you will participate in the first portion. The purpose of the first portion is to test the safety and to determine the highest tolerable dose of tarextumab, when given in combination with etoposide and cisplatin or carboplatin. Cisplatin and carboplatin both contain platinum (called platinum therapy). Cisplatin and carboplatin have similar anti-tumor activities, but with slightly different side effects. Etoposide and platinum therapy (either cisplatin or carboplatin) are a standard treatment for extensive small cell lung cancer. The purpose of the second portion is to test if tarextumab, when given in combination with etoposide and platinum therapy (cisplatin or carboplatin), is able to slow tumor growth in subjects with extensive small cell lung cancer or shrink tumors in subjects with extensive small cell lung cancer.

You have been asked to participate in this research study because you have small cell lung cancer that has spread to other parts of your body and you have not been treated for this disease, and your doctor feels that etoposide and platinum therapy (cisplatin or carboplatin) in combination with tarextumab, may be a treatment option for you.

Although tarextumab has been given to cancer patients, it has not been given in combination with etoposide and platinum therapy (cisplatin or carboplatin). It is not known if it will provide any benefit to you and may cause harmful side effects.

PROCEDURES

The first portion of the study will include approximately 40 subjects at about 12 centers in the United States.

During the first portion of the study, initially all subjects will receive tarextumab intravenously (through vein) on Day 1, etoposide 100mg/m^2 on Days 1, 2 and 3, and cisplatin 80 mg/m^2 on Day 1 of every 21-day cycle for 6 cycles. After 6 cycles, subjects will continue on tarextumab only on Day 1 of every 21-day cycle. A group of 3 to 6 subjects will be treated at each tarextumab dose with etoposide and cisplatin, until the highest tolerable dose of tarextumab is reached. Once the highest tolerable dose is determined for tarextumab in combination with etoposide and cisplatin, a group of 6 subjects will be entered into the study to receive the highest tolerable dose of tarextumab in combination with etoposide and carboplatin to confirm the tolerability of the highest tolerable dose in combination with etoposide and carboplatin.

When the first portion is completed, the study will then proceed to the second portion. The study participation consists of the following periods:

- Screening
- Treatment: If you participate in the first portion of the study before the highest tolerable dose is determined, you will receive tarextumab with etoposide and cisplatin for 6 cycles followed by treatment with tarextumab alone. If you are entered into the first portion of the study after the highest tolerable dose is determined, you will receive tarextumab with etoposide and carboplatin. If you participate in the second portion of the study, you may receive either tarextumab with etoposide and cisplatin or carboplatin, or Placebo with etoposide and cisplatin or carboplatin for 6 cycles followed by treatment with tarextumab alone. This period may last until you experience severe side effects or your tumor has grown or spread or you have decided to stop the treatment.
- Treatment termination: This visit will occur approximately 4 weeks after your last dose of study drug, etoposide, or cisplatin/carboplatin, whichever you discontinue the last, but prior to the start of new anti-cancer therapy that your doctor has chosen for you.

- Follow-up: You will be followed about every three months to check on your health status and the new type of cancer therapy you are receiving. This may be done by phone or a clinic visit.

SCREENING

If you decide to be in this study and you sign this informed consent form, you will be asked to complete the procedures listed below at a screening visit within 28 days before your first dose of study drug to make sure that you are a suitable candidate.

Informed Consent: You will read, confirm understanding, and sign this informed consent. No study-related tests will be performed prior to signing this informed consent form.

Medical History: Your doctor and/or nurse will ask you questions about your past and current health and medication use.

Physical Examination: Your doctor will examine you. Your blood pressure, temperature, heart rate, rate of breathing, height, and weight will also be measured.

Electrocardiogram (ECG): You will have an ECG. An ECG traces the electrical activity of the heart. It is a non-invasive test and requires no needles.

Blood and Urine Sample Collection: Blood will be taken from a vein in your arm using a needle. The blood (about 1 tablespoon) and a urine sample will be used to check your general health and, if you are a female who is able to get pregnant, to make sure that you are not pregnant.

Tumor tissues: If you had your tumor tissue biopsied previously and your doctor still has some of that tissue available, you will be asked to allow your doctor to send some of that tissue for testing for this study. If you don't have previously collected tumor tissues available, your doctor will perform a biopsy at one of your tumor sites. This is a required procedure in order for you to be able to participate in the study. This will help your doctor understand the nature of your cancer and other people's small cell lung cancer and why certain people may be more likely to respond to certain treatment. If you are participating in the second portion of the study, you might not be eligible for the study if your cancer does not contain certain level of gene as determined by a OncoMed appointed laboratory.

Optional tumor biopsy: You will sign a separate consent page if you agree to this procedure. If you sign this separate consent, you will be asked to get a tumor biopsy within 28 days of your first study drug administration. This will help to see certain genes and/or proteins that are involved in your cancer development have changed with the study treatment. This procedure is optional.

Tumor assessments: An examination of your tumor(s) by CT (computerized tomography test, like an x-ray that produces a picture of your body including tumors using radiation), or MRI (magnetic resonance imaging - use of a magnetic field to produce an image of your body including tumors) or PET/CT (positron emission tomography- measures metabolic activity within the body. When combined with CT, PET/CT will determine abnormal metabolic activity at a specific anatomic location) or bone scan (an X-ray to look at your bone). Your study doctor will determine which type of test (CT or MRI, or PET/CT or bone scan) is best to assess your cancer. This is part of your routine cancer care.

TREATMENT PHASE

If you are found to be eligible to participate, you will be enrolled in the study.

*Y*ou will be assigned to a pre-determined dose level of tarextumab. The dose levels of tarextumab that will be tested in this study will start at 5mg/kg and increase in 2.5 mg/kg increments not to exceed 15 mg/kg(if the lower doses are tolerable) administered through the vein. You will be given the following drugs every 21 days: tarextumab on Day1, etoposide 100 mg/m^2 on Days 1, 2, and 3, and cisplatin 80 mg/m^2 on Day 1 or carboplatin (if you are entered into the first portion of the study after the highest tolerable dose is determined) at AUC of 5 mg/mL•min – a target drug concentration in your blood that is calculated based on your gender, age, weight and kidney function.

The study drug is tarextumab and will be given in "cycles." Each cycle is 3 weeks long for a total of 21 days. The first day of the first cycle will be called "Cycle 1 Day 1", followed by "Cycle 1 Day 2", and so on.

Your study drug (tarextumab) will be given through the vein for 30 minutes or longer depending on the dose you are assigned, your weight and if you have experienced any allergic reaction to study drug. Your study staff will let you know how long your treatment with study drug will be. Etoposide will be given through the vein for 30 to 60 minutes.

You will be treated with platinum therapy, cisplatin or carboplatin as determined by the Investigator prior to randomization. Cisplatin will be given through the vein for 30 minutes to 2 hours. Carboplatin will be given through the vein for 15 minutes or longer depending on your kidney function. On days when the study drug, etoposide and platinum therapy are given together, the study drug will be given first, followed by etoposide, and then cisplatin. You will receive study drug, etoposide, and platinum therapy for 6 cycles. After that, you will receive study drug only on Day 1 of each following cycle.

You will receive this combination of drugs until you have experienced severe side effects, or your tumor has grown or spread or you have decided to stop your treatment. If you experience side effects that are related to one of the three drugs, you may continue the other drugs if your tumor has not grown or spread.

If your disease is at least stable or have responded to therapy at the end of cycle 6 and you doctor think it is appropriate, you will also receive radiation to your brain to help prevent tumors recurring within 8 weeks after the last administration of chemotherapy. You will continue study drug treatment between the completion of 6 cycles of chemotherapy and the start of the brain radiation. The study drug will not be given within 2 weeks of the start and completion of the brain radiation and will not be given during the brain radiation.

Your doctor and/or nurse will review tests and complete pre-dose procedures once you are at the clinic. If he/she feels that you are in a good health, you will be receiving study drug, etoposide and platinum therapy.

During each visit, your doctor will also review any changes in the medications you have been taking or any changes in your health since the previous visit.

The following procedures will take place at each of the following visits.

Additional blood samples (approximately 1 to 2 teaspoons for each blood sample) might be taken to check the level of study drug (tarextumab) and/or proteins against tarextumab in your body:

Cycle 1 Day 1

This is the first day of study treatment (Cycle 1 Day 1).You will receive study drug, etoposide, and platinum therapy on this day.-You will have the following procedures done during this visit:

- Physical Examination before dosing (if this was done more than 7 days ago)
- Electrocardiogram (ECG) before dosing (if this was done more than 7 days ago)
- Urine Sample Collection before dosing (if this was done more than 7 days ago)
- Blood Sample Collection before dosing – about 1 tablespoon of blood for your health condition-(if this was done more than 7 days ago)
- Weight before dosing
- Hair follicles: Six hairs will be plucked from your head for additional marker testing
- Additional Blood Sample Collection before dosing – about 2 tablespoons of blood to assess the level of certain markers and proteins that might be against tarextumab
- 1 teaspoon of blood taken before starting study drug dosing to check the level of tarextumab in the blood
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about any changes in your health status after taking your initial dose of the study drug, etoposide, and platinum therapy.

You will have your blood drawn 1 more time about 5 minutes after completing study drug dosing but before the start of etoposide and platinum therapy treatment. About 1 teaspoon of blood will be collected to measure the amount of tarextumab in your blood.

Cycle 1 Day 2

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 1 Day 3

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- *Y*ou will also have 1 teaspoon of blood taken before starting etoposide to measure the amount of tarextumab in your blood.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 1 Day 8

- About 3 tablespoons of blood sample will be taken to check the level of certain markers, the level of tarextumab in the blood and your health status
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 1

You will receive study drug, etoposide, and platinum therapy on this day.-The following procedures will be done prior to study drug dosing:

- Physical Examination: only if you report changes in your health or how you feel
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured.
- About 1 tablespoon of blood will be taken to review your health condition.
- Urine Sample Collection.
- Electrocardiogram (ECG).

- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 2

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- About 2 tablespoons of blood will be taken to assess the level of certain markers.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 3

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 8

- About 3 tablespoons of blood will be taken to check the level of certain markers and your health status.
- Hair follicles: Six hairs will be plucked from your head for additional marker testing. You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.
- Optional Tumor Biopsy, if you agree to this procedure. If your doctor feels this is not a good time to have the biopsy, your biopsy might be taken later instead

End of Cycle 2 (about every 6 weeks):

Tumor assessment: A CT scan or MRI or PET/CT will be done approximately every 6 weeks after your initial study drug dosing (Day 1 of Cycle 3 and every 6 weeks thereafter). If a bone scan is used, bone scan may be repeated as indicated by your doctor

Cycle 3 Day 1

You will receive study drug, etoposide, and platinum therapy on this day.-The following procedures will be done prior to study drug dosing:

- Physical Examination: only if you report changes in your health or how you feel
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured.
- Blood Sample Collection (about 2 tablespoons to check your health condition and to measure the level of tarextumab in your blood and proteins that might be against tarextumab.
- Urine Sample Collection before dosing
- Electrocardiogram (ECG) before dosing
- You will also have your blood drawn 1 more time about 5 minutes after completing study drug dosing but before the start of etoposide and platinum therapy. About 1 teaspoon of blood will be collected to measure the amount of tarextumab in your blood.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 3 Day 2

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- About 2 tablespoons of blood will be taken to assess the level of certain markers.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 3 Day 3

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured.
- *Y*ou will also have 1 teaspoon of blood drawn before starting etoposide to measure the amount of tarextumab in your blood.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 3 Day 8

- About 3 tablespoon of blood to check the level of certain markers and your health status.
- *Y*ou will also have 1 teaspoon of blood drawn before starting etoposide to measure the amount of tarextumab in your blood.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycles 4-6: Day 1

You will receive study drug, etoposide, and platinum therapy on this day.–The following procedures will be done prior to study drug dosing:

- Physical Examination: only if you report changes in your health or how you feel
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- Blood Sample Collection (about 1 tablespoon) to check your health condition.
- About 1 tablespoon of blood sample will be taken to check the level of certain markers at Cycles 4 and 5 only
- About 1 tablespoon of blood will also be taken to check proteins that might be against tarextumab and to measure the level of tarextumab in the blood. This sample will be collected at Cycle 4 only if you are participating in the first portion of the study and at Cycle 3 and 5 if you are participating in the second portion of the study
- Urine Sample Collection
- Electrocardiogram (ECG) before dosing
- You will also have your blood drawn 1 more time about 5 minutes after completing study drug dosing but before the start of etoposide and cisplatin or carboplatin treatment at Cycle 3. You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Tumor assessment: A CT scan or MRI or PET/CT will be done approximately every 6 weeks after your initial study drug dosing (Day 1 of Cycle 3 and every 6 weeks thereafter). If a bone scan is used, bone scan may be repeated as indicated by your doctor.

Cycles 4-6: Day 2

You will receive etoposide treatment only on Day 2. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycles 4-6: Day 3

You will receive etoposide treatment only on Day 3. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.
- *Y*ou will have 1 teaspoon of blood drawn to measure the amount of tarextumab in your blood at Cycle 3.

End of Cycle 6

- Tumor assessment: A CT scan or MRI or PET/CT will be done approximately every 6 weeks after your initial study drug dosing. A bone scan may be repeated as indicated by your doctor
- At the end of cycle 6, if your disease is at least stable or have responded to therapy, you doctor may decide that you will receive radiation to your brain to help prevent tumors before continuing with study drug treatment.

Cycle 7 and beyond

Starting at cycle 7, you will receive study drug on Day 1 of each cycle only. The following procedures will be performed on Day 1 of Cycle 7 and every cycle thereafter.

- Physical Examination before dosing: only if you report changes in your health or how you feel
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- Blood Sample Collection before dosing (about 1 tablespoon) to check your health condition.
- Blood sample collection before dosing (about 1 teaspoon) to check proteins that might be against tarextumab. This sample will be collected at Cycle 7 and every 3rd cycle thereafter (e.g. Cycle 10, Cycle 13, etc).
- Urine Sample Collection before dosing
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.
- Tumor assessment: A CT scan or MRI or PET/CT will be done approximately every 6 weeks after your initial study drug dosing. If a bone scan is used, bone scan will be done at every other tumor assessment (approximately every 12 weeks after initial study drug dosing).

TREATMENT TERMINATION

You will be asked to return to complete the procedures listed below at the termination visit if you will no longer be continuing on study drug, etoposide, or cisplatin/carboplatin. This visit will be done about 4 weeks after your last dose of study, etoposide, or cisplatin/carboplatin whichever is discontinued last.

- Physical Examination
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- Electrocardiogram (ECG)
- Urine Sample Collection
- Blood Sample Collection – about 3 tablespoons of blood to check your health condition and to check the level of certain markers, proteins that might be against tarextumab, and the level of OMP59R5 in the blood
- Tumor assessment: either by CT or MRI or PET/CT, or bone scan, if these procedures were not done within the last 4 weeks and if the last tumor assessment did not show that your tumor has grown or spread

You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Optional Tumor Biopsy: *A*n optional tumor biopsy will be done only if you agree.

FOLLOW UP

After you stopped study drug and your tumor has not grown, a tumor assessment (CT or MRI approximately every 6 weeks and bone scan approximately every 12 weeks) will be done until your tumor has grown.

After you have stopped receiving study drug, the study staff will call you about every 3 months after your last clinic visit to follow your health status. If necessary, your doctor may be contacted by OncoMed or OncoMed's designee to obtain this information.

If you withdraw from the study treatment but not from study follow-up, the study staff will still contact you about every 3 months after your last visit to check on your health status, or the study staff may use a public information (like county records) to obtain information about your survival status only, which will be reported to OncoMed as part of the data for the study.

POSSIBLE RISKS AND DISCOMFORTS

Tarextumab:

As of *November 17, 2015*, tarextumab *or placebo* has been tested in *356* subjects who have cancer;

The following side effects have been noted in subjects receiving tarextumab *or placebo* and were considered possibly related to tarextumab *or placebo* treatment:

Common one (occurred in >10% of the subjects who used the drug):

- Diarrhea
- Fatigue-tiredness
- Nausea
- Decreased appetite
- Vomiting
- Low red blood counts that might make you feel tired,
- Low blood counts that might make you easy to be bruised
- *Low blood count that might make you easier to get infection*

Less Common (occurring in 5% to 10% of subjects who used the drug):

- *Hands/feet swollen*
- Low potassium level
- *Hair loss*
- *Nose bleeding*
- Redness of skin and/or rashes/hives
- Dehydration
- Change in taste

Most of the above-mentioned side effects were mild and moderate. Diarrhea was the most common side effect and can be severe if it is not treated immediately. You will be given some medications after your first dose of tarextumab to take home to treat diarrhea. In addition, you will be advised to drink enough fluid and eat a balanced diet to avoid the dehydration and imbalanced electrolytes.

Tarextumab will be given as an intravenous infusion. There may be minor discomfort from the needle in your arm. Bruising, swelling, and, in rare instances, infection and blood clot may occur at the infusion site.

Tarextumab is a monoclonal antibody. There is the possibility of a reaction to the monoclonal antibody as it is being infused (given) through your vein; these are called infusion reactions. Symptoms can include fever, chills, rash, and/or hives, changes in blood pressure, temperature and heart rate. As of *November 17, 2015*, *twelve* of *356* subjects who have been given tarextumab *or placebo* have experienced infusion reactions; all of these infusion reactions were mild or moderate. You will be watched carefully during the infusion and after the completion of the infusion. If you do have a reaction to the study drug, your study doctor may need to give the study drug at a slower rate (over a longer period of time) and /or give you some medications to prevent the reaction. If after slowing the rate of infusion and giving you some medications to prevent the infusion reaction, you continue to have infusion reactions, you may need to stop taking tarextumab.

During the course of this study, your blood will be drawn for laboratory tests (**1-3** tablespoons will be collected at each blood draw). The risks of drawing blood include some discomfort from the needle in your arm, bruising, swelling at the needle site and, in rare instances, infection or fainting.

You should discuss the risk and side effects with your study doctor. There may be other side effects that we cannot predict. You will be informed of any new significant side effects that develop during the course of this research study, or others regarding the use of tarextumab.

There may be side effects that we cannot predict and in some cases they may be serious, long-lasting, or fatal.

ETOPOSIDE:

The following side effects have been noted in subjects receiving etoposide:

Common one (occurred in > 10% of the subjects who used this drug)

- Low blood counts: Your white and red blood cells and platelets may temporarily decrease. This may put you at an increased risk for infection, anemia, and/or bleeding
- Nausea
- Vomiting
- Feeling weak and low energy
- Chills
- Fever
- Hair loss
- Poor appetite
- Sores, ulcers, or white spots on the lips or in the mouth

Less common (occurred in 5 to 10% of the subjects who used this drug)

- Diarrhea
- Constipation
- Taste alteration
- Abdominal pain
- Dizziness
- Injection site inflammation or vein inflammation

Rarely (occurred in < 5% of the subjects who used this drug)

- Increased or decreased blood pressure

- Allergic reaction: This medicine may cause a serious type of allergic reaction called anaphylaxis that is presented with symptoms such as chills, fever, fast heartbeat, sudden constriction of airway, shortness of breath, excessive sweating, itchiness of the skin or rash, change in blood pressure, and loss of consciousness, etc . Anaphylaxis can be life-threatening and requires immediate medical attention. Tell your doctor or nurse right away if you have chills; fever; lightheadedness, dizziness, or fainting; fast, pounding heartbeat; swelling of the face, tongue, and throat; or trouble with breathing after you receive the medicine

Other side effects may occur following the administration of etoposide. Your doctor will further explain the side effects of etoposide.

CISPLATIN:

The following side effects have been noted in subjects receiving cisplatin:

Common one (occurred in > 10% of the subjects who used this drug)

- Low blood counts: Your white and red blood cells and platelets may temporarily decrease. This may put you at an increased risk for infection, anemia, and/or bleeding
- Nausea
- Vomiting
- Ringing in the ears or Hearing loss
- Impairment of kidney function and damages to kidney
- Changes in how food tastes
- Diarrhea
- Damages to nerve that causes pain, numbness, tingling of hands and feet, and sometimes even have the difficulty in motion
- Hair loss
- Imbalance of electrolyte
- Extreme fatigue
- Mild elevation of liver enzymes

Less common or rare (occurred in ≤ 10% of the subjects who used this drug)

- Change in vision or inflammation of optic nerve and blindness
- Injection site inflammation or vein inflammation
- Change in blood vessels that trigger heart attack and heart problem, stroke or brain injury

- Allergic reaction: This medicine may cause a serious type of allergic reaction called anaphylaxis that is presented with symptoms such as chills, fever, fast heartbeat, sudden constriction of airway, shortness of breath, excessive sweating, itchiness of the skin or rash, change in blood pressure, and loss of consciousness, etc . Anaphylaxis can be life-threatening and requires immediate medical attention. Tell your doctor or nurse right away if you have chills; fever; lightheadedness, dizziness, or fainting; fast, pounding heartbeat; swelling of the face, tongue, and throat; or trouble with breathing after you receive the medicine

Other side effects may occur following the administration of cisplatin. The side effects are generally reversible and gradually disappears when treatment ends. However, some side effects might take a long time to disappear. Your doctor will further explain the side effects of cisplatin.

CARBOPLATIN:

The following side effects have been noted in subjects receiving carboplatin:

Common ones (occurred in >10% of the subjects who used this drug)

- Low blood counts: Your white and red blood cells and platelets may temporarily decrease. This may put you at an increased risk for infection, anemia, and/or bleeding
- Nausea
- Vomiting
- Damages to nerve that causes pain, numbness, tingling of hands and feet, and sometimes even have the difficulty in motion
- Ringing in the ears or hearing loss
- Hair loss
- Imbalance of electrolytes
- Extreme fatigue
- Elevation of liver enzymes
- Pain
- Allergic reaction
- Muscle weakness

Less common or rare (occurred in ≤10% of the subjects who used this drug)

- Sores, ulcers, or white spots on the lips or in the mouth
- Loss of vision for light or color
- Impairment of kidney function and damages to kidney. Your carboplatin dose will be modified if you have impairment of kidney function

Other side effects may occur following the administration of carboplatin. The side effects are generally reversible and gradually disappears when treatment ends. However, some side effects might take a long time to disappear. Your doctor will further explain the side effects of carboplatin

PREGNANCY

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

Therefore, women who are pregnant or breastfeeding may not participate in this study. Women must have a negative pregnancy test before beginning the study. It is important that both men and women take steps to prevent pregnancy during this study through the use of adequate contraception (for example, a barrier or hormone method or abstinence) 30 days prior to first study drug administration and for the duration of the study until 30 days after the last dose of study drug or etoposide or cisplatin whichever is discontinued last.

If you become pregnant or suspect that you are pregnant, or if your partner becomes pregnant or suspects that she is pregnant during the study or within 30 days after the last dose of study drug or etoposide or cisplatin whichever is discontinued last, you must notify the study *I*nvestigator immediately. If you become pregnant, you will be taken off of treatment and will undergo assessments listed under the Treatment Termination Section of this document, except for the radiographic studies, which will not be performed. If your partner becomes pregnant, you will remain on the study. If either you or your partner becomes pregnant during the study or within 30 days after the last dose of study drug or etoposide or cisplatin whichever is discontinued last, you and/or your partner will be followed through outcome of the birth.

POTENTIAL BENEFITS

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

SIGNIFICANT NEW FINDINGS

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

ALTERNATIVE TREATMENTS AND PROCEDURES

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

TERMINATION OF SUBJECT PARTICIPATION

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

Your doctor may decide to hold or stop the study drug infusions at any time during the study for safety reasons.

If your doctor or the sponsor decides to withdraw you from the study, you will undergo the same assessments listed under **Treatment Termination**.

COSTS AND COMPENSATION

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

You will not be paid for participation in this study.

COMPENSATION FOR RESEARCH-RELATED INJURY

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

CONFIDENTIALITY

Every effort will be made to keep your medical information confidential (secret). You will be identified by a code and no information that identifies you will be released without your written permission, except as required by law. To the extent permitted by law and by signing the consent form, you allow access by representatives of the Food and Drug Administration (FDA), other regulatory bodies, Institutional Review Boards, Independent Ethics Committees, and OncoMed monitors/representatives and collaborators to inspect your research and medical records without removal of identifying information, such as your name, initials, date of birth, sex, race, and location of the research study. If information from this study is presented publicly or published in a medical journal, you will not be identified by name, picture, or by any other personally identifying information.

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

OR IF SITE DOES NOT HAVE OWN HIPAA FORM:

AUTHORIZATION TO USE AND DISCLOSE MY HEALTH INFORMATION

I authorize (give permission to) insert name of study site to use and disclose (share) my health information solely for the purposes of this research study and research directly related to the use of tarextumab. I understand that my health information that I am authorizing to be used and disclosed (Authorized Health Information) includes all health information about me that has been and will be created or received by (SITE) and that is in my medical records maintained by (SITE).

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

AUTHORIZED PERSONS AND RECIPIENTS

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

RE-DISCLOSURES TO THIRD PARTIES

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

EXPIRATION DATE

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

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

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

QUESTIONS

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

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

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

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

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

CONSENT FOR OPTIONAL TUMOR BIOPSY

_____ _____ **If you give your consent for a punch biopsy of your tumor lesion, please check the box and write your initials and the date in the space provided.**

Initials **Date**

_____ _____ **If you do not give your consent for a punch biopsy of your tumor lesion, please check the box and write your initials and the date in the space provided.**

Initials **Date**

_____

Printed Name of Subject or Subject's Authorized Representative

_____ _____

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

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent **Date**

_____

Printed Name of Witness*

_____ _____ _____

Signature of Witness* **Date**

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

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

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

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

_____ _____

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

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent **Date**

_____

Printed Name of Witness*

_____ _____

Signature of Witness* **Date**

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

APPENDIX G: SAMPLE INFORMED CONSENT – PHASE 2

PROTOCOL 59R5-003: A Phase 1b/2 Study of Tarextumab (OMP-59R5) in Combination with Etoposide and Platinum Therapy in Subjects with Untreated Extensive Stage Small Cell Lung Cancer

Principal Investigator: _____

Before you decide whether or not to take part in this research study, it is important for you to understand the purpose of the study, what risks may be involved, and what is expected of you during the study. Your participation in this study is entirely voluntary. If you have any questions that are not answered or if there are words that you do not understand in this consent form, your study doctor will give you more information. Once you understand the purpose of this study, and if you decide to volunteer to participate in the study, you will be asked to sign this consent form. Once you sign the consent form, you will be referred to as a "subject".

PURPOSE AND BACKGROUND

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

The study drug, tarextumab, used in this study is experimental. That means the United States Food and Drug Administration (FDA) has not approved it for use by the general public. tarextumab is a humanized monoclonal antibody and was developed to target cancer stem cells. tarextumab may block the growth of cancer stem cells, the remaining tumor cells. The sponsor for this study is OncoMed Pharmaceuticals.

The research study consists of two portions and you will participate in the second portion. The purpose of the first portion is to test the safety and to determine the highest tolerable dose of tarextumab, when given in combination with etoposide and cisplatin or carboplatin. The purpose of the second portion is to test if tarextumab, when given in combination with etoposide and platinum therapy (cisplatin or carboplatin), is able to slow tumor growth in subjects with extensive small cell lung cancer or shrink tumors in subjects with extensive small cell lung cancer.

You have been asked to participate in this research study because you have small cell lung cancer that has spread to other parts of your body and you have not been treated for this disease, and your doctor feels that etoposide and platinum therapy (cisplatin or carboplatin) in combination with tarextumab may be a treatment option for you.

Although tarextumab has been given to cancer patients, it has not been given in combination with etoposide and platinum therapy (cisplatin or carboplatin). It is not known if it will provide any benefit to you and may cause harmful side effects.

In one other study with tarextumab in subjects with cancer of the pancreas (also known as the ALPINE study), a group of independent physicians and statisticians called a "Data Safety Monitoring Board" or DSMB who are responsible for monitoring the safety and efficacy of clinical studies, reviewed the data and made recommendations to OncoMed, the Sponsor of the study, about the pancreatic cancer study. While they did not see unexpected safety findings (side-effects) between the patients on the study who received tarextumab and placebo, they reported that on average patients treated with tarextumab had a lower chance of their tumors shrinking than those treated with placebo. Also, patients who received tarextumab had their cancer under control for a shorter period of time. Patients treated with tarextumab on the pancreatic cancer study may not seem to be living as long as those treated with placebo. The cancer type that you have is called small cell lung cancer and it is very different from pancreatic cancer. Also, the chemotherapy that you are receiving is very different from the chemotherapy used in the pancreatic cancer study. The PINNACLE study also has a DSMB that has been meeting since the start of this study, consisting of 3 lung cancer doctors and one statistician. This group reviews the data from the clinical study at least 4 times a year. If the DSMB informs OncoMed of any new information regarding the safety of tarextumab on the PINNACLE you and your doctor will be informed immediately.

PROCEDURES

The second portion of the study will include approximately 135 subjects at about 50 centers in the United States.

Your study doctor will determine the type of platinum therapy (cisplatin or carboplatin) you will receive. You will then be randomly assigned (by chance) to one of two treatment arms: Subjects in one arm will receive etoposide and platinum therapy (cisplatin or carboplatin) plus tarextumab. Subjects in the other arm will receive etoposide and platinum therapy (cisplatin or carboplatin) plus Placebo (an inactive substance that looks like tarextumab). The choice of platinum therapy (cisplatin or carboplatin) you will receive will not change during the study once it is selected by your doctor. After 6cycles of treatment, you will continue on tarextumab or Placebo on Day 1 of every 21-day cycle. If you discontinue etoposide and platinum therapy prior to 6 cycles because of side effects, you will still be allowed to stay on the study and receive tarextumab or Placebo. Your chance of being randomized to one of the treatment arms is 50%.

Neither you nor your doctor will know whether you are receiving tarextumab or Placebo. Both tarextumab and Placebo are considered "study drug".

The study participation consists of the following periods:

- Screening
- Treatment: You may receive either tarextumab with etoposide and platinum therapy (cisplatin or carboplatin), or Placebo with etoposide and platinum therapy (cisplatin or carboplatin) for6 cycles followed by treatment with tarextumab or Placebo alone. This treatment period may last until you experience severe side effects or your tumor has grown or spread or you have decided to stop the treatment.
- Treatment termination: This visit will occur approximately 4 weeks after your last dose of study drug, etoposide, or platinum therapy (cisplatin or carboplatin), whichever you discontinue the last, but prior to the start of new anti-cancer therapy that your doctor has chosen for you.
- Follow-up: You will be followed about every three months to check on your health status and the new type of cancer therapy you are receiving. This may be done by phone or a clinic visit.

SCREENING

If you decide to be in this study and you sign this informed consent form, you will be asked to complete the procedures listed below at a screening visit within 28 days before your first dose of study drug to make sure that you are a suitable candidate.

Informed Consent: You will read, confirm understanding, and sign this informed consent. No study-related tests will be performed prior to signing this informed consent form.

Medical History: Your doctor and/or nurse will ask you questions about your past and current health and medication use.

Physical Examination: Your doctor will examine you. Your blood pressure, temperature, heart rate, rate of breathing, height, and weight will also be measured.

Electrocardiogram (ECG): You will have an ECG. An ECG traces the electrical activity of the heart. It is a non-invasive test and requires no needles.

Blood and Urine Sample Collection: Blood will be taken from a vein in your arm using a needle. The blood (about 1 tablespoon) and a urine sample will be used to check your general health and, if you are a female who is able to get pregnant, to make sure that you are not pregnant.

Tumor tissues: If you had your tumor tissue biopsied previously and your doctor still has some of that tissue available, you will be asked to allow your doctor to send some of that tissue for testing for this study. If you don't have previously collected tumor tissues available, your doctor will perform a biopsy at one of your tumor sites. This is a required procedure in order for you to be able to participate in the study. This will help your doctor understand the nature of your cancer and other people's small cell lung cancer and why certain people may be more likely to respond to certain treatment.

Optional tumor biopsy: You will be asked to sign a separate consent page if you agree to this procedure. If you sign this separate consent, you will be asked to get a tumor biopsy within 28 days of your first study drug administration. This will help to see certain genes and/or proteins that are involved in your cancer development have changed with the study treatment. This procedure is optional.

Tumor assessments: An examination of your tumor(s) by CT (computerized tomography test, like an x-ray that produces a picture of your body including tumors using radiation), or MRI (magnetic resonance imaging - use of a magnetic field to produce an image of your body including tumors), or PET/CT (positron emission tomography- measures metabolic activity within the body. When combined with CT, PET/CT will determine abnormal metabolic activity at a specific anatomic location), or bone scan (an X-ray to look at your bone). Your study doctor will determine which type of test (CT or MRI, or PET/CT or bone scan) is best to assess your cancer. This is part of your routine cancer care.

TREATMENT PHASE

If you are found to be eligible to participate, you will be enrolled in the study.

You will be randomly (by chance) assigned to one of the two treatment arms, where you will either receive etoposide and platinum therapy (cisplatin or carboplatin) plus tarextumab or etoposide and platinum therapy (cisplatin or carboplatin) plus Placebo (an inactive substance that looks like tarextumab). Your study doctor will determine the type of platinum therapy (cisplatin or carboplatin) you will receive. Then you will be randomized to receive either tarextumab or Placebo. Your chance of being randomized to each of the treatment arm is 50%. Neither you nor your doctor will know whether you are receiving tarextumab or Placebo. The choice of platinum therapy (cisplatin or carboplatin) you will receive will not change during the study once it is selected by your study doctor.

The study drug is either tarextumab or Placebo (an inactive substance that looks like tarextumab) and will be given in "cycles." Each cycle is 3 weeks long for a total of 21 days. The first day of the first cycle will be called "Cycle 1 Day 1", followed by "Cycle 1 Day 2", and so on.

Your study drug (tarextumab or Placebo) will be given through the vein for 90 minutes or longer depending on the dose you are assigned, your weight and if you have experienced any allergic reaction to study drug. Your study staff will let you know how long your treatment with study drug will be. Etoposide will be given through the vein for 30 to 60 minutes.

You will be treated with platinum therapy (cisplatin or carboplatin) as determined by your study doctor prior to randomization. Cisplatin will be given through the vein for 30 minutes to 2 hours. Carboplatin will be given through the vein for 15 minutes or longer depending on your kidney function. On days when the study drug, etoposide and platinum therapy (cisplatin or carboplatin) are given together, the study drug will be given first, followed by etoposide, and then cisplatin. You will receive study drug, etoposide, and platinum therapy (cisplatin or carboplatin) for 6 cycles. After that, you will receive study drug only on Day 1 of each following cycle. If you discontinue platinum therapy prior to 6 cycles because of side effects, you will still be allowed to stay on the study and receive study drug.

You will receive this combination of drugs until you have experienced severe side effects, or your tumor has grown or spread or you have decided to stop your treatment. If you experience side effects that are related to one of the three drugs, you may continue the other drugs if your tumor has not grown or spread.

If your disease is at least stable or has responded to therapy at the end of cycle 6 and your doctor thinks it is appropriate, you will also receive radiation to your brain to help prevent tumors recurring within 8 weeks after the last administration of chemotherapy. You will continue study drug treatment between the completion of 4 cycles of chemotherapy and the start of the brain radiation. The study drug will not be given within 2 weeks of the start and completion of the brain radiation and will not be given during the brain radiation.

Your doctor and/or nurse will review tests and complete pre-dose procedures once you are at the clinic. If he/she feels that you are in a good health, you will be receiving study drug, etoposide and platinum therapy (cisplatin or carboplatin).

During each visit, your doctor will also review any changes in the medications you have been taking or any changes in your health since the previous visit.

Cycle 1 Day 1

This is the first day of study treatment (Cycle 1 Day 1).You will receive study drug, etoposide, and platinum therapy (cisplatin or carboplatin) on this day. You will have the following procedures done during this visit:

- Physical Examination before dosing (if this was done more than 7 days ago)
- Electrocardiogram (ECG) before dosing (if this was done more than 7 days ago)
- Urine Sample Collection before dosing (if this was done more than 7 days ago)
- Blood Sample Collection before dosing – about 1 tablespoon of blood to check your health condition (if this was done more than 7 days ago)
- Weight before dosing
- Additional Blood Sample Collection before dosing – about 2 tablespoons of blood to assess the level of certain markers and proteins that might be against tarextumab
- You will also have about 1 teaspoon of blood taken before starting study drug dosing to check the level of tarextumab in the blood
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about any changes in your health status after taking your initial dose of the study drug, etoposide, and platinum therapy (cisplatin or carboplatin).
- You will have your blood drawn 1 more time about 5 minutes after completing study drug dosing but before the start of etoposide and platinum therapy (cisplatin or carboplatin) treatment. About 1 teaspoon of blood will be collected to measure the amount of tarextumab in your blood.

Cycle 1 Day 2

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 1 Day 3

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will also have 1 teaspoon of blood taken before starting etoposide to measure the amount of tarextumab in your blood.

- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 1 Day 8

- About 3 tablespoons of blood sample will be taken to check the level of certain markers, the level of tarextumab in the blood and your health status
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 1

You will receive study drug, etoposide, and platinum therapy (cisplatin or carboplatin) on this day. The following procedures will be done prior to study drug dosing:

- Physical Examination: only if you report changes in your health or how you feel
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured.
- About 1 tablespoon of blood will be taken to review your health condition.
- Urine Sample Collection.
- Electrocardiogram (ECG).
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 2

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- About 2 tablespoons of blood will be taken to assess the level of certain markers.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 3

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 8

- About 3 tablespoons of blood will be taken to check the level of certain markers and your health status.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.
- Optional Tumor Biopsy, if you agree to this procedure. If your doctor feels this is not a good time to have the biopsy, your biopsy might be taken later instead

End of Cycle 2 (about every 6 weeks):

Tumor assessment: A CT scan or MRI or PET/CT will be done approximately every 6 weeks after your initial study drug dosing (Day 1 of Cycle 3 and every 6 weeks thereafter). If a bone scan is used, bone scan may be repeated as indicated by your doctorCycle 3 Day 1

You will receive study drug, etoposide, and platinum therapy (cisplatin or carboplatin) on this day. The following procedures will be done prior to study drug dosing:

- Physical Examination: only if you report changes in your health or how you feel
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured.
- Blood Sample Collection (about 2 tablespoons to check your health condition and to measure the level of tarextumab in your blood and proteins that might be against tarextumab).
- Urine Sample Collection before dosing
- Electrocardiogram (ECG) before dosing
- You will also have your blood drawn 1 more time about 5 minutes after completing study drug dosing but before the start of etoposide and platinum therapy (cisplatin or carboplatin). About 1 teaspoon of blood will be collected to measure the amount of tarextumab in your blood.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 3 Day 2

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- About 2 tablespoons of blood will be taken to assess the level of certain markers.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 3 Day 3

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured.
- You will also have 1 teaspoon of blood drawn before starting etoposide to measure the amount of tarextumab in your blood.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 3 Day 8

- About 3 tablespoon of blood to check the level of certain markers and your health status.
- You will also have 1 teaspoon of blood drawn before starting etoposide to measure the amount of tarextumab in your blood.
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycles 4-6: Day 1

You will receive study drug, etoposide, and platinum therapy (cisplatin or carboplatin) on this day. The following procedures will be done prior to study drug dosing:

- Physical Examination: only if you report changes in your health or how you feel
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- Blood Sample Collection (about 1 tablespoon) to check your health condition.
- About 1 tablespoon of blood sample will be taken to check the level of certain markers at Cycles 4 and 5 only.
- About 1 tablespoon of blood will also be taken to check proteins that might be against tarextumab and to measure the level of tarextumab in the blood. This sample will be collected at Cycle 3 and 5
- Urine Sample Collection
- Electrocardiogram (ECG) before dosing
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycles 4-6: Day 2

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycles 4-6: Day 3

You will receive etoposide treatment only on this day. Before your etoposide treatment, the following procedures will be done:

- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.
- You will have 1 teaspoon of blood drawn to measure the amount of tarextumab in your blood at Cycle 5

End of Cycles 4 and 6

- Tumor assessment: A CT scan or MRI or PET/CT will be done approximately every 6 weeks after your initial study drug dosing. A bone scan may be repeated as indicated by your doctor

After the completion of 6 planned cycles etoposide and platinum therapy

- If your disease is at least stable or have responded to therapy, you doctor may decide that you will receive radiation to your brain to help prevent tumors before continuing with study drug treatment.

Cycle 7 and beyond

Starting at Cycle 7, you will receive study drug on Day 1 of each cycle only. The following procedures will be performed on Day 1 of Cycle 7 and every cycle thereafter.

- Physical Examination before dosing: only if you report changes in your health or how you feel
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- Blood Sample Collection before dosing (about 1 tablespoon) to check your health condition.
- Blood sample collection before dosing (about 1 teaspoon) to check proteins that might be against tarextumab and the level of study drug in the blood. These samples will be collected at Cycle 7 and every other cycle (i.e., Cycle 7, Cycle 9, Cycle 11, etc.)
- Urine Sample Collection before dosing
- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.
- Tumor assessment: A CT scan or MRI or PET/CT will be done approximately every 6 weeks after your initial study drug dosing. If a bone scan is used, bone scan may be repeated as indicated by your doctor.

TREATMENT TERMINATION

You will be asked to return to complete the procedures listed below at the termination visit if you will no longer be continuing on study drug, etoposide, or platinum therapy (cisplatin or carboplatin). This visit will be done about 4 weeks after your last dose of study, etoposide, or platinum therapy (cisplatin or carboplatin) whichever is discontinued last.

- Physical Examination
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- Electrocardiogram (ECG)
- Urine Sample Collection
- Blood Sample Collection – about 3 tablespoons of blood to check your health condition, to check the level of certain markers, to check for proteins that might be against tarextumab, and to check the level of OMP59R5 in the blood
- Tumor assessment: either by CT or MRI or PET/CT, or bone scan, if these procedures were not done within the last 4 weeks and if the last tumor assessment did not show that your tumor has grown or spread

You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Optional Tumor Biopsy: An optional tumor biopsy will be done only if you agree.

FOLLOW UP

After you have stopped receiving study drug and your tumor has not grown, a tumor assessment (CT scan or MRI or PET/CT will be done approximately every 6 weeks after your initial study drug dosing. If a bone scan is used, bone scan may be repeated as indicated by your doctor) will be done until your tumor has grown.

After you have stopped receiving study drug, the study staff will call you about every 3 months after your last clinic visit to follow your health status. If necessary, your doctor may be contacted by OncoMed or OncoMed's designee to obtain this information.

If you withdraw from the study treatment but not from study follow-up, the study staff will still contact you about every 3 months after your last visit to check on your health status, or the study staff may use public information (like county records) to obtain information about your survival status only, which will be reported to OncoMed as part of the data for the study.

POSSIBLE RISKS AND DISCOMFORTS

tarextumab:

As of *November 17*, *2015*, tarextumab *or placebo* has been tested in *356* subjects who have cancer;

The following side effects have been noted in subjects receiving tarextumab and were considered possibly related to tarextumab treatment:

Common (occurred in >10% of the subjects who used the drug):

- *Low red blood counts that might make you feel tired, easier to get infections or bruised/bleeding*
- Diarrhea
- Fatigue-tiredness
- Nausea
- Decreased appetite
- Vomiting

Less Common (occurring in 5% to 10% of subjects who used the drug):

- Low potassium level
- Infusion related or allergic reactions
- Weight loss
- Redness of skin and/or rashes/hives

Most of the above-mentioned side effects were mild and moderate, *with the exception of one subject who experienced fatal cardiac arrest, considered to be related to study drug*. Diarrhea was the most common side effect and can be severe if it is not treated immediately. You will be given some medications after your first dose of tarextumab to take home to treat diarrhea. In addition, you will be advised to drink enough fluid and eat a balanced diet to avoid the dehydration and imbalanced electrolytes.

Tarextumab will be given as an intravenous infusion. There may be minor discomfort from the needle in your arm. Bruising, swelling, and, in rare instances, infection and blood clots may occur at the infusion site.

Tarextumab is a monoclonal antibody. There is the possibility of a reaction to the monoclonal antibody as it is being infused (given) through your vein; these are called infusion reactions. Symptoms can include fever, chills, rash and/or hives, changes in blood pressure, temperature and heart rate. As of *November 17*, *2015*, *eighteen* of *356* subjects who have been given tarextumab *or placebo* have experienced infusion *or hypersensitivity* reactions; *most* of these infusion reactions were mild or moderate. You will be watched carefully during the infusion and after the completion of the infusion. If you do have a reaction to the study drug, your study doctor may need to give the study drug at a slower rate (over a longer period of time) and /or give you some medications to prevent the reaction. If after slowing the rate of infusion and giving you some medications to prevent the infusion reaction, you continue to have infusion reactions, you may need to stop taking tarextumab.

During the course of this study, your blood will be drawn for laboratory tests (1-3 tablespoons will be collected at each blood draw). The risks of drawing blood include some discomfort from the needle in your arm, bruising, swelling at the needle site and, in rare instances, infection or fainting.

You should discuss the risk and side effects with your study doctor. There may be other side effects that we cannot predict. You will be informed of any new significant side effects that develop during the course of this research study regarding the use of tarextumab.

There may be side effects that we cannot predict and in some cases they may be serious, long-lasting, or fatal.

ETOPOSIDE:

The following side effects have been noted in subjects receiving etoposide:

Common (occurred in > 10% of the subjects who used this drug)

- Low blood counts: Your white and red blood cells and platelets may temporarily decrease. This may put you at an increased risk for infection, anemia, and/or bleeding
- Nausea
- Vomiting
- Feeling weak and low energy
- Chills
- Fever
- Hair loss
- Poor appetite
- Sores, ulcers, or white spots on the lips or in the mouth

Less common (occurred in 5 to 10% of the subjects who used this drug)

- Diarrhea
- Constipation
- Taste alteration
- Abdominal pain
- Dizziness
- Injection site inflammation or vein inflammation

Rarely (occurred in < 5% of the subjects who used this drug)

- Increased or decreased blood pressure
- Allergic reaction: This medicine may cause a serious type of allergic reaction called anaphylaxis that is presented with symptoms such as chills, fever, fast heartbeat, sudden constriction of airway, shortness of breath, excessive sweating, itchiness of the skin or rash, change in blood pressure, and loss of consciousness, etc. Anaphylaxis can be life-

threatening and requires immediate medical attention. Tell your doctor or nurse right away if you have chills; fever; lightheadedness, dizziness, or fainting; fast, pounding heartbeat; swelling of the face, tongue, and throat; or trouble with breathing after you receive the medicine

Other side effects may occur following the administration of etoposide. Your doctor will further explain the side effects of etoposide.

CISPLATIN:

The following side effects have been noted in subjects receiving cisplatin:

Common (occurred in > 10% of the subjects who used this drug)

- Low blood counts: Your white and red blood cells and platelets may temporarily decrease. This may put you at an increased risk for infection, anemia, and/or bleeding
- Nausea
- Vomiting
- Ringing in the ears or hearing loss
- Impairment of kidney function and damages to kidney
- Changes in how food tastes
- Diarrhea
- Damages to nerve that causes pain, numbness, tingling of hands and feet, and sometimes even have the difficulty in motion
- Hair loss
- Imbalance of electrolyte
- Extreme fatigue
- Mild elevation of liver enzymes

Less common or rare (occurred in ≤ 10% of the subjects who used this drug)

- Change in vision or inflammation of optic nerve and blindness
- Injection site inflammation or vein inflammation
- Change in blood vessels that trigger heart attack and heart problem, stroke or brain injury
- Allergic reaction: This medicine may cause a serious type of allergic reaction called anaphylaxis that is presented with symptoms such as chills, fever, fast heartbeat, sudden constriction of airway, shortness of breath, excessive sweating, itchiness of the skin or rash, change in blood pressure, and loss of consciousness, etc. Anaphylaxis can be life-threatening and requires immediate medical attention. Tell your doctor or nurse right away if you have chills; fever; lightheadedness, dizziness, or fainting; fast, pounding heartbeat; swelling of the face, tongue, and throat; or trouble with breathing after you receive the medicine

Other side effects may occur following the administration of cisplatin. The side effects are generally reversible and gradually disappear when treatment ends. However, some side effects might take a long time to disappear. Your doctor will further explain the side effects of cisplatin.

CARBOPLATIN:

The following side effects have been noted in subjects receiving carboplatin:

Common (occurred in >10% of the subjects who used this drug)

- Low blood counts: Your white and red blood cells and platelets may temporarily decrease. This may put you at an increased risk for infection, anemia, and/or bleeding
- Nausea
- Vomiting
- Damages to nerve that causes pain, numbness, tingling of hands and feet, and sometimes even have the difficulty in motion
- Ringing in the ears or hearing loss
- Hair loss
- Imbalance of electrolytes
- Extreme fatigue
- Elevation of liver enzymes
- Pain
- Allergic reaction
- Muscle weakness

Less common or rare (occurred in ≤10% of the subjects who used this drug)

- Sores, ulcers, or white spots on the lips or in the mouth
- Loss of vision for light or color
- Impairment of kidney function and damages to kidney. Your carboplatin dose will be modified if you have impairment of kidney function

Other side effects may occur following the administration of carboplatin. The side effects are generally reversible and gradually disappear when treatment ends. However, some side effects might take a long time to disappear. Your doctor will further explain the side effects of carboplatin

PREGNANCY

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

Therefore, women who are pregnant or breastfeeding may not participate in this study. Women must have a negative pregnancy test before beginning the study. It is important that both men and women take steps to prevent pregnancy during this study through the use of adequate contraception (for example, a barrier or hormone method or abstinence) 30 days prior to first study drug administration and for the duration of the study until 30 days after the last dose of study drug or etoposide or platinum therapy (cisplatin or carboplatin) whichever is discontinued last.

If you become pregnant or suspect that you are pregnant, or if your partner becomes pregnant or suspects that she is pregnant during the study or within 30 days after the last dose of study drug, etoposide, or platinum therapy (cisplatin or carboplatin) whichever is discontinued last, you must notify the study doctor immediately. If you become pregnant, you will be taken off of treatment and will undergo assessments listed under the Treatment Termination Section of this document, except for the radiographic studies, which will not be performed. If your partner becomes pregnant, you will remain on the study. If either you or your partner becomes pregnant during the study or within 30 days after the last dose of study drug, etoposide, or platinum therapy (cisplatin or carboplatin) whichever is discontinued last, you and/or your partner will be followed through outcome of the birth.

POTENTIAL BENEFITS

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

SIGNIFICANT NEW FINDINGS

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

ALTERNATIVE TREATMENTS AND PROCEDURES

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

TERMINATION OF SUBJECT PARTICIPATION

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

Your doctor may decide to hold or stop the study drug infusions at any time during the study for safety reasons.

If your doctor or the sponsor decides to withdraw you from the study, you will undergo the same assessments listed under Treatment Termination.

COSTS AND COMPENSATION

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

You will not be paid for participation in this study.

COMPENSATION FOR RESEARCH-RELATED INJURY

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

CONFIDENTIALITY

Every effort will be made to keep your medical information confidential (secret). You will be identified by a code and no information that identifies you will be released without your written permission, except as required by law. To the extent permitted by law and by signing the consent form, you allow access by representatives of the Food and Drug Administration (FDA), other regulatory bodies, Institutional Review Boards, Independent Ethics Committees, and OncoMed monitors/representatives and collaborators to inspect your research and medical records without removal of identifying information, such as your name, initials, date of birth, sex, race, and location of the research study. If information from this study is presented publicly or published in a medical journal, you will not be identified by name, picture, or by any other personally identifying information.

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

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

OR IF SITE DOES NOT HAVE OWN HIPAA FORM:

AUTHORIZATION TO USE AND DISCLOSE MY HEALTH INFORMATION

I authorize (give permission to) insert name of study site to use and disclose (share) my health information solely for the purposes of this research study and research directly related to the use of tarextumab. I understand that my health information that I am authorizing to be used and disclosed (Authorized Health Information) includes all health information about me that has been and will be created or received by (SITE) and that is in my medical records maintained by (SITE).

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

AUTHORIZED PERSONS AND RECIPIENTS

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

monitors, and OncoMed collaborators and licensees. I authorize (SITE) to disclose my Authorized Health Information to these persons and groups or persons.

RE-DISCLOSURES TO THIRD PARTIES

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

EXPIRATION DATE

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

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

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

QUESTIONS

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

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

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

Your decision to participate in this study is entirely voluntary. You may refuse to participate in or withdraw from the study at any time without prejudice or loss of benefits to which you are

otherwise entitled. A signed copy of this consent form will be given to you for your records and a copy will be retained by the study doctor for his or her files.

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

CONSENT FOR OPTIONAL TUMOR BIOPSY

_____ _____ If you give your consent for a core biopsy of your tumor lesion, please check the box and write your initials and the date in the space provided.
Initials Date

_____ _____ If you do not give your consent for a core biopsy of your tumor lesion, please check the box and write your initials and the date in the space provided.
Initials Date

_____

Printed Name of Subject or Subject's Authorized Representative

_____ _____

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

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent **Date**

_____

Printed Name of Witness*

_____ _____ _____

Signature of Witness* **Date**

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

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

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

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

_____ _____

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

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent **Date**

_____

Printed Name of Witness*

_____ _____

Signature of Witness* **Date**

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

APPENDIX H: SAMPLE PHARMACOGENOMICS/DNA INFORMED CONSENT

WHAT IS THE PURPOSE OF THIS PART OF THE STUDY?

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

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

WHAT AM I BEING ASKED TO DO?

You are being asked to give one small blood sample (10 mL, about 2 teaspoons) on Day 1 of Cycle 1 prior to the administration of study drug. Blood will be drawn from a vein using a needle. DNA will be extracted from your blood sample. Additionally, you are being asked to allow the Sponsor to perform the DNA testing on the mandatory tumor tissues you have provided for the study entry. If you had agreed to have optional tumor biopsies performed, you are also being asked to allow the Sponsor to perform DNA testing on these tissues.

Your DNA may be tested for specific genes relevant to tarextumab (the study drug), the Notch/DLL4 pathways (the targets of the tarextumab) and/or other genes related to your cancer. Only DNA research related to tarextumab or to the diseases for which this drug is developed will be performed. The Sponsor will store the tissue samples until there is no DNA left. The Sponsor will also destroy the blood sample used for DNA testing after 10 years.

You can also decide not to take part at all in DNA research. No blood sample for DNA research will be taken from you unless you sign and date this Informed Consent Form, and No DNA testing will be performed on the tumor tissues collected from you. Your decision to give, or not to give, a DNA sample will not affect the medical care that you receive from your study doctor or his/her staff. Your participation is voluntary.

HOW WILL MY IDENTITY AND RESULTS BE KEPT CONFIDENTIAL?

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

a) Coding of your DNA Sample

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

b) Restricted Access to Your DNA Sample

The Sponsor will control your DNA sample. Your DNA sample will be stored in a secure room at a facility in Redwood City, CA, or other site designated by the sponsor. Only authorized staff are allowed to enter the room. Your DNA sample may be transferred to other research partners working with the Sponsor. DNA samples transferred to research partners will not contain your Subject number. Your DNA sample will not be sold, loaned, or given to any other independent groups for their own use. Research partners working with the Sponsor are not allowed to share DNA samples with anyone else.

c) Restricted Access to Results

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

- The Sponsor
- Research partners working with the Sponsor
- Independent Ethics Committees/Institutional Review Boards
- Regulatory authorities, like the Food and Drug Administration (FDA) or the European Medicines Evaluation Agency (EMEA)

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

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

d) Separate Storage of DNA Forms

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

WHAT IF I CHANGE MY MIND LATER?

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

WILL I GET MY DNA TEST RESULTS?

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

WHAT ARE THE BENEFITS?

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

WHAT ARE THE RISKS?

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

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

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

QUESTIONS

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

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

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

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

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

_____ _____ **Initials Date**	**If you give your consent for a small blood sample for DNA research, please check the box and write your initials and the date in the space provided.**
_____ _____ **Initials Date**	**If you do not give your consent for a small blood sample for DNA research, please check the box and write your initials and the date in the space provided.**
_____ _____ **Initials Date**	**If you give your consent to allow DNA testing on the tumor tissue collected from you, please check the box and write your initials and the date in the space provided.**
_____ _____ **Initials Date**	**If you do not give your consent to allow DNA testing on the tumor tissue collected from you, please check the box and write your initials and the date in the space provided.**

Printed Name of Subject or Subject's Authorized Representative

_____ _____
Signature of Subject or Subject's Authorized Representative **Date**

_____
Printed Name of Person Obtaining Informed Consent

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

_____
Printed Name of Witness*

_____ _____
Signature of Witness* **Date**

*If the Principal Investigator or Ethic's Committee deems a witness signature is necessary

APPENDIX I: PROTOCOL AMENDMENT SUMMARY OF CHANGES

AMENDMENT 1: 09 MAY 2013

The following changes were made to the protocol. Italics in the text indicate new text.

RATIONALE

The protocol has been amended to allow the enrollment of current smokers, to exclude concurrent use of therapeutic warfarin, and to allow enrollment of a subject with treated brain metastasis provided that the subject has stable neurologic condition for at least 2 weeks after the completion of the radiation and is not receiving corticosteroid of > 40 mg prednisone daily equivalent dose to control the symptoms, to clarify the definition of DLT for Grade 4 neutropenia, and to clarify study drug preparation and administration. Additional minor changes have been made to improve clarity and consistency.

SUMMARY OF CHANGES:

SYNOPSIS

Diagnosis and Main Criteria for Eligibility: (Cont'd)

Inclusion Criteria:

Previously Read:

d. Prothrombin Time (PT)/International Normalized Ration (INR) ≤1.5 × ULN, activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless the subject is on heparin or warfarin or other similar anti-coagulants.

Now Reads:

d. Prothrombin Time (PT)/International Normalized Ration (INR) ≤1.5 × ULN, activated partial thromboplastin time (aPTT) ≤1.5 × ULN.

Additionally, for individuals eligible to participate in Phase 2 portion of the study:

Previously Read:

2. Prior therapy including radiation, chemotherapy or surgery for newly diagnosed extensive stage small cell lung cancer. Exceptions to this exclusion criterion include: 1) prophylactic cranial irradiation or whole brain radiation (WBRT) prior to the first administration of study drug provided that the subject has stable neurologic condition for at least 2 weeks after the completion of the radiation, 2) focused radiation for symptomatic relief for isolated bone

metastases; 3) bisphosphonate or denosumab therapy for bone metastasis initiated prior to study entry.

3. Symptomatic brain metastases requiring whole brain irradiation within 4 weeks prior to first study drug administration or requiring daily doses of >40mg of oral prednisone, or require use of anti-epileptic drugs.

4. Presence of uncontrolled Grade ≥ 1 diarrhea within 4 weeks prior to the first study drug administration.

5. Current smoker.

6. Presence of any serious or uncontrolled illness including, but not limited to: ongoing or active infection, symptomatic congestive heart failure unstable angina pectoris, cardiac arrhythmia, arterial thrombosis, symptomatic pulmonary embolism, and psychiatric illness that would limit compliance with study requirement.

7. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty and/or stenting within 6 months prior to the first administration of study drug.

8. A history of malignancy with the exception of:
   a. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer
   b. Adequately treated stage I cancer from which the subject is currently in remission, or
   c. Any other cancer from which the subject has been disease-free for ≥ 3 years

9. Known human immunodeficiency virus (HIV) infection.

10. Females who are pregnant or breastfeeding.

Now Reads:

2. Prior therapy including radiation, chemotherapy or surgery for newly diagnosed extensive stage small cell lung cancer. Exceptions to this exclusion criterion include: 1) prophylactic cranial irradiation or whole brain radiation (WBRT) prior to the first administration of study drug provided that the subject has stable neurologic condition for at least 2 weeks after the completion of the radiation *and is not receiving corticosteroid of > 40 mg prednisone daily equivalent dose to control the symptoms, 2) focused radiation* for symptomatic relief for isolated bone metastases; 3) bisphosphonate or denosumab therapy for bone metastasis initiated prior to study entry.

3. Presence of uncontrolled Grade ≥ 1 diarrhea within 4 weeks prior to the first study drug administration.

4. Presence of any serious or uncontrolled illness including, but not limited to: ongoing or active infection, symptomatic congestive heart failure unstable angina pectoris, *uncontrolled* cardiac arrhythmia, *uncontrolled* arterial thrombosis, symptomatic pulmonary embolism, and psychiatric illness that would limit compliance with study requirement.

5. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty and/or stenting within 6 months prior to the first administration of study drug.

6. A history of malignancy with the exception of:
   a. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer
   b. Adequately treated stage I cancer from which the subject is currently in remission, or
   c. Any other cancer from which the subject has been disease-free for ≥ 3 years

7. Known human immunodeficiency virus (HIV) infection.

8. Females who are pregnant or breastfeeding.

9. C*on*current use *of therapeutic warfarin (prophylactic low dose of warfarin, i.e., 1 mg daily for port catheter is allowed).*

Test Product, Dose, and Mode of Administration

Previously Read:

OMP-59R5 must be delivered through either polyvinyl chloride (PVC) or non-PVC tubing that contains a 0.22-micron filter and should be infused over 30 minutes as an IV infusion.

Placebo is a formulation of 50mM Histidine, 100mM Sodium Chloride, 45mM Sucrose and 0.01% (v/v) Polysorbate-20, pH 6.0. Placebo will be administered in the same manner as OMP-59R5; i.e., withdraw the necessary amount of Placebo and dilute with 5% Dextrose in Water (D5W) to a total volume of 250 mL and infuse over 30 minutes.

Now Reads:

OMP-59R5 must be delivered through either polyvinyl chloride (PVC) or non-PVC tubing *containing a Baxter 0.22-micron high pressure extended life filter (part number 2H5660) which will be provided by OncoMed* and should be infused over 30 minutes (*+/- 5 minutes*) as an IV infusion.

Placebo is a formulation of 50mM Histidine, 100mM Sodium Chloride, 45mM Sucrose and 0.01% (v/v) Polysorbate-20, pH 6.0. Placebo will be administered in the same manner as OMP-59R5; i.e., withdraw the necessary amount of Placebo and dilute with *either half normal saline (NS) (0.45% Sodium Chloride (NaCl) or 5% Dextrose and 0.45% NaCl (D5W ½ NS)* to a

total volume of 250 mL and infuse over 30 minutes *(+/- 5 minutes). The diluted study drug should be administered within 4 hours of preparation.*

3.4 Clinical Background

Previously Read:

As of November 5, 2012, a total of thirty-nine subjects have been treated in Study 59R5-001: three at 0.5 mg/kg weekly, three at 1 mg/kg weekly, six at 2.5 mg/kg weekly, nine at 5 mg/kg weekly, six at 5 mg/kg every other week, three at 7.5mg/kg every other week, three at 10 mg/kg every other week, and six at 7.5mg/kg every three weeks.

The initial dose levels of OMP-59R5 in this study were 0.5, 1, 2.5, and 5 mg/kg administered IV once weekly. There were no DLTs observed at the 0.5 mg/kg (n=3), 1 mg/kg (n=3) or 2.5 mg/kg (n=3) dose levels. Two of the six subjects treated at 5 mg/kg once weekly experienced DLTs: one had Grade 3 hypokalemia secondary to diarrhea and the other had Grade 3 diarrhea. As a result, 5mg/kg once weekly exceeded the MTD and an additional three subjects were treated at 2.5 mg/kg once weekly. These three additional subjects tolerated treatment without a DLT thus defining an MTD as 2.5mg/kg once weekly for OMP-59R5.

Once the initial MTD was defined as described above, the protocol was amended to use a standard treatment algorithm to treat diarrhea and the DLT criteria was revised to define Grade 3 and above diarrhea that does not respond to standard medical treatment within 48 hours as a DLT. An additional three subjects were treated at the dose level of 5 mg/kg weekly with concomitant use of anti-diarrheal medications: all subjects were given a prescription for loperamide at study entry with instructions to take an initial 4 mg dose following the first loose stool, followed by 2 mg after every unformed stool with a maximum of 16 mg per day. Loperamide was continued until the subject was diarrhea-free for 12 hours. If Grade 3 diarrhea develops, loperamide would be discontinued and the subject would be started on second-line therapy (i.e., Lomotil 2 tablets 4 times daily and/or octreotide 100-150 μg subcutaneously [sc] three times daily and up to a maximum 500μg 3 times daily). One subject with prostate cancer developed Grade 2 anorexia and Grade 1 diarrhea. The second subject at 5mg/kg weekly, with colorectal cancer, developed Grade 2 diarrhea, Grade 2 dehydration, and Cycle 3 of OMP-59R5 was held at the discretion of the treating physician. The third subject at this dose level with non-small cell lung cancer developed Grade 1 diarrhea and Grade 1 abdominal pain. Due to poor tolerability of the 5 mg/kg weekly dose, despite the concomitant use of anti-diarrheal medication, a revised dosing schedule was implemented to define a new MTD with dosing of OMP-59R5 every other week.

Three subjects were treated at 5 mg/kg every other week and only Grade 1 diarrhea was noted from each of these three subjects. Dose escalation proceeded to 10 mg/kg every other week and two out of three subjects experienced DLT with Grade 3 diarrhea. Thus, 10 mg/kg every other week was defined as a dose above the MTD and the 5 mg/kg every other week dose level was expanded to enroll three additional subjects. A total of six subjects have been treated at 5 mg/kg

every other week and no DLT was noted. The dosing schedule was revised to explore an intermediary dose of 7.5mg/kg of OMP-59R5 every three weeks. Six subjects were treated at dose of 7.5mg/kg every three weeks with no DLTs noted, establishing the MTD of every three weeks schedule of 7.5 mg/kg. In addition, an intermediary dose of 7.5mg/kg every other week is also being explored. As of November 5, 2012, three subjects have been treated at 7.5mg/kg every other week and no DLT were noted. Exploration of 7.5 mg/kg every other week is ongoing with enrolling 3 additional subjects.

Diarrhea has been the most common adverse event, occurring in 58% (21 of 36) of subjects treated on the study regardless of schedule, which was expected based on the observance of diarrhea in the cynomolgus monkey toxicology study. Diarrhea was observed at 2.5 mg/kg weekly and above dose cohorts, and was dose dependent. Table 2 below tabulates the incidence and severity of diarrhea among dose levels according NCI-CTCAE criteria v4.02.

Table 2: Study 59R5-001: Treatment Related Diarrhea (N=21/36)

Diarrhea Grade	0.5 mg/kg QW (n=0/3)	1 mg/kg QW (n=0/3)	2.5 mg/kg QW (n=4/6)	5 mg/kg QW (n=8/9)	5 mg/kg QoW (n=2/3)	10 mg/kg Q0W (n=3/3)	7.5 mg/kg Q3W (n=4/6)
1	-	-	2	4	2	-	2
2	-	-	2	2	-	-	2
3	-	-	-	2	-	3	-

Additional common treatment-related adverse events included fatigue (28%), nausea (22%), decreased appetite (14%), vomiting (11%), dizziness (8%), increased alanine transaminase (ALT) (8%), dehydration (8%), hypokalemia (8%), abdominal pain (8%), anemia (8%), and thrombocytopenia (8%).

Table 2 and Table 3 summarize all treatment related CTC Grade 3 adverse events that occurred in Study 59R5-001 by body system; there were no Grade 4 or 5 events on study.

Table 3: Study 59R5-001: Grade 3 Treatment Related Adverse Events by Body System (N=36)

Body System	Preferred Term	Number of Subjects
Gastrointestinal Disorders	Diarrhea	5
Blood and Lymphatic System Disorders	Anemia	2
Investigations	Alanine Aminotransferase Increased (Grade 3)	1
Metabolism and Nutrition Disorders	Hypokalaemia	1
General Disorders and Administration Site Conditions	Fatigue	1

No RECIST complete or partial responses have been noted on this Phase 1 study. However, six subjects have had RECIST stable disease (SD) lasting greater than 56 days (ranging from 61 days to 165 days, all of them have come off the study).

Treatment with etoposide and cisplatin is the standard of care for subjects with untreated extended stage small cell lung cancer. The most common AE of OMP-59R5 is diarrhea, whereas cytopenia is the most common adverse event with EP administration. Therefore, the most common AEs of OMP-59R5 and EP do not overlap, providing the justification for investigating this combination in the study. Subjects enrolled in this study will receive a starting dose of 5 mg/kg of OMP-59R5 once every three weeks, which is one dose below the MTD of 7.5 mg/kg every three weeks in Study 59R5-001. Phase 1b lead-in portion of the study will provide preliminary safety and tolerability profile of this combination before the initiation of Phase 2 portion of the study. OMP-59R5 has an estimated apparent half time of 2 to 3 days at 7.5 mg/kg in Study 59R5-001, subjects will not receive PCI or WBRT within 2 weeks of study drug administration and will not receive OMP-59R5 during the radiation to alleviate any potential interaction between the study drug and the radiation. Therefore, risks and potential benefits of participation have been appropriately mitigated for this patient population.

Now Reads:

As of *April 25*, *2013*, a total of *forty-two* subjects have been treated in Study 59R5-001: three at 0.5 mg/kg weekly, three at 1 mg/kg weekly, six at 2.5 mg/kg weekly, nine at 5 mg/kg weekly, six at 5 mg/kg every other week, *six* at 7.5mg/kg every other week, three at 10 mg/kg every other week, and six at 7.5mg/kg every three weeks.

Two DLTs occurred in two of nine subjects treated at 5 mg/kg weekly: one Grade 3 hypokalemia secondary to Grade 3 diarrhea in one subject and one Grade 3 diarrhea in another subject, which led to the MTD for weekly dosing schedule to be 2.5 mg/kg. No DLTs occurred in 6 subjects treated at 7.5 mg/kg every three weeks that led to the MTD for every three week schedule to be 7.5 mg/kg. Two DLTs both Grade 3 diarrhea, occurred in two of three subjects treated with a single dose of OMP-59R5 at 10 mg/kg every other week and no DLTs occurred in 6 subjects treated at 7.5 mg/kg every other week, which led to the MTD for every other week schedule to be 7.5 mg/kg every other week.

Toxicities observed to date have been mostly Grades 1 and 2, and were manageable with supportive care and/or interruption or dose reduction of OMP-59R5. There were no AEs of a Grade 4 severity reported. AEs with a severity of Grade 3 were uncommon and have been primarily diarrhea.

Diarrhea has been the most common adverse event, occurring in *81*% (*34* of *42*) of subjects treated on the study regardless of schedule, which was expected based on the observance of diarrhea in the cynomolgus monkey toxicology study. Diarrhea was observed at 2.5 mg/kg

weekly and above dose cohorts, and was dose dependent. Table 2 below tabulates the incidence and *worse* severity of diarrhea *occurred while receiving OMP-59R5* among dose levels according NCI-CTCAE criteria v4.02.

Table 2: Study 59R5-001: *Worse Grade* Treatment Related Diarrhea (N=*34*/*42*)

Diarrhea Grade	0.5 mg/kg QW (n=*2*/3)	1 mg/kg QW (n=0/3)	2.5 mg/kg QW (n=*6*/6)	5 mg/kg QW (n=8/9)	5 mg/kg QoW (n=4/*6*)	10 mg/kg Q*o*W (n=3/3)	7.5 mg/kg Q3W (n=*5*/6)	*7.5 mg/kg QoW (n=6/6)*
1	*1*	-	*3*	4	*3*	-	*4*	*3*
2	*1*	-	*3*	2	-	-	*1*	*3*
3	-	-	-	2	*1*	3	-	

Additional common treatment-related adverse events included *(as of November 17, 2012 data cutoff with 39 subjects treated)* fatigue (*30.8*%), nausea (*28.2*%), decreased appetite (*17.9*%), vomiting (*15.4*%), increased alanine transaminase (ALT) (*10.3*%), hypokalemia (*15.4* and *dizziness* (*10.3*%).

Table 2 and Table 3 summarize all treatment related CTC Grade 3 adverse events that occurred in Study 59R5-001 by body system *as of November 17, 2012*; there were no Grade 4 or 5 events on study.

Table 3: Study 59R5-001: Grade 3 Treatment Related Adverse Events by Body System (N=*39*)

Body System	Preferred Term	Number of Subjects
Gastrointestinal Disorders	Diarrhea	*6 (15.4%*)
Blood and Lymphatic System Disorders	Anemia	2 (*5.1%*)
Investigations	Alanine Aminotransferase Increased *Aspartate Aminotransferase Increase*	*1 (2.6%)* *1 (2.6%)*
Metabolism and Nutrition Disorders	Hypokalaemia	*2 (5.1%)*
General Disorders and Administration Site Conditions	Fatigue	1 *(2.6*%)

No RECIST complete or partial responses have been noted on this Phase 1 study. However, six subjects have had RECIST stable disease (SD) lasting greater than 56 days (ranging from 61 days to 165 days, all of them have come off the study).

OMP-59R5 is also being studied in a phase 1b/2 study in combination with nab-paclitaxel and gemcitabine in subjects with previously untreated stage IV pancreatic cancer (Study OMP-59R5-

*002). The study was initially conducted in combination with gemcitabine alone and was amended to incorporate nab-paclitaxel into the chemotherapy backbone in response to the changes in standard of care in this disease population. As of April 26, 2013, thirteen subjects have been treated in Study OMP-59R5-002: five at 2.5 mg/kg every other week in combination with gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, four at 5 mg/kg every other week in combination with gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, four at 5 mg/kg every other week in combination with nab-paclitaxel at 125 mg/m^2 and gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, No DLTs have been reported, and Grade 1 diarrhea was noted in one subject each treated with OMP-59R5 at 5 mg/kg with gemcitabine, and with nab-paclitaxel and gemcitabine.*Treatment with etoposide and cisplatin is the standard of care for subjects with untreated extended stage small cell lung cancer. The most common AE of OMP-59R5 is diarrhea, whereas cytopenia is the most common adverse event with EP administration. Therefore, the most common AEs of OMP-59R5 and EP do not overlap, providing the justification for investigating this combination in the study. Subjects enrolled in this study will receive a starting dose of 5 mg/kg of OMP-59R5 once every three weeks, which is one dose below the MTD of 7.5 mg/kg every three weeks in Study 59R5-001. Phase 1b lead-in portion of the study will provide preliminary safety and tolerability profile of this combination before the initiation of Phase 2 portion of the study. OMP-59R5 has an estimated apparent half time of 2 to 3 days at 7.5 mg/kg in Study 59R5-001, subjects will not receive PCI or WBRT within 2 weeks of study drug administration and will not receive OMP-59R5 during the radiation to alleviate any potential interaction between the study drug and the radiation. Therefore, risks and potential benefits of participation have been appropriately mitigated for this patient population.

5.2 Dose Limiting Toxicity

Previously Read:

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (see Study Reference Binder). Dose-limiting toxicity (DLT) is defined as either of the following OMP-59R5 treatment-related toxicities occurring within the first 21 days (Cycle 1):

- Grade 4 neutropenia lasting >7 days in the absence of growth factor support

Now Reads:

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0*2* (see Study Reference Binder). Dose-limiting toxicity (DLT) is defined as either of the following OMP-59R5 treatment-related toxicities occurring within the first 21 days (Cycle 1):

- Grade 4 neutropenia lasting >7 days

6.0 SELECTION OF STUDY POPULATION

6.1 Inclusion Criteria

Previously Read:

d. Prothrombin Time (PT)/International Normalized Ration (INR) ≤1.5 × ULN, activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless the subject is on heparin or warfarin or other similar anti-coagulants.

Now Reads:

d. Prothrombin Time (PT)/International Normalized Ration (INR) ≤1.5 × ULN, activated partial thromboplastin time (aPTT) ≤1.5 × ULN.

6.2 Exclusion Criteria

Previously Read:

2. Prior therapy including radiation, chemotherapy or surgery for newly diagnosed extensive stage small cell lung cancer. Exceptions to this exclusion criterion include: 1) prophylactic cranial irradiation or whole brain radiation (WBRT) prior to the first administration of study drug provided that the subject has stable neurologic condition for at least 2 weeks after the completion of the radiation, 2) focused radiation for symptomatic relief for isolated bone metastases; 3) bisphosphonate or denosumab therapy for bone metastasis initiated prior to study entry.

3. Symptomatic brain metastases requiring whole brain irradiation within 4 weeks prior to first study drug administration or requiring daily doses of >40mg of oral prednisone, or require use of anti-epileptic drugs.

4. Presence of uncontrolled Grade ≥ 1 diarrhea within 4 weeks prior to the first study drug administration.

5. Current smoker.

6. Presence of any serious or uncontrolled illness including, but not limited to: ongoing or active infection, symptomatic congestive heart failure unstable angina pectoris, cardiac arrhythmia, arterial thrombosis, symptomatic pulmonary embolism, and psychiatric illness that would limit compliance with study requirement.

7. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty and/or stenting within 6 months prior to the first administration of study drug.

8. A history of malignancy with the exception of:
    a. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer
    b. Adequately treated stage I cancer from which the subject is currently in remission, or
    c. Any other cancer from which the subject has been disease-free for ≥ 3 years

9. Known human immunodeficiency virus (HIV) infection.

10. Females who are pregnant or breastfeeding.

Now Reads:

2. Prior therapy including radiation, chemotherapy or surgery for newly diagnosed extensive stage small cell lung cancer. Exceptions to this exclusion criterion include: 1) prophylactic cranial irradiation or whole brain radiation (WBRT) prior to the first administration of study drug provided that the subject has stable neurologic condition for at least 2 weeks after the completion of the radiation *and is not receiving corticosteroid of > 40 mg prednisone daily equivalent dose to control the symptoms*, 2) focused radiation for symptomatic relief for isolated bone metastases; 3) bisphosphonate or denosumab therapy for bone metastasis initiated prior to study entry.

3. Presence of uncontrolled Grade ≥ 1 diarrhea within 4 weeks prior to the first study drug administration.

4. Presence of any serious or uncontrolled illness including, but not limited to: ongoing or active infection, symptomatic congestive heart failure unstable angina pectoris, *uncontrolled* cardiac arrhythmia, *uncontrolled* arterial thrombosis, symptomatic pulmonary embolism, and psychiatric illness that would limit compliance with study requirement.

5. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty and/or stenting within 6 months prior to the first administration of study drug.

6. A history of malignancy with the exception of:
    a. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer
    b. Adequately treated stage I cancer from which the subject is currently in remission, or
    c. Any other cancer from which the subject has been disease-free for ≥ 3 years

7. Known human immunodeficiency virus (HIV) infection.

8. Females who are pregnant or breastfeeding.

9. *Con*current use *of therapeutic warfarin (prophylactic low dose of warfarin, i.e., 1 mg daily for port catheter is allowed).*

7.0 TREATMENT OF SUBJECTS

Previously Read:

Study drug will be OMP-59R5 in the Phase 1b portion, and either OMP-59R5 or Placebo in the Phase 2 portion. Study drug will be administered by IV infusion over 30 minutes on Day 1 of every 21-day cycle. The subject should not take two consecutive doses of study drug within 18 days.

Now Reads:

Study drug will be OMP-59R5 in the Phase 1b portion, and either OMP-59R5 or Placebo in the Phase 2 portion. Study drug will be administered by IV infusion over 30 minutes *(+/- 5 minute*s) on Day 1 of every 21-day cycle. The subject should not take two consecutive doses of study drug within 18 days.

7.1 Study Drug (OMP-59R5 or Placebo)

7.1.1 Study Drug Administration

Previously Read:

During Phase 1b and 2, OMP-59R5 must be delivered through tubing that contains a 0.22-micron filter and should be infused over 30 minutes as an IV infusion.

During Phase 2, Placebo will be administered in exactly the same manner as OMP-59R5; i.e., withdraw the necessary amount of Placebo and dilute with 5% Dextrose in Water (D5W) to a total volume of 250 mL and infuse over 30 minutes.

Now Reads:

During Phase 1b and 2, OMP-59R5 must be delivered through tubing *containing a* ***Baxter 0.22-micron high pressure extended life filter*** *(part number 2H5660) which will be provided by OncoMed* and should be infused over 30 minutes *(+/- 5 minutes)* as an IV infusion.

During Phase 2, Placebo will be administered in exactly the same manner as OMP-59R5; i.e., withdraw the necessary amount of Placebo and dilute with *either half normal saline (NS) (0.45% Sodium Chloride (NaCl) or5% Dextrose and 0.45% NaCl (D5W ½ NS)*to a total volume of 250 mL and infuse over 30 minutes *(+/- 5 minutes). The diluted study drug should be administered within 4 hours of preparation.*

7.1.5 Study Drug Preparation

Previously Read:

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

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

The diluted study drug solutions may be stored at room temperature (19°C–25°C) for up to 24 hours.

Now Reads:

The study drug should be diluted for infusion using aseptic technique. Withdraw the necessary amount of the study drug to obtain the required dose and dilute with *either half normal saline (NS) (0.45% Sodium Chloride (NaCl) or 5% Dextrose and 0.45% NaCl (D5 ½ NS)*, to a total volume of 250 mL. For example, if a 70-kg subject is to be dosed at 5 mg/kg, then the subject's dose would be 350 mg. Because the vials contain a concentration of 10 mg/mL, a total of 35 mL containing 350 mg should be withdrawn from the vial and diluted with *either 0.45% NaCl or 5% Dextrose and 0.45% NaCl (D5W ½ NS)*, to a total volume of 250 mL.

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

The diluted study drug solutions may be stored at room temperature (19°C–25°C) for up to *4* hours.

7.4 Dose Modifications or Delay for Treatment-Related Toxicities

Previously Read:

The investigator should hold OMP-59R5/placebo for treatment related toxicity according to Table 5, along with his/her best judgment. Subjects with a starting dose of 5 mg/kg study drug will have dose reduced to ≥2.5 mg/kg if dose reduction is required. Study drug will be discontinued permanently if study drug dosing is delayed for > 21 consecutive days despite supportive treatment, or if more than 2 dose reductions of study drug are required or dose reduction to < 2.5 mg/kg is required. Subjects continuing EP after discontinuing study drug will continue to receive etoposide on days 1, 2, and 3, and cisplatin on day 1 of each 21-day cycle for

a total of 6 cycles. Special attention should be paid to diarrhea as this is an expected adverse event of OMP-59R5 and Section 1.3 describes the recommended diarrhea management approach in this study.

Now Reads:

The investigator should hold OMP-59R5/placebo for treatment related toxicity according to Table 5, along with his/her best judgment. Subjects with a starting dose of 5 mg/kg study drug will have dose reduced to ≥2.5 mg/kg if dose reduction is required. Study drug will be discontinued permanently if study drug dosing is delayed for > 21 consecutive days *due to treatment –related toxicity (this is not applicable when PCI is administered as study drug will be held for > 21 consecutive days during PCI administration and will resume ≥ 14 days after the completion of PCI)* despite supportive treatment, or if more than 2 dose reductions of study drug are required or dose reduction to < 2.5 mg/kg is required. Subjects continuing EP after discontinuing study drug will continue to receive etoposide on days 1, 2, and 3, and cisplatin on day 1 of each 21-day cycle for a total of 6 cycles. Special attention should be paid to diarrhea as this is an expected adverse event of OMP-59R5 and Section 1.3 describes the recommended diarrhea management approach in this study.

Table 5: Suggested Guidelines for Study Drug and Etoposide-Cisplatin Dose Modification and Delay

Added:

Adverse Event	Study Drug Dose Reduction and/or Delay	Etoposide Dose Reduction and/or Delay	Cisplatin Dose Reduction and/or Delay
Absolute Neutrophil Count (ANC)			
500 -999/mm^3 without fever	*No change*	*Hold etoposide till ANC ≥ 1000/ mm^3. Resume etoposide based on timing of recovery and number of previous episodes* ➢ *≤ 3 consecutive weeks of interruption* • *1st episode, no change. Consider prophylactic myeloid growth factor according to institution's standard* • *2nd episode: reduce etoposide dose by 25% from starting dose for all subsequent administration* • *3rd episode, reduce etoposide dose by 50% from starting dose for all subsequent administration* • *4th episode, discontinue etoposide treatment* ➢ *> 3 consecutive weeks of interruption, discontinue etoposide permanently* *Continue supportive care according to institution's standard*	*Hold cisplatin till ANC ≥ 1000/ mm^3. Resume cisplatin based on timing of recovery and number of previous episodes* ➢ *≤ 3 consecutive weeks of interruption* • *1st episode, no change. Consider prophylactic myeloid growth factor according to institution's standard* • *2nd episode: reduce cisplatin dose by 25% for all subsequent administration* • *3rd episode, reduce cisplatin dose by 50% from starting dose for all subsequent administration* • *4th episode, discontinue cisplatin treatment.* ➢ *> 3 consecutive weeks of interruption, discontinue cisplatin permanently* *Continue supportive care according to institution's standard*

7.5 Anti-Emetics, Anti-diarrhea and Hematopoietic Supportive Care

Previously Read:

Hematopoietic growth factors, transfusion of blood and blood products should not be used in Cycle 1 of the dose escalation phase unless absolutely clinically necessary and after discussion with the OncoMed Medical Monitor. However, hematopoietic growth factors, transfusion of blood and blood products may be administered after Cycle 1 in the dose escalation phase or anytime during phase 2 portion as needed.

Now Read:

Hematopoietic growth factors, transfusion of blood and blood products should not be used *prophylactically prior to the dosing of the study drug and EP on Day 1 of Cycle 1, but may be administered per standard clinical practice during the course of the study as needed.*

7.6 Concomitant and Prohibited Therapy

Previously Read:

All concomitant medication administered within 28 days prior to the first administration of study drug through 30 days following the administration of the last dose of study drug will be recorded on the Concomitant Medication eCRF. Investigational medicinal products and anticancer agents (e.g., cytotoxic agents and biologics with known activity against small cell lung cancer) may not be administered from enrollment through the first line therapy.

Now Read:

All concomitant medication administered within 28 days prior to the first administration of study drug through 30 days following the administration of the last dose of study drug will be recorded on the Concomitant Medication eCRF. Investigational medicinal products, *therapeutic warfarin (prophylactic low dose of warfarin, i.e., 1 mg daily is allowed for port catheter)* and anticancer agents (e.g., cytotoxic agents and biologics with known activity against small cell lung cancer) may not be administered from enrollment through the first line therapy.

8.1 Adverse Events Definitions and Reporting Procedures

Previously Read:

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). The grading of the adverse events will be done using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (see Study Reference Binder).

Now Read:

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). The grading of the adverse events will be done using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0*2* (see Study Reference Binder).

10.0 BIOMARKERS AND EXPLORATORY ASSESSMENTS

Previously Read:

Optional Tumor Biomarkers: Optional tumor specimens will be collected during study visits and at the time of progression if feasible according to Schedule of Assessments (Appendix B and C) from subjects who are consented and who have tumor lesions that are amenable to core biopsies. Tumor samples will be analyzed for treatment-induced changes in Notch-related gene expression (i.e., mRNA) and/or protein markers and cancer stem cell–related gene expression.

Now Read:

Optional Tumor Biomarkers: Optional tumor specimens will be collected during study visits and at the time of *treatment termination,* if feasible according to Schedule of Assessments (APPENDIX B and APPENDIX C) from subjects who are consented and who have tumor lesions that are amenable to core biopsies. Tumor samples will be analyzed for treatment-induced changes in Notch-related gene expression (i.e., mRNA) and/or protein markers and cancer stem cell–related gene expression.

11.1 Screening

Deleted:

- Hair follicle samples (6 hairs) collected from subjects enrolled in Phase 1b portion only

11.2 Treatment Visits

Previously Read:

…Study drug administration (OMP-59R5 or placebo) should continue at every 21-day cycle between the completion of chemotherapy and the initiation of PCI.

Now Read:

…Study drug administration (OMP-59R5 or placebo) should continue at every 21-day (± *1 day*) cycle between the completion of chemotherapy and the initiation of PCI.

11.2.1 Cycle 1

11.2.1.1 Cycle 1 Day 1

Previously Read:

The following assessments will be completed prior to study drug infusion. These assessments will be repeated if they were done more than 3 days prior to Cycle 1 Day 1.

- Physical examination
- Weight
- ECOG performance status
- Hematology
- Serum chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)
- Electrocardiogram (ECG) including PR interval, RR interval, QRS duration, and QTc interval

The following assessments will be done prior to study drug infusion on Cycle 1 Day 1:

- Serum sample for anti-OMP-59R5 antibody on all subjects
- Blood sample for biomarker
- Plasma sample for OMP-59R5 PK from subjects enrolled in Phase 1b portion only
- Blood sample for pharmaco-genomics **(Optional and only if subject has signed the separate pharmacogenomics Informed Consent Form)**
- Concomitant medications
- Vital Signs

Now Reads:

The following assessments will be completed prior to study drug infusion. These assessments will be repeated if they were done more than *7* days prior to Cycle 1 Day 1.

- Physical examination
- ECOG performance status
- Hematology

- Serum chemistry
- Coagulation
- Urinalysis (dip stick is sufficient)
- Electrocardiogram (ECG) including PR interval, RR interval, QRS duration, and QTc interval

The following assessments will be done prior to study drug infusion on Cycle 1 Day 1:

- *Weight*
- Serum sample for anti-OMP-59R5 antibody on all subjects
- Blood sample for biomarker
- Plasma sample for OMP-59R5 PK from subjects enrolled in Phase 1b portion only
- *Hair follicle samples (6 hairs) collected from subjects enrolled in Phase 1b portion only*
- Blood sample for pharmaco-genomics **(Optional and only if subject has signed the separate pharmacogenomics Informed Consent Form)**
- Concomitant medications
- Vital Signs

Previously Read:

11.2.2.1 Day 1 of Cycles 2-6

Now Reads:

11.2.2.1 Day 1 (± *1 day*) of Cycles 2-6

Previously Read:

11.2.4.1 Day 1 of Cycle 7 and every cycle thereafter

Now Reads:

11.2.4.1 Day 1 *(± 1 day)* of Cycle 7 and every cycle thereafter

11.3 Treatment Termination

Previously Read:

Subjects who have agreed to the optional tumor core biopsy in the Informed Consent and have pre and post-treatment optional tumor biopsy collected, will have tumor core biopsy at the time of progression if feasible.

Now Reads:

Subjects who have agreed to the optional tumor core biopsy in the Informed Consent and have pre and post-treatment optional tumor biopsy collected, will have tumor core biopsy at the time of *treatment termination visit*, if feasible.

11.4 Follow up

Previously Read:

…

Additionally, subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during the Follow-up Period according to standard of care until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Now Reads:

…

Additionally, subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) *and bone scan every 12 weeks (+/- 5 days)* during the Follow-up Period according to standard of care until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

13.5.2 Safety Endpoints

Adverse Events

Previously Read:

…The incidence of adverse events in each treatment group will be tabulated by NCI-CTCAE v 4.03 grade and relationship to study drug.

Now Reads:

…The incidence of adverse events in each treatment group will be tabulated by NCI-CTCAE v 4.0*2* grade and relationship to study drug.

NOTES TO APPENDIX B and APPENDIX C:

Additional tests were added and the Schedule of Assessments Tables were revised to reflect changes made in the protocol. Footnotes were revised accordingly.

APPENDIX B: SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 1B

Previously Read:

d. The assessment (except for vital sign that needs to be obtained prior to the infusion) does not need to be repeated if it was done within 3 days prior to the first dose

e. Height required at screening only. Vital signs: screening, day 1 of each cycle prior to the start of study drug dosing, days 2 and 3 prior to etoposide administration during Cycles 1 through 6 and treatment termination.

f. Hematology includes complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count. The results need to be reviewed by the investigator prior to each study drug and EP administration. Hematology on Day 1 of each cycle can be performed up to 3 days prior to Day 1 dosing.

g. Full chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, albumin, calcium, phosphate, and magnesium. Chemistry on Day 1 of each cycle can be performed up to 3 days prior to Day 1 dosing.

h. Plasma samples will be obtained for OMP-59R5 pharmacokinetic analysis at pre-dose and 5 minutes (±2 minutes) after the end of OMP-59R5 infusion on Day 1 of Cycle 1 and Cycle 3, and on Days 3 (pre-dose) and 8 of Cycles 1 and 3, as well as at treatment termination. On days when OMP-59R5 and etoposide and/or cisplatin are given together, the plasma sample should be obtained 5 minutes (±2 minutes) after the completion of the infusion of OMP-59R5, but prior to EP administration.

k. Hair follicle mRNA expression: Predose hair samples (6 hairs) will be collected at screening and on Day 8 of Cycle 2 only for gene expression analysis of Notch pathway–related gene expression as described in Section 11.0. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder.

l. Only on Day 1 of Cycle 1 prior to OMP-59R5 infusion.

m. FFPE tumor specimens obtained will be collected. Notch3 expression levels will be assessed in FFPE tumor specimens, either archived or fresh core needle biopsied at study entry (two FFPE cores preferred whenever possible). FFPE samples must be obtained during screening. Notch3 levels will be measured by immunohistochemistry and/or a quantitative PCR gene expression assay. Notch 2 and other Notch-related genes and proteins may also be measured. In addition, DNA testing may be performed on the FFPE tumor specimens for subjects who sign the optional FFPE Informed Consent for DNA testing. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder.

n. Optional tumor biopsy will be done at screening, on Day 8 of Cycle 2, and at the time of progression if feasible. The site can call the Sponsor's medical monitor to discuss an alternative timepoint if it is not feasible to collect the optional tumor biopsy on Day 8 (±2) of Cycle 2.

o. Contrast CT of chest, abdomen and pelvis, and brain MRI/CT with contrast will be performed every 6 weeks (±5 days) after initial study drug dosing (prior to the start of Cycle 3 and every 6 weeks±5 days thereafter). MRI can be used in lieu of contrast-enhanced CT for subjects who are allergic to contrast. The same methodology should be used throughout the study to follow the same lesion.

p. Subjects who have not demonstrated disease progression will have contrast CT of chest and abdomen (or MRI for subjects who are allergic to contrast), MRI/CT of brain conducted every 6 weeks (± 5 days) after initial study drug dosing until disease progression or initiation of new anti-cancer therapy. The same methodology should be used throughout the study.

Now Reads:

d. The assessment does not need to be repeated if it was done within *7* days prior to the first dose

e. Height required at screening only. Vital signs *and weight*: screening, day 1 of each cycle prior to the start of study drug dosing, days 2 and 3 prior to etoposide administration during Cycles 1 through 6 and treatment termination.

f. Hematology includes complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count. The results need to be reviewed by the investigator prior to each study drug and EP administration. Hematology on Day 1 of each cycle *starting from Cycle 2* can be performed up to 3 days prior to Day 1 dosing.

g. Full chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, albumin, calcium, phosphate, and magnesium.

Chemistry on Day 1 of each cycle *starting from Cycle 2* can be performed up to 3 days prior to Day 1 dosing.

h. Plasma samples will be obtained for OMP-59R5 pharmacokinetic analysis at pre-dose and 5 minutes (±2 minutes) after the end of OMP-59R5 infusion *and prior to the EP administration* on Day 1 of Cycle 1 and Cycle 3, and on Days 3 (pre-dose) and 8 of Cycles 1 and 3, as well as at treatment termination. On days when OMP-59R5 and etoposide and/or cisplatin are given together, the plasma sample should be obtained 5 minutes (±2 minutes) after the completion of the infusion of OMP-59R5, but prior to EP administration.

k. Hair follicle mRNA expression: Predose hair samples (6 hairs) will be collected at *Day 1 of Cycle 1 (pre-dose)* and on Day 8 of Cycle 2 only for gene expression analysis of Notch pathway-related gene expression as described in Section 11.0. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder.

l. Only on Day 1 of Cycle 1 prior to OMP-59R5 infusion *from subjects who have signed separate pharmacogenomics Informed Consent Form*.

m. FFPE tumor specimens obtained will be collected. Notch3 expression levels will be assessed in FFPE tumor specimens, either archived or fresh core needle biopsied at study entry (two FFPE cores preferred whenever possible). FFPE samples must be obtained during screening. Notch3 levels will be measured by immunohistochemistry and/or a quantitative PCR gene expression assay. Notch 2 and other Notch-related genes and proteins may also be measured. In addition, DNA testing may be performed on the FFPE tumor specimens for subjects who sign the optional FFPE Informed Consent for DNA testing. Instructions for the collection, handling, storage, and shipment of these samples are provided in the Study Reference Binder.

n. Optional tumor biopsy will be done at screening, on Day 8 of Cycle 2, and at the time of *treatment* termination*,* if feasible. The site can call the Sponsor's medical monitor to discuss an alternative timepoint if it is not feasible to collect the optional tumor biopsy on Day 8 (±2) of Cycle 2.

o. Contrast CT of chest, abdomen and pelvis, and brain MRI/CT with contrast will be performed at screening. Contrast CT of chest, abdomen and pelvis will be performed every 6 weeks (±5 days) after initial study drug dosing (prior to the start of Cycle 3 and every 6 weeks±5 days thereafter). MRI can be used in lieu of contrast-enhanced CT for subjects who are allergic to contrast. The same methodology should be used throughout the study to follow the same lesion.

p. Subjects who have not demonstrated disease progression will have contrast CT of chest, *pelvis* and abdomen (or MRI for subjects who are allergic to contrast), conducted every 6 weeks (± 5 days) after initial study drug dosing until disease progression or initiation of new anti-cancer therapy. The same methodology should be used throughout the study.

APPENDIX C SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 2

Previously Read:

d. The assessment (except for vital sign that needs to be obtained prior to the infusion) does not need to be repeated if it was done within 3 days prior to the first dose.

e. Height required at screening only. Vital signs: screening, day 1 of each cycle prior to the start of the treatment, days 2 and 3 prior to etoposide administration from Cycles 1 thru 6, and treatment termination.

f. Hematology includes complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count. The results need to be reviewed by the investigator prior to each study drug administration. Hematology on day 1 of each cycle can be performed up to 3 days prior to Day 1 dosing.

g. Full chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, albumin, calcium, phosphate, and magnesium. Chemistry on Day 1 of each cycle can be performed up to 3 days prior to Day 1 dosing.

j. Only on Day 1 of Cycle 1 prior to OMP-59R5 infusion.

m. Optional tumor biopsy will be done at screening, on Day 8 of Cycle 2, and at the time of progression if feasible. The site can call the Sponsor's medical monitor to discuss an alternative timepoint if it is not feasible to collect the optional tumor biopsy on Day 8 (±2) of Cycle 2.

n. Contrast CT of chest, abdomen and pelvis, and MRI of brain will be performed every 6 week s ± 5 days) after initial study drug dosing (prior to the start of Cycle 3 and every two cycles thereafter). MRI can be used in lieu of contrast-enhanced CT for subjects who are allergic to contrast. The same methodology should be used throughout the study to follow the same lesion.

o. Subjects who have not demonstrated disease progression will have contrast CT of chest, abdomen and pelvis (or MRI for subjects who are allergic to contrast), and MRI/CT of brain conducted every 6 weeks (±5 days) after initial study drug dosing until disease progression or initiation of new anti-cancer therapy. The same methodology should be used throughout the study.

Now Reads:

d. The assessment does not need to be repeated if it was done within *7* days prior to the first dose.

e. Height required at screening only. Vital signs *and weight*: screening, day 1 of each cycle prior to the start of the treatment, days 2 and 3 prior to etoposide administration from Cycles 1 thru 6, and treatment termination.

f. Hematology includes complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count. The results need to be reviewed by the investigator prior to each study drug administration. Hematology on day 1 of each cycle *starting from Cycle 2* can be performed up to 3 days prior to Day 1 dosing.

g. Full chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, albumin, calcium, phosphate, and magnesium. Chemistry on Day 1 of each cycle *starting from Cycle 2* can be performed up to 3 days prior to Day 1 dosing.

j. Only on Day 1 of Cycle 1 prior to OMP-59R5 infusion *from subjects who have signed separate pharmacogenomics Informed Consent Form.*

m. Optional tumor biopsy will be done at screening, on Day 8 of Cycle 2, and at the time of *treatment termination,* if feasible. The site can call the Sponsor's medical monitor to discuss an alternative timepoint if it is not feasible to collect the optional tumor biopsy on Day 8 (±2) of Cycle 2.

n. *Contrast CT of chest, abdomen and pelvis, and MRI of brain will be performed at screening.* Contrast CT of chest, abdomen and pelvis will be performed every 6 week s ± 5 days) after initial study drug dosing (prior to the start of Cycle 3 and every two cycles thereafter). MRI can be used in lieu of contrast-enhanced CT for subjects who are allergic to contrast. The same methodology should be used throughout the study to follow the same lesion.

o. Subjects who have not demonstrated disease progression will have contrast CT of chest, abdomen and pelvis (or MRI for subjects who are allergic to contrast), conducted every 6 weeks (±5 days) after initial study drug dosing until disease progression or initiation of new anti-cancer therapy. The same methodology should be used throughout the study.

APPENDIX F: SAMPLE INFORMED CONSENT

SCREENING

Blood and Urine Sample Collection:

Deleted:

Hair Follicles: Six hairs will be plucked from your head for additional marker testing if you are participating in the first portion of the study

Previously Read:

Tumor assessments: An examination of your tumor(s) by CT (computerized tomography test, like an x-ray that produces a picture of your body including tumors using radiation), or MRI (magnetic resonance imaging - use of a magnetic field to produce an image of your body including tumors) or bone scan (an X-ray to look at your bone). Your study doctor will determine which type of test (either CT or MRI) is best to assess your cancer. A bone scan will also be done to find out if tumors have spread to your bones. This is part of your routine cancer care.

Now Reads:

Tumor assessments: An examination of your tumor(s) by CT (computerized tomography test, like an x-ray that produces a picture of your body including tumors using radiation), or MRI (magnetic resonance imaging - use of a magnetic field to produce an image of your body including tumors) *and* bone scan (an X-ray to look at your bone). Your study doctor will determine which type of test (either CT or MRI) is best to assess your cancer. A bone scan will also be done to find out if tumors have spread to your bones. This is part of your routine cancer care.

Cycle 1 Day 1

Previously Read:

This is the first day of study treatment (Cycle 1 Day 1).You will receive study drug, etoposide, and cisplatin on this day.-You will have the following procedures done during this visit:

- Physical Examination and weight before dosing (if this was done more than 3 days ago)
- Electrocardiogram (ECG) before dosing (if this was done more than 3 days ago)
- Urine Sample Collection before dosing (if this was done more than 3 days ago)
- Blood Sample Collection before dosing – about 1 tablespoon of blood for your health condition-(if this was done more than 3 days ago)
- Additional Blood Sample Collection before dosing – about 2 tablespoons of blood to assess the level of certain markers and proteins that might be against OMP-59R5
- If you are participating in the first portion of the study, you will also have 1 teaspoon of blood taken before starting study drug dosing tocheck the level of OMP59R5 in the blood
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about any changes in your health status after taking your initial dose of the study drug, etoposide, and cisplatin.

Now Reads:

This is the first day of study treatment (Cycle 1 Day 1).You will receive study drug, etoposide, and cisplatin on this day.-You will have the following procedures done during this visit:

- Physical Examination before dosing (if this was done more than 7 days ago)
- Electrocardiogram (ECG) before dosing (if this was done more than 7 days ago)
- Urine Sample Collection before dosing (if this was done more than 7 days ago)
- Blood Sample Collection before dosing – about 1 tablespoon of blood for your health condition-(if this was done more than 7 days ago)
- *Weight before dosing*
- *Hair follicles: Six hairs will be plucked from your head for additional marker testing if you are participating in the first portion of the study*
- Additional Blood Sample Collection before dosing – about 2 tablespoons of blood to assess the level of certain markers and proteins that might be against OMP-59R5
- If you are participating in the first portion of the study, you will also have 1 teaspoon of blood taken before starting study drug dosing tocheck the level of OMP59R5 in the blood
- Your blood pressure, temperature, heart rate, rate of breathing, and weight will be measured
- You will be asked about any changes in your health status after taking your initial dose of the study drug, etoposide, and cisplatin.

TREATMENT TERMINATION

Previously Read:

Optional Tumor Biopsy: If your tumor has grown or spread, an optional tumor biopsy will be done only if you agree.

Now Reads:

Optional Tumor Biopsy: *A*n optional tumor biopsy will be done only if you agree.

PREGNANCY

Previously Read:

… If either you or your partner becomes pregnant during the study or within 30 days after the last dose of study drug or etoposide or cisplatin whichever is discontinued last, you and/or your partner will be followed through the first well-baby visit or longer if any abnormality is present.

Now Reads:

…If either you or your partner becomes pregnant during the study or within 30 days after the last dose of study drug or etoposide or cisplatin whichever is discontinued last, you and/or your partner will be followed through *outcome of the birth*.

AMENDMENT 2: 19 AUGUST 2013

The following changes were made to the protocol. Italics in the text indicate new text.

RATIONALE

The protocol has been amended to allow the dose escalation beyond 7.5 mg/kg if the MTD is not reached. Additionally, the protocol clarifies that PET/CT scan can be used in lieu of bone scan to follow bone lesions throughout the study. Day 2 and Day 3 blood draws for hematology have been eliminated as they are not part of standard of care. Blood sample for hematology was added to Day 8 of Cycles 1 through 3 only when blood samples are taken for biomarkers and PK.

SUMMARY OF CHANGES:

Study Design (Cont'd):

Previously Read:

Additionally, subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up according to standard of care until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Now Reads:

Additionally, subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Exclusion Criteria:

Added:

b. Superficial bladder cancer

Efficacy Evaluation:

Previously Read:

…Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up according to

standard of care until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Now Reads:

… Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

3.4 Clinical Background

Previously Read:

…As of April 26, 2013, thirteen subjects have been treated in Study OMP-59R5-002: five at 2.5 mg/kg every other week in combination with gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, four at 5 mg/kg every other week in combination with gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, four at 5 mg/kg every other week in combination with nab-paclitaxel at 125 mg/m^2 and gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, No DLTs have been reported, and Grade 1 diarrhea was noted in one subject each treated with OMP-59R5 at 5 mg/kg with gemcitabine, and with nab-paclitaxel and gemcitabine.

Now Reads:

…As of *August 19*, 2013, *twenty four* subjects have been treated in Study OMP-59R5-002: five and *four* at 2.5 mg/kg *and 5.0 mg/kg respectively* every other week in combination with gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, four, *six and four* at 5 mg/kg, *7.5 mg/kg and 10 mg/kg respectively* every other week in combination with nab-paclitaxel at 125 mg/m^2 and gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle. No DLTs have been reported, and *the most common reported OMP-59R5 treatment-related event is diarrhea, fatigue and nausea that are mostly grade 1 or 2, managed with supportive care. One Grade 3 diarrhea was noted in one of four subjects treated with 10 mg/kg OMP-59R5 with Nab-P+Gem, lasted less than 48 hours and resolved to Grade 1 diarrhea after concurrent use of lomotil.*

5.3 Dose Escalation Plan

Previously Read:

…

The starting dose of OMP-59R5 is 5 mg/kg on Day 1 of each 21-day cycle. The subsequent dose level will be 7.5 mg/kg on Day 1 of each 21-day cycle. Dose escalation will proceed if no DLT

is observed in a cohort of 3 subjects after discussion and agreement between the participating Investigators and Sponsor's Medical Monitor.

Now Reads:

…

The starting dose of OMP-59R5 is 5 mg/kg on Day 1 of each 21-day cycle. The subsequent dose level will be *increased in 2.5 mg/kg increments (i.e., 7.5 mg/kg, 10 mg/kg, etc) until the MTD is reached*. Dose escalation will *only* proceed if no DLT is observed in a cohort of *at least* 3 subjects after discussion and agreement between the participating Investigators and Sponsor's Medical Monitor.

5.4.1 Follow-Up

Previously Read:

Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during follow-up according to standard of care until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Now Reads:

Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

5.5.2 Follow-up

Previously Read:

Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up according to standard of care until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Now Reads:

Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

6.2 Exclusion Criteria

Previously Read:

6. A history of malignancy with the exception of:

   a. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer

   b. Adequately treated stage I cancer from which the subject is currently in remission, or

Now Reads:

6. A history of malignancy with the exception of:

   a. Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer

   b. Superficial bladder cancer

7.5 Anti-Emetics, Anti-diarrhea and Hematopoietic Supportive Care

Previously Read:

Antiemetic therapy and anti-diarrheal may be administered at the discretion of the Investigator.

Now Reads:

Antiemetic therapy and anti-diarrheal *medications* may be administered at the discretion of the Investigator.

9.0 EFFICACY ASSESSMENTS

Previously Read:

Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up according to standard of care until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Now Reads:

Subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) during Follow-up until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

11.1 Screening

Previously Read:

- Radiographic evaluation: CT with contrast, or MRI of the chest, abdomen, pelvis, and brain, and bone scan performed as outlined by the RECIST criteria 1.1 (see APPENDIX E). Note: The same method (CT or MRI) must be used consistently throughout the study to follow the same anatomical location.

Now Reads:

- Radiographic evaluation: CT with contrast, or MRI of the chest, abdomen, pelvis, and brain, and bone scan performed as outlined by the RECIST criteria 1.1 (see APPENDIX E). Note: PET/CT can be used in lieu of bone scan to identify and follow up bone lesions. The same method (CT or MRI, bone scan or PET/CT for bone lesions) must be used consistently throughout the study to follow the same anatomical location.

11.2.1.2 Cycle 1 Day 2

The following assessments will be completed prior to etoposide infusion:

Deleted:

- Hematology

Administration of etoposide:

Previously Read:

Hematology results must be reviewed by the investigator prior to etoposide dosing.

Now Reads:

- *Etoposide dosing will be given.*

11.2.1.3 Cycle 1 Day 3

The following assessments will be completed prior to etoposide infusion:

Deleted:

- Hematology

Added:

- *Adverse event reporting*

Administration of etoposide:

Previously Read:

Hematology results must be reviewed by the investigator prior to etoposide dosing.

Now Reads:

- *Etoposide dosing will be given.*

11.2.1.4 Cycle 1 Day 8

Added:

- Hematology

11.2.2.1 Day 1 (± 1 day) of Cycles 2-6

Previously Read:

- Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, and pelvis will be done every 6 weeks+5 days after Day 1 of Cycle 1 (Day 1 of Cycle 3 and every 6 weeks+5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. Bone scan will be completed every other tumor assessment (Day 1 of Cycle 5 and every 12 weeks/+5 days).

Now Reads:

Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, *and* pelvis will be done every 6 weeks±5 days after Day 1 of Cycle 1 (Day 1 of Cycle 3 and every 6 weeks±5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. *If bone scan is used to follow bone lesions, b*one scan will be completed every other tumor assessment (Day 1 of Cycle 5 and every 12 weeks/±5 days). *If PET/CT is used to follow bone lesions, PET/CT will be done at the same schedule as the assessments for other lesions (every 6 weeks ±5 days thereafter).*

11.2.2.2 Day 2 of Cycles 2-6

The following assessments will be completed prior to etoposide infusion:

Added:

- *Adverse event recording*

Now Reads:

- Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, and pelvis will be done every 6 weeks+5 days after Day 1 of Cycle 1 (Day 1 of Cycle 3 and every 6 weeks+5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. *If bone scan is used to follow bone lesions, b*one scan will be completed every other tumor assessment (Day 1 of Cycle 5 and every 12 weeks/+5 days). *If PET/CT is used to follow bone lesions, PET/CT will be done at the same schedule as the assessments for other lesions (every 6 weeks +5 days thereafter).*

11.2.2.2 Day 2 of Cycles 2-6

The following assessments will be completed prior to etoposide infusion:

Deleted:

- Hematology

Added:

- *Adverse event recording*

Administration of etoposide:

Deleted:

- Adverse event recording

Previously Read:

Hematology results must be reviewed by the investigator prior to etoposide dosing.

Now Reads:

- *Etoposide dosing will be given.*

11.2.2.3 Day 3 of Cycles 2-6

The following assessments will be completed prior to etoposide infusion:

Deleted:

- Hematology

Added:

- *Adverse event recording*

Administration of etoposide:

Deleted:

- Adverse event recording

Previously Read:

Hematology results must be reviewed by the investigator prior to etoposide dosing.

Now Reads:

- *Etoposide dosing* will be given.

11.2.2.4. Day 8 of Cycles 2 and 3 Only

The following assessments will be completed prior to etoposide infusion:

Deleted:

- Hematology

Added:

- *Adverse event reporting*

Administration of etoposide:

Previously Read:

Hematology results must be reviewed by the investigator prior to etoposide dosing.

Now Reads:

- *Etoposide dosing will be given.*

Deleted:

- Adverse event reporting

Day 3 of Cycles 2-6

The following assessments will be completed prior to etoposide infusion:

Deleted:

- Hematology

Added:

- *Adverse event reporting*

Administration of etoposide:

Previously Read:

Hematology results must be reviewed by the investigator prior to etoposide dosing.

Now Reads:

- *Etoposide dosing will be given.*

Deleted:

- Adverse event reporting

11.2.2.4 Day 8 of Cycles 2 and 3 Only

Added:

- Hematology

11.2.4.1 Day 1 (± *1 day*) of Cycle 7 and every cycle thereafter

Previously Read:

- Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, pelvis, will be done every 6 weeks±5 days after Day 1 of Cycle 1 (Day 1 of Cycle 7 and every 6 weeks±5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. Bone scan will be completed every other tumor assessment (Day 1 of Cycle 9, and every 12 weeks/±5 days thereafter).

Now Reads:

- Tumor assessment with CT (with contrast), or MRI scan of chest, abdomen, pelvis, will be done every 6 weeks±5 days after Day 1 of Cycle 1 (Day 1 of Cycle 7 and every 6 weeks±5 days thereafter). The same method should be used throughout the study to follow the same anatomical location. If bone scan is used to follow bone lesions, bone scan will be completed every other tumor assessment (Day 1 of Cycle 9, and every 12 weeks/±5 days thereafter). If PET/CT is used to follow bone lesions, PET/CT will be done at the same schedule as the assessments for other lesions (every 6 weeks ±5 days thereafter).

11.4 Follow up

Previously Read:

…

Additionally, subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) and bone scan every 12 weeks (+/- 5 days) during the Follow-up Period according to standard of care until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

Now Reads:

…

Additionally, subjects who discontinue study treatment for any reason other than disease progression will be followed with tumor assessment every 6 weeks/42 days (±5 days) and bone scan every 12 weeks (+/- 5 days) during the Follow-up Period until documented disease progression or initiation of new anti-cancer therapy, whichever is sooner.

13.1 Power and Sample Size

Previously Read:

The Phase 1b portion of the trial is a 3+3 dose escalation design. Table 6 shows the probability of declaring a dose as the MTD for a variety of underlying toxicity rates. For example there is an 83 percent probability to declare a dose with an incidence of dose limiting toxicity of 50 percent as the MTD. This compares with a probability of 29 percent for a dose with an incidence of dose limiting toxicity of 20 percent.

Table 6: Power to Declare a Dose as the MTD for Various Incidence Rates

Now Reads:

The Phase 1b portion of the trial is a 3+3 dose escalation design. Table 6 shows the probability of declaring a dose as *exceeding* the MTD for a variety of underlying toxicity rates. For example there is an 83 percent probability to declare a dose with an incidence of dose limiting toxicity of 50 percent as *exceeding* the MTD. This compares with a probability of 29 percent for a dose with an incidence of dose limiting toxicity of 20 percent.

Table 6: Power to Declare a Dose as *Exceeding* the MTD for Various Incidence Rates

APPENDIX B: SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 1B

Previously Read:

	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
Procedure	Day -28 to -1	Day-14 to -1	Day 1 (±1 day)	Day 2	Day 3	Day 8 (Cycles 1-3 only)	Post Cycle 6	Day 1(± 1 day)	Treatment Termination[a]	Every 3 months
Hematology[f]		X	X[d]	X	X			X	X	

Now Reads:

	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
Procedure	Day -28 to -1	Day-14 to -1	Day 1 (±1 day)	Day 2	Day 3	Day 8 (Cycles 1-3 only)	Post Cycle 6	Day 1(± 1 day)	Treatment Termination[a]	Every 3 months
Hematology[f]		X	X[d]			*X*		X	X	

NOTES TO APPENDIX B: (Cont'd)

Previously Read:

q. Bone scan will be done at screening and every other tumor assessment (every 12 weeks ±5 days) until disease progression or initiation or new anti-cancer therapy.

Now Reads:

q. *If bone scan is used to follow bone lesions, b*one scan will be done at screening and every other tumor assessment (every 12 weeks ±5 days) until disease progression or initiation or new anti-cancer therapy. *If PET/CT is used to follow bone lesions, PET/CT will be completed at the same schedule as the assessments for other lesions (every 6 weeks ±5 days). The same method (bone scan or PET/CT) should be used throughout the study to follow bone lesions.*

APPENDIX C SCHEDULE OF ASSESSMENTS FOR SUBJECTS IN PHASE 2

Previously Read:

	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
Procedure	**Day -28 to -1**	**Day-14 to -1**	**Day 1 (±1 day)**	**Day 2**	**Day 3**	**Day 8 (Cycles 1-3 only)**	**Post Cycle 6**	**Day 1(± 1 day)**	**Treatment Termination[a]**	**Every 3 months**
Hematology[f]		X	X[d]	X	X			X	X	

Now Reads:

	Screening		Treatment Period							Follow-Up[b]
			Cycles 1-6 (every 21 days)					≥ Cycles 7 (every 21 days)		
Procedure	**Day -28 to -1**	**Day-14 to -1**	**Day 1 (±1 day)**	**Day 2**	**Day 3**	**Day 8 (Cycles 1-3 only)**	**Post Cycle 6**	**Day 1(± 1 day)**	**Treatment Termination[a]**	**Every 3 months**
Hematology[f]		X	X[d]			*X*		X	X	

NOTES TO APPENDIX C: (Cont'd)

Previously Read:

p. Bone scan will be done at screening and every other tumor assessment (every 12 weeks ±5 days) until disease progression or initiation or new anti-cancer therapy.

Now Reads:

p. *If bone scan is used to follow bone lesions, b*one scan will be done at screening and every other tumor assessment (every 12 weeks ±5 days) until disease progression or initiation or new anti-cancer therapy. *If PET/CT is used to follow bone lesions, PET/CT will be completed at the same schedule as the assessments for other lesions (every 6 weeks ±5 days) The same method (bone scan or PET/CT) should be used throughout the study to follow bone lesions.*

APPENDIX F: SAMPLE INFORMED CONSENT

Previously Read:

PROCEDURES

The first portion of the study will include approximately 16 patients at about 5 centers in the United States and Europe. The second portion of the study will include approximately 80 patients at about 35 centers in the United States and Europe.

Now Reads:

The first portion of the study will include approximately 16 patients at about *7* centers in the United States. The second portion of the study will include approximately 80 patients at about 35 centers in the United States and Europe.

Previously Read:

Tumor assessments: An examination of your tumor(s) by CT (computerized tomography test, like an x-ray that produces a picture of your body including tumors using radiation), or MRI (magnetic resonance imaging - use of a magnetic field to produce an image of your body including tumors) *and* bone scan (an X-ray to look at your bone). Your study doctor will determine which type of test (either CT or MRI) is best to assess your cancer. A bone scan will also be done to find out if tumors have spread to your bones. This is part of your routine cancer care.

Now Reads:

Tumor assessments: An examination of your tumor(s) by CT (computerized tomography test, like an x-ray that produces a picture of your body including tumors using radiation), or MRI (magnetic resonance imaging - use of a magnetic field to produce an image of your body including tumors) *or PET/CT (positron emission tomography- measures metabolic activity within the body. When combined with CT, PET/CT will determine abnormal metabolic activity at a specific anatomic location) or* bone scan (an X-ray to look at your bone). Your study doctor will determine which type of test (CT or MRI, *or PET/CT or bone scan*) is best to assess your cancer. This is part of your routine cancer care.

TREATMENT PHASE

Previously Read:

If you are found to be eligible to participate, you will be enrolled in the study.

If you are in the first portion of the study, you will be assigned to a pre-determined dose level of OMP-59R5. The initial dose levels of OMP-59R5 that will be tested in this study are 5mg/kg and 7.5 mg/kg (if the lower doses are tolerable) administered through the vein. You will be given the following drugs every 21 days: OMP-59R5 on Day1, etoposide 100 mg/m^2 on Days 1, 2, and 3, and cisplatin 80 mg/m^2 on Day 1.

… If your disease is at least stable or have responded to therapy at the end of cycle 6 and you doctor think it is appropriate, you will also receive radiation to your brain to help prevent tumors recurring around 8 weeks after the last administration of chemotherapy.

Now Reads:

If you are found to be eligible to participate, you will be enrolled in the study.

If you are in the first portion of the study, you will be assigned to a pre-determined dose level of OMP-59R5. The dose levels of OMP-59R5 that will be tested in this study are 5 mg/kg, 7.5 mg/kg *and at 2.5 mg/kg per increment* (if the lower doses are tolerable) administered through the vein. You will be given the following drugs every 21 days: OMP-59R5 on Day1, etoposide 100 mg/m2 on Days 1, 2, and 3, and cisplatin 80 mg/m2 on Day 1.

…

If your disease is at least stable or have responded to therapy at the end of cycle 6 and you doctor think it is appropriate, you will also receive radiation to your brain to help prevent tumors recurring *within* 8 weeks after the last administration of chemotherapy.

Cycle 1 Day 2

Deleted:

- About 1 tablespoon of blood sample will be taken to review your health condition.

Cycle 1 Day 3

- About 1 tablespoon of blood sample will be taken to review your health condition.

Cycle 1 Day 8

Previously Read:

- About 2 tablespoons of blood sample will be taken to check the level of certain markers and the level of OMP-59R5 in the blood

Now Reads:

- About *3* tablespoons of blood sample will be taken to check the level of certain markers, the level of OMP-59R5 in the blood *and your health status*

Cycle 2 Day 2

Previously Read:

- About 3 tablespoons of blood will be taken to review your health condition and to assess the level of certain markers.

Now Reads:

- About *2* tablespoons of blood will be taken to assess the level of certain markers.

Cycle 2 Day 3

Previously Read:

- About 1 tablespoon of blood will be taken to review your health condition. You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Now Reads:

- You will be asked about changes in your medical status or any new health issues and any medications you are taking since the previous study visit.

Cycle 2 Day 8

Previously Read:

- About 2 tablespoons of blood will be taken to check the level of certain markers.

Now Reads:

- About *3* tablespoons of blood will be taken to check the level of certain markers *and your health status.*

Cycle 3 Day 1

Previously Read:

Tumor assessment: A CT scan or MRI will be done approximately every 6 weeks after your initial study drug dosing (Day 1 of Cycle 3 and every 6 weeks thereafter). A bone scan will be done at every other tumor assessment (approximately every 12 weeks after initial study drug dosing).

Now Reads:

Tumor assessment: A CT scan or MRI *or PET/CT* will be done approximately every 6 weeks after your initial study drug dosing (Day 1 of Cycle 3 and every 6 weeks thereafter). *If a bone scan is used,* bone scan will be done at every other tumor assessment (approximately every 12 weeks after initial study drug dosing).

Cycle 3 Day 2

Previously Read:

- About 3 tablespoons of blood will be taken to review your health condition and to assess the level of certain markers.

Now Reads:

- About *2* tablespoons of blood will be taken to assess the level of certain markers.

Cycle 3 Day 3

Deleted:

- About 1 tablespoon of blood will be taken to review your health condition.

Cycle 3 Day 8

Previously Read:

- About 2 tablespoon of blood to check the level of certain markers.

Now Reads:

- About *3* tablespoon of blood to check the level of certain markers *and your health status*.

Cycles 4-6: Day 1

Previously Read:

- Tumor assessment: A CT scan or MRI will be done approximately every 6 weeks after your initial study drug dosing. A bone scan will be done at every other tumor assessment (approximately every 12 weeks after initial study drug dosing).

Now Reads:

- Tumor assessment: A CT scan or MRI *or PET/CT* will be done approximately every 6 weeks after your initial study drug dosing. A bone scan will be done at every other tumor assessment (approximately every 12 weeks after initial study drug dosing) *if a bone scan is used.*

Cycles 4-6: Day 2

Deleted:

- About 1 tablespoon of blood will be taken to review your health condition.

End of Cycle 6

Previously Read:

- At the end of cycle 6, if your disease is at least stable or have responded to therapy, you will receive radiation to your brain to help prevent tumors before continuing with study drug treatment.

Now Reads:

- At the end of cycle 6, if your disease is at least stable or have responded to therapy, you *doctor may decide that you* will receive radiation to your brain to help prevent tumors before continuing with study drug treatment.

Cycle 7 and beyond

Previously Read:

- Tumor assessment: A CT scan or MRI will be done approximately every 6 weeks after your initial study drug dosing. A bone scan will be done at every other tumor assessment (approximately every 12 weeks after initial study drug dosing).

Now Reads:

- Tumor assessment: A CT scan or MRI *or PET/CT* will be done approximately every 6 weeks after your initial study drug dosing. *If a bone scan is used, b*one scan will be done at every other tumor assessment (approximately every 12 weeks after initial study drug dosing).

TREATMENT TERMINATION

Previously Read:

- Tumor assessment: either by CT or MRI, and bone scan, if these procedures were not done within the last 4 weeks and if the last tumor assessment did not show that your tumor has grown or spread

Now Reads:

- Tumor assessment: either by CT or MRI *or PET/CT, or* bone scan, if these procedures were not done within the last 4 weeks and if the last tumor assessment did not show that your tumor has grown or spread

POSSIBLE RISKS AND DISCOMFORTS

OMP-59R5:

Previously Read:

OMP-59R5 is being testing in small number of patients who have cancer; diarrhea is the most common side effect and all three patients who were treated at 5 mg/kg every other week had mild diarrhea. You will be given some medications to take home to treat diarrhea. Other comment side effects reported are: fatigue-tiredness (30%), nausea (22%), decreased appetite (15%), increased liver function (ALT) (11%), dehydration (11%), low potassium level (11%), vomiting (11%), low blood counts that might make you feel tired or easy to bruise (11%).

Now Reads:

OMP-59R5 is being testing in small number of patients who have cancer; diarrhea is the most common side effect *in the first in man study* and all three patients who were treated at 5 mg/kg every other week had mild diarrhea. You will be given some medications to take home to treat diarrhea. Other comment side effects reported are: fatigue-tiredness (30%), nausea (22%), decreased appetite (15%), increased liver function (ALT) (11%), dehydration (11%), low potassium level (11%), vomiting (11%), low blood counts that might make you feel tired or easy to bruise (11%).

AMENDMENT 3: 23 OCTOBER 2013

The following changes were made to the protocol. Italics in the text indicate new text.

RATIONALE

The protocol has been amended to refer the details on study drug (OMP-59R5/Placebo) preparation and administration in the Pharmacy Manual, to collect additional blood sample for PK and/or anti-OMP-59R5 antibody analysis at other protocol-specified times as clinically indicated such as when significant toxicities develop, to modify inclusion criterion 5c to allow medical judgment of adequate hepatic function when the lab values are outside of the corresponding cutoff. Sample Informed Consent template has been updated to reflect the changes on infusion duration, possible additional blood samples for PK and/or anti-OMP-59R5 antibody analysis when significant toxicities develop, incidences of infusion reactions in 71 patients treated with OMP-59R5 and the management of the infusion reaction.

Additionally, Table 7 has been updated to reflect the probability of 4 or more subjects developing DLTs in a total of 10 subjects in the expansion to be more in line with ≥ 33% incidence of DLTs in a standard 3+3 dose escalation study.

SUMMARY OF CHANGES:

SYNOPSIS

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria:

Previously Read:

5. Adequate organ function:
   a. Adequate hematologic function (absolute neutrophil count [ANC] ≥ 1,500 cells/μL; hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/μL).
   b. Adequate renal function (serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 60 mL/min using Cockroft Gault formula). Adequate hepatic function (alanine aminotransferase [ALT] ≤ 3 x upper limit of normal [ULN], aspartate
   c. aminotransferase [AST] ≤ 3 x ULN); ALT and AST may be ≤ 5 x ULN if due to liver metastases but cannot be associated with concurrent elevated bilirubin >1.5xULN).
   d. Prothrombin Time (PT)/International Normalized Ration (INR) ≤1.5 × ULN, activated partial thromboplastin time (aPTT) ≤1.5 × ULN.

Now Reads:

5. Adequate organ function:
   a. Adequate hematologic function (absolute neutrophil count [ANC] ≥ 1,500 cells/μL; hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/μL).
   b. Adequate renal function (serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 60 mL/min using Cockroft Gault formula).
   c. Adequate hepatic function (alanine aminotransferase [ALT] ≤ 3 x upper limit of normal [ULN], ALT may be ≤ 5 x ULN if due to liver metastases but cannot be associated with concurrent elevated bilirubin >1.5xULN *unless it is approved by the Sponsor's Medical Monitor*).
   d. Prothrombin Time (PT)/International Normalized Ration (INR) ≤1.5 × ULN, activated partial thromboplastin time (aPTT) ≤1.5 × ULN.

Test Product, Dose, and Mode of Administration

Previously Read:

OMP-59R5 is an IgG2 fully human monoclonal antibody that is directed against the Notch2/3 receptors. OMP-59R5 is supplied at a concentration of 10 mg/mL in 25mL single-use glass vial filled to 20 mL to deliver at total of 200 mg per vial. OMP-59R5 vials must be stored at 2°C–8°C. DO NOT FREEZE. DO NOT SHAKE.

OMP-59R5 must be delivered through either polyvinyl chloride (PVC) or non-PVC tubing containing a **Baxter 0.22-micron high pressure extended life filter** (part number 2H5660) which will be provided by OncoMed and should be infused over 30 minutes (+/- 5 minutes) as an IV infusion. Placebo is a formulation of 50mM Histidine, 100mM Sodium Chloride, 45mM Sucrose and 0.01% (v/v) Polysorbate-20, pH 6.0. Placebo will be administered in the same manner as OMP-59R5; i.e., withdraw the necessary amount of placebo and dilute with either half normal saline (NS) (0.45% Sodium Chloride (NaCl) or 5% Dextrose and 0.45% NaCl (D5W ½ NS)to a total volume of 250 mL and infuse over 30 minutes (+/- 5 minutes). The diluted study drug should be administered within 4 hours of preparation.

Now Reads:

OMP-59R5 is an IgG2 fully human monoclonal antibody that is directed against the Notch2/3 receptors. OMP-59R5 is supplied at a concentration of 10 mg/mL in 25mL single-use glass vial filled to 20 mL to deliver at total of 200 mg per vial. OMP-59R5 vials must be stored at 2°C-8°C. DO NOT FREEZE. DO NOT SHAKE.

Please refer to the Pharmacy Manual for the details on OMP-59R5 preparation and administration. Placebo is a formulation of 50mM Histidine, 100mM Sodium Chloride, 45mM Sucrose and 0.01% (v/v) Polysorbate-20, pH 6.0. Placebo will be administered in the same

manner as OMP-59R5. *Please refer to the Pharmacy Manual for details regarding Placebo preparation and administration*.

Immunogenicity:

Previously Read:

Serum samples will be obtained for immunogenicity assessment prior to study drug administration on Day 1 of Cycle 1, every three cycles thereafter (Day 1 of Cycle 4, 7, 10, etc.) and at the time of treatment termination for all subjects enrolled in Phase 1b and Phase 2 portions. Samples that test positive will be assessed for neutralizing capability.

Now Reads:

Serum samples will be obtained for immunogenicity assessment prior to study drug administration on Day 1 of Cycle 1, every three cycles thereafter (Day 1 of Cycle 4, 7, 10, etc.), *at other times as clinically indicated such as when significant toxicities occur* and at the time of treatment termination for all subjects enrolled in Phase 1b and Phase 2 portions. Samples that test positive will be assessed for neutralizing capability.

Pharmacokinetic Evaluation:

Previously Read:

For subjects enrolled in Phase 1b portion only: Plasma samples from all subjects enrolled in Phase 1b portion will be obtained for pharmacokinetic analysis of OMP-59R5 at pre-dose and 5 minutes post infusion on Day 1 of Cycles 1 and 3, on Days 3 and 8 of Cycles 1 and 3, as well as at the time of treatment termination, as outlined in the Schedule of Assessments (APPENDIX B). Pharmacokinetic parameters (i.e. area under the curve [AUC], clearance, volume of distribution and apparent half life) of OMP-59R5 will be assessed for each evaluable subject.

Now Reads:

For subjects enrolled in Phase 1b portion only: Plasma samples from all subjects enrolled in Phase 1b portion will be obtained for pharmacokinetic analysis of OMP-59R5 at pre-dose and 5 minutes post infusion on Day 1 of Cycles 1 and 3, on Days 3 and 8 of Cycles 1 and 3, *at other times as clinically indicated such as when significant toxicities occur* as well as at the time of treatment termination, as outlined in the Schedule of Assessments (APPENDIX B). Pharmacokinetic parameters (i.e. area under the curve [AUC], clearance, volume of distribution and apparent half life) of OMP-59R5 will be assessed for each evaluable subject.

3.4 Clinical Background

Previously Read:

…

No RECIST complete or partial responses have been noted on this Phase 1 study. However, six subjects have had RECIST stable disease (SD) lasting greater than 56 days (ranging from 61 days to 165 days, all of them have come off the study).

OMP-59R5 is also being studied in a phase 1b/2 study in combination with nab-paclitaxel and gemcitabine in subjects with previously untreated stage IV pancreatic cancer (Study 59R5-002). The study was initially conducted in combination with gemcitabine alone and was amended to incorporate nab-paclitaxel into the chemotherapy backbone in response to the changes in standard of care in this disease population. As of August 19, 2013, twenty four subjects have been treated in Study 59R5-002: five *and four* at 2.5 mg/kg and 5.0 mg/kg respectively every other week in combination with gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, four, six and four at 5 mg/kg, 7.5 mg/kg and 10 mg/kg respectively every other week in combination with nab-paclitaxel at 125 mg/m^2 and gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle. No DLTs have been reported, and the most common reported OMP-59R5 treatment-related event is diarrhea, fatigue and nausea that are mostly grade 1 or 2, managed with supportive care. One Grade 3 diarrhea was noted in one of four subjects treated with 10 mg/kg OMP-59R5 with Nab-P+Gem, lasted less than 48 hours and resolved to Grade 1 diarrhea after concurrent use of lomotil. Treatment with etoposide and cisplatin is the standard of care for subjects with untreated extended stage small cell lung cancer. The most common AE of OMP-59R5 is diarrhea, whereas cytopenia is the most common adverse event with EP administration. Therefore, the most common AEs of OMP-59R5 and EP do not overlap, providing the justification for investigating this combination in the study. Subjects enrolled in this study will receive a starting dose of 5 mg/kg of OMP-59R5 once every three weeks, which is one dose below the MTD of 7.5 mg/kg every three weeks in Study 59R5-001. Phase 1b lead-in portion of the study will provide preliminary safety and tolerability profile of this combination before the initiation of Phase 2 portion of the study. OMP-59R5 has an estimated apparent half time of 2 to 3 days at 7.5 mg/kg in Study 59R5-001, subjects will not receive PCI or WBRT within 2 weeks of study drug administration and will not receive OMP-59R5 during the radiation to alleviate any potential interaction between the study drug and the radiation. Therefore, risks and potential benefits of participation have been appropriately mitigated for this patient population.

Now Reads:

...

No RECIST complete or partial responses have been noted on this Phase 1 study. However, six subjects have had RECIST stable disease (SD) lasting greater than 56 days (ranging from 61 days to 165 days, all of them have come off the study).

As of October 22, 2013, three subjects have been treated in the current study (Study 59R5-003) at 5 mg/kg dose cohort with EP; two of which have completed 6 cycles of chemotherapy and are continuing OMP-59R5 alone, and the other one is currently in Cycle 5. No significant OMP-59R5 treatment-related toxicities were reported.

OMP-59R5 is also being studied in a phase 1b/2 study in combination with nab-paclitaxel and gemcitabine in subjects with previously untreated stage IV pancreatic cancer (Study 59R5-002). The study was initially conducted in combination with gemcitabine alone and was amended to incorporate nab-paclitaxel into the chemotherapy backbone in response to the changes in standard of care in this disease population. As of *October 22,* 2013*,* twenty *six* subjects have been treated in Study 59R5-002: five *and four* at 2.5 mg/kg and 5.0 mg/kg respectively every other week in combination with gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle, four*,* six, *six and one* at 5 mg/kg, 7.5 mg/kg*,* 10 mg/kg *and 12.5 mg/kg* respectively every other week in combination with nab-paclitaxel at 125 mg/m^2 and gemcitabine at 1000 mg/m^2 on Days 1, 8 and 15 of every 28 day cycle. No DLTs have been reported, and the most common reported OMP-59R5 treatment-related event is diarrhea, fatigue and nausea that are mostly grade 1 or 2, managed with supportive care. One Grade 3 diarrhea was noted in one of *six* subjects treated with 10 mg/kg OMP-59R5 with Nab-P+Gem, lasted less than 48 hours and resolved to Grade 1 diarrhea after concurrent use of lomotil. *Three subjects have experienced grade 2 infusion-related reactions: one at 5mg/kg OMP-59R5 dose cohort with Nab-P+Gem at Cycle 4 Day 1(the baseline weight was 87kg), two at 10 mg/kg OMP-59R5 dose cohort with Nab-P+Gem at Cycle 1 Day 15 and Cycle 2 Day 1 respectively(the baseline weight was 106 kg and 84 kg respectively). Infusion reaction was also reported from two of forty two subjects treated in Study 59R5-001: one at 1.0 mg/kg weekly and the other at 5.0 mg/kg weekly dose cohorts (the baseline weight was 54.7 kg and 104 kg respectively), both occurred with the first OMP-59R5 infusion and were Grade 1 or Grade 2; Four of these five subjects have responded to use of antihistamines and/or steroids, and the subsequent doses were administered at a slower infusion rate in addition to premedication. However, one subject from the 10 mg/kg dose cohort in the ALPINE study experienced a recurrent infusion reaction even with premedication and slower infusion rate. Thus far, no infusion reactions have been reported in three subjects treated with OMP-59R5 in the PINNACLE study (59R5-003). However, in response to the incidence of infusion reactions reported at higher OMP-59R5 doses in the ALPINE study, and in heavier subjects, the details on preparation and administration of OMP-59R5 have been provided in the Pharmacy Manual.*

Treatment with etoposide and cisplatin is the standard of care for subjects with untreated extended stage small cell lung cancer. The most common AE of OMP-59R5 is diarrhea, whereas cytopenia is the most common adverse event with EP administration. Therefore, the most common AEs of OMP-59R5 and EP do not overlap, providing the justification for investigating this combination in the study. Subjects enrolled in this study will receive a starting dose of 5 mg/kg of OMP-59R5 once every three weeks, which is one dose below the MTD of 7.5 mg/kg every three weeks in Study 59R5-001. Phase 1b lead-in portion of the study will provide preliminary safety and tolerability profile of this combination before the initiation of Phase 2 portion of the study. OMP-59R5 has an estimated apparent half time of 2 to 3 days at 7.5 mg/kg in Study 59R5-001, subjects will not receive PCI or WBRT within 2 weeks of study drug administration and will not receive OMP-59R5 during the radiation to alleviate any potential interaction between the study drug and the radiation. Therefore, risks and potential benefits of participation have been appropriately mitigated for this patient population.

6.1 Inclusion Criteria

Previously Read:

…

c. Adequate hepatic function (alanine aminotransferase [ALT] ≤ 3 x upper limit of normal [ULN], aspartate aminotransferase [AST] ≤ 3 x ULN); ALT and AST may be ≤ 5 x ULN if due to liver metastases but cannot be associated with concurrent elevated bilirubin > 1.5xULN).

Now Reads:

…

c. Adequate hepatic function (alanine aminotransferase [ALT] ≤ 3 x upper limit of normal [ULN], ALT may be ≤ 5 x ULN if due to liver metastases but cannot be associated with concurrent elevated bilirubin > 1.5xULN *unless it is approved by the Sponsor's Medical Monitor*).

7.0 TREATMENT OF SUBJECTS

Previously Read:

…

Study drug will be OMP-59R5 in the Phase 1b portion, and either OMP-59R5 or placebo in the Phase 2 portion. Study drug will be administered by IV infusion over 30 minutes (+/- 5 minutes) on Day 1 of every 21-day cycle. The subject should not take two consecutive doses of study drug within 18 days.

Now Reads:

…

Study drug will be OMP-59R5 in the Phase 1b portion, and either OMP-59R5 or placebo in the Phase 2 portion. Study drug will be administered by IV infusion on Day 1 of every 21-day cycle. The subject should not take two consecutive doses of study drug within 18 days.

7.1.1 Study Drug Administration

Previously Read:

During Phase 1b and 2, OMP-59R5 must be delivered through tubing containing a **Baxter 0.22-micron high pressure extended life filter** (part number 2H5660) which will be provided by OncoMed and should be infused over 30 minutes (+/- 5 minutes) as an IV infusion.

During Phase 2, Placebo will be administered in exactly the same manner as OMP-59R5; i.e., withdraw the necessary amount of placebo and dilute with either half normal saline (NS) (0.45% Sodium Chloride (NaCl) or5% Dextrose and 0.45% NaCl (D5W ½ NS) to a total volume of 250 mL and infuse over 30 minutes (+/- 5 minutes). The diluted study drug should be administered within 4 hours of preparation.

There is no provision for intra-subject dose escalation of study drug. Weight-based doses will not be recalculated unless there is a weight change ≥10%.

Now Reads:

Please refer to the Pharmacy Manual for the details on OMP-59R5 or Placebo preparation and administration.

\There is no provision for intra-subject dose escalation of study drug. Weight-based doses will not be recalculated unless there is a weight change ≥10%.

7.1.5 Study Drug Preparation

Previously Read:

The study drug should be diluted for infusion using aseptic technique. Withdraw the necessary amount of the study drug to obtain the required dose and dilute with either half normal saline (NS) (0.45% Sodium Chloride (NaCl) or 5% Dextrose and 0.45% NaCl (D5 ½ NS), to a total volume of 250 mL. For example, if a 70-kg subject is to be dosed at 5 mg/kg, then the subject's dose would be 350 mg. Because the vials contain a concentration of 10 mg/mL, a total of 35 mL containing 350 mg should be withdrawn from the vial and diluted with either 0.45% NaCl or 5% Dextrose and 0.45% NaCl (D5W ½ NS), to a total volume of 250 mL.

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

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

Now Reads:

Please refer to the Pharmacy Manual for details on study drug preparation.

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

7.4.1 Infusion Reaction Management

Previously Read:

... For subjects whose infusion-associated events were either Grade 1 or 2, and completely resolved on the day of the infusion, the infusion may be resumed at the discretion of the Investigator at one-half of the initial rate of infusion. All subsequent infusions for that subject should then be administered at the reduced rate of infusion.

Now Reads:

... For subjects whose infusion-associated events were either Grade 1 or 2, and completely resolved on the day of the infusion, the infusion may be resumed at the discretion of the Investigator at *a rate that is slower than* the initial rate of infusion. *Please refer to the Pharmacy Manual for details on study drug administration*. All subsequent infusions for that subject should then be administered at the reduced rate of infusion.

8.5 Immunogenicity Assessments

Previously Read:

(Anti-OMP-59R5) prior to study drug administration on Day 1 of Cycle 1, every three cycles thereafter (Day 1 of Cycle 4, 7, 10, etc.) and at the time of treatment termination for all subjects enrolled in Phase 1b and Phase 2 portions. Samples that test positive will be assessed for neutralizing capability. Instructions for sample collection, handling, storage, and shipping can be found in the Study Reference Binder.

Now Reads:

Serum samples will be obtained for immunogenicity assessment (Anti-OMP-59R5) prior to study drug administration on Day 1 of Cycle 1, every three cycles thereafter (Day 1 of Cycle 4, 7, 10, etc.)*, at other times as clinically indicated such as when significant toxicities occur* and at the time of treatment termination for all subjects enrolled in Phase 1b and Phase 2 portions. Samples that test positive will be assessed for neutralizing capability. Instructions for sample collection, handling, storage, and shipping can be found in the Study Reference Binder.

8.6 Pharmacokinetic Assessments

Previously Read:

For subjects enrolled in Phase 1b portion only: Plasma samples from all subjects enrolled in Phase 1b portion will be obtained for pharmacokinetic analysis of OMP-59R5 at pre-dose and 5 minutes post OMP-59R5 infusion on Day1 of Cycles 1 and 3, on Days 3 and 8 of Cycles 1 and 3, as well as at the time of treatment termination, as outlined in the Schedule of Assessments (APPENDIX B and APPENDIX C). Pharmacokinetic parameters (i.e. area under the curve [AUC], clearance, volume of distribution and apparent half life) of OMP-59R5 will be assessed for each evaluable subject. Instructions for sample collection, handling, storage, and shipping can be found in the Study Reference Binder.

Now Reads:

For subjects enrolled in Phase 1b portion only: Plasma samples from all subjects enrolled in Phase 1b portion will be obtained for pharmacokinetic analysis of OMP-59R5 at pre-dose and 5 minutes post OMP-59R5 infusion on Day1 of Cycles 1 and 3, on Days 3 and 8 of Cycles 1 and 3, *at other times as clinically indicated such as when significant toxicities occur* as well as at the time of treatment termination, as outlined in the Schedule of Assessments (APPENDIX B and APPENDIX C). Pharmacokinetic parameters (i.e. area under the curve [AUC], clearance, volume of distribution and apparent half life) of OMP-59R5 will be assessed for each evaluable subject. Instructions for sample collection, handling, storage, and shipping can be found in the Study Reference Binder.

13.1 Power and Sample Size

Previously Read:

Table 7 presents the probability that more than 3 subjects will experience a DLT in the expansion cohort of 10 subjects. The probability of seeing 3 or more subjects with a dose limiting toxicity when the true incidence is 40 percent is 83.3 percent compared with 69 percent with the 3+3 design.

Table 7: Probability of that 3 or more Subjects will have a Dose Limiting Toxicity

Probability of Toxicity	≥ 3/10 Not Tolerable
0.05	0.0115
0.10	0.0702
0.15	0.1798
0.20	0.3222
0.25	0.4744
0.30	0.6172
0.35	0.7384
0.40	0.8327
0.45	0.9004
0.50	0.9453

Now Reads:

Table 7 presents the probability that more than *4* subjects will experience a DLT in the expansion cohort of 10 subjects. The probability of seeing *4* or more subjects with a dose limiting toxicity when the true incidence is 40 percent is *3.5* percent compared with 69 percent with the 3+3 design.

Table 7: Probability of that *4* or more Subjects will have a Dose Limiting Toxicity

	Probability of 4 or more DLT's in 10 Subjects		
Probability of Dose Limiting Toxicity	***Given 0 DLT out of the first 6 subjects***	***Given 1 DLT out of the first 6 subjects***	***Given 0 or 1 DLT's out of the first 6 subjects***
0.05	*0.000*	*0.000*	*0.000*
0.10	*0.000*	*0.001*	*0.001*
0.15	*0.000*	*0.005*	*0.005*
0.20	*0.000*	*0.011*	*0.011*
0.25	*0.001*	*0.018*	*0.019*
0.30	*0.001*	*0.025*	*0.026*
0.35	*0.001*	*0.031*	*0.032*
0.40	*0.001*	*0.033*	*0.035*
0.45	*0.001*	*0.033*	*0.034*
0.50	*0.001*	*0.029*	*0.030*

NOTES TO APPENDIX B:

Previously Read:

h. Plasma samples will be obtained for OMP-59R5 pharmacokinetic analysis at pre-dose and 5 minutes (±2 minutes) after the end of OMP-59R5 infusion and prior to the EP administration on Day 1 of Cycle 1 and Cycle 3, and on Days 3 (pre-dose) and 8 of Cycles 1 and 3, as well as at treatment termination. On days when OMP-59R5 and etoposide and/or cisplatin are given together, the plasma sample should be obtained 5 minutes (±2 minutes) after the completion of the infusion of OMP-59R5, but prior to EP administration.

i. Serum samples will be obtained for anti-OMP-59R5 pre-dose on Day 1 of every three cycles starting from Cycle 1, and at the Treatment Termination visit.

Now Reads:

h. Plasma samples will be obtained for OMP-59R5 pharmacokinetic analysis at pre-dose and 5 minutes (±2 minutes) after the end of OMP-59R5 infusion and prior to the EP administration on Day 1 of Cycle 1 and Cycle 3, and on Days 3 (pre-dose) and 8 of Cycles 1 and 3, *at other times as clinically indicated such as when significant toxicities occur,* as well as at treatment termination. On days when OMP-59R5 and etoposide and/or cisplatin are given together, the plasma sample should be obtained 5 minutes (±2 minutes) after the completion of the infusion of OMP-59R5, but prior to EP administration.

i. Serum samples will be obtained for anti-OMP-59R5 pre-dose on Day 1 of every three cycles starting from Cycle 1, *at other times as clinically indicated such as when significant toxicities occur,* and at the Treatment Termination visit.

NOTES TO APPENDIX C:

Previously Read:

h. Serum samples will be obtained for anti-OMP-59R5 pre-dose on Day 1 of every third cycle starting from Cycle 1, and at the Treatment Termination visit.

Now Reads:

h. Serum samples will be obtained for anti-OMP-59R5 pre-dose on Day 1 of every third cycle starting from Cycle 1, *at other times as clinically indicated such as when significant toxicities occur* and at the Treatment Termination visit.

APPENDIX F: SAMPLE INFORMED CONSENT

TREATMENT PHASE

Previously Read:

…

Your study drug (OMP59R5 or placebo) will be given through the vein for 30 minutes. Etoposide will be given through the vein for 30 to 60 minutes. Cisplatin will be given through the vein for 30 minutes to 2 hours. On days when the study drug, etoposide and cisplatin are given together, the study drug will be given first, followed by etoposide, and then cisplatin. You will receive study drug, etoposide, and cisplatin up to 6 cycles. After that, you will receive study drug only on Day 1 of each following cycle.

…

The following procedures will take place at each of the following visits.

Now Reads:

…

Your study drug (OMP-59R5 or placebo) will be given through the vein for 30 minutes *or longer depending on the dose you are assigned, your weight and if you have experienced any allergic reaction to study drug. Your study staff will let you know how long your treatment with study drug will be.* Etoposide will be given through the vein for 30 to 60 minutes. Cisplatin will be given through the vein for 30 minutes to 2 hours. On days when the study drug, etoposide and cisplatin are given together, the study drug will be given first, followed by etoposide, and then cisplatin. You will receive study drug, etoposide, and cisplatin up to 6 cycles. After that, you will receive study drug only on Day 1 of each following cycle.

…

The following procedures will take place at each of the following visits.

Additional blood samples (approximately 1 to 2 teaspoons for each blood sample) might be taken to check the level of study drug (OMP-59R5) and/or proteins against OMP-59R5 in your body:

POSSIBLE RISKS AND DISCOMFORTS

OMP-59R5:

Previously Read:

OMP-59R5 is being testing in small number of patients who have cancer; diarrhea is the most common side effect in the first in man study and all three patients who were treated at 5 mg/kg every other week had mild diarrhea. You will be given some medications to take home to treat diarrhea. Other comment side effects reported are: fatigue-tiredness (30%), nausea (22%), decreased appetite (15%), increased liver function (ALT) (11%), dehydration (11%), low potassium level (11%), vomiting (11%), low blood counts that might make you feel tired or easy to bruise (11%). In addition, as with all antibody treatments, there is the possibility of an allergic reaction, such as fever, chills, rash, and/or hives associated with the infusion of OMP-59R5. Rarely, a severe or serious allergic reaction can occur during or following the administration of an antibody.

Now Reads:

OMP-59R5 is being testing in small number of patients who have cancer; diarrhea is the most common side effect in the first in man study and all three patients who were treated at 5 mg/kg every other week had mild diarrhea. You will be given some medications to take home to treat diarrhea. Other *common* side effects reported are: fatigue-tiredness (30%), nausea (22%), decreased appetite (15%), increased liver function (ALT) (11%), dehydration (11%), low potassium level (11%), vomiting (11%), low blood counts that might make you feel tired or easy to bruise (11%). *There may be side effects that we cannot predict and in some cases they may be serious, long-lasting, or fatal.* In addition, as with all antibody treatments, there is the possibility of an allergic reaction, such as fever, chills, rash, hives, *changes in blood pressure, temperature and heart rate* associated with the infusion of OMP-59R5. Rarely, a severe or serious allergic reaction can occur during or following the administration of an antibody. *As of October 22, 2013, five of 71 patients who have been given OMP-59R5 have experienced allergic reactions; all of these allergic reactions were mild or moderate. If you do have a reaction to OMP-59R5, your study doctor may need to give OMP-59R5 at a slower rate (over a longer period of time) and may give you additional medications to prevent a reaction. If after slowing the rate of infusion and giving you additional medications you continue to have the allergic reactions, you may need to stop taking OMP-59R5.*

AMENDMENT 4: 17 APRIL 2014

The following changes were made to the protocol. Italics in the text indicate new text.

RATIONALE

The protocol has been amended to add a cohort of 6 subjects to be treated with etoposide and carboplatin after the highest tolerable dose is determined with OMP-59R5 in combination with etoposide and cisplatin, the non-clinical section has been updated to include an experiment using carboplatin, to specify 15 mg/kg of OMP-59R5 as the highest dose to be tested in Phase 1b portion of the study if the MTD has not been determined after 15 mg/kg of tarextumab has been tested, in phase 2 portion of the study, the randomization will be balanced on the choice of platinum therapy (cisplatin versus carboplatin) regions (US vs Europe) and the prior use of whole brain radiation or prophylactic cranial irradiation. Choice of platinum therapy won't be changed once the subject is randomized. Additional blood samples have been added for PK and immunogenicity assessment. Inclusion criterion of Notch 3 selection has been eliminated and statistical section has been updated to include analysis on all treated subjects and Notch 3 high subjects. Subjects are required to have radiation-related adverse events recovered to be ≤ Grade 1 in order to be eligible for the study.

SUMMARY OF CHANGES:

As a result, all the corresponding sections of the protocol have been updated to reflect the changes outlined above, (i.e., Synopsis, Section 2.0 List of Abbreviations, Section 3.3 Nonclinical Data, Section 3.4 Clinical Background, Section 3.5 Dose Rationale, Section 3.7 Subject Population, Section 4.1 Study Objectives, Section 5.0 Overall Study Design and Plan - Description, Section 5.1 Phase 1b Portion, Section 5.3 Dose Escalation Plan, Section 5.4 Maximum Tolerated Dose, Section 5.5 Phase 2 Portion, Section 5.5.1 Blinded Treatment Phase, Section 6.1 Inclusion Criteria, Section 6.2 Exclusion Criteria, Section 6.3 Removal of Subjects from Study Treatment, Section 6.4 Subject Identification and Replacement of Subjects, Section 7.0 Treatment of Subjects, Section 7.1.1 Study Drug Administration, Section 7.4.1 Administration, Section 7.4.2 Description, Section 7.4.3 Storage, Section 7.4.4 Packaging, Section 7.5 Dose Modifications or Delay for Treatment-Related Toxicities, Section 7.6 Anti-Emetics, Anti-diarrhea and Hematopoietic Supportive Care, Section 7.8 Treatment Compliance, Section 6.1 Inclusion Criteria, Section 8.1.4 Serious Adverse Event Reporting Procedure, Section 8.2.1 Hematology, Section 8.2.2 Serum Chemistry, Section 8.2.3 Urinalysis, Section 8.3 Vital Signs and Other Physical Findings, Section 8.4 Cardiac Studies, Section 8.5 Immunogenicity Assessments, Section 8.6 Pharmacokinetic Assessments, Section 11.0 Study Visit Schedule and Assessments, Section 11.2 Treatment Visits, Section 11.2.1.1 Cycle 1 Day 1, Section 11.2.1.2 Cycle 1 Day 2, Section 11.2.1.3 Cycle 1 Day 3, Section 11.2.2.1 Day 1 (± 1 day) of Cycles 2-6, Section 11.2.2.2 Day 2 of Cycles 2-6, Section 11.2.2.3 Day 3 of Cycles 2-6,

Section 11.2.2.4 Day8 of Cycles 2 and 3 Only, Section 11.2.3 After Cycle 6 of Etoposide and Cisplatin/Carboplatin with Study Drug, Section 11.2.4.1 Day 1 (± 1 day) of Cycle 7 and Every Cycle Thereafter, Section 11.2.4.2 Anytime between Day 3 thru Day 14 of Cycle 7 and Cycle 9, Section 11.2 Treatment Termination, Section 13.1.1 Phase 1b, Section 13.1.2 Sample Size Justification – Phase 2, Section 13.2 Randomization and Blinding, Section 13.4.1 Subject Populations for Analysis, Section 13.4.2 Analysis Sets, Section 13.5.1 Efficacy Endpoints, Section 13.5.3 Immunogenicity Endpoint, Section 13.5.4 Pharmacokinetic Endpoints, Section 13.5.5 Exploratory Endpoints, Section 13.6 Statistical Method, Section 13.6.1 Progression Free Survival, Section 13.6.2 Response Rate (Best Overall Response), Section 13.6.3 Duration of Response, Section 13.6.4 Overall Survival, Section 13.6.5 Landmark Survival, Section 13.7 Demographics and Baseline Characteristics, Section 13.8 Treatment Exposure, Section 13.9 Termination Criteria, Section 13.11 Data Safety Monitory Board, Section 14.0 Direct Access to Source Data/Documentation, Section 16.3 Study Monitoring, Section 16.5 Data collection, Section 17.0 References, Appendix A Study Schema, Appendix B Schedule of Assessments for Subjects in Phase 1B, Notes to Appendix B, Appendix C Schedule of Assessments for Subjects in Phase 2, Notes to Appendix C, Appendix F Sample Informed Consent, Appendix G Sample Pharmacogenomics Informed Consent for Phase 1B, and Appendix H Technical Details Supporting Calculation of Power and Type 1 Error.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the previous amendments.

AMENDMENT 5: 10 SEPTEMBER 2014

The following changes were made to the protocol. Italics in the text indicate new text.

RATIONALE

The protocol has been amended to decrease the cisplatin dose to 75 mg/m^2 in the Phase 2 portion of the study. Pharmacokinetic (PK) sampling in the Phase 2 portion has been modified. The amendment also provides additional flexibility on treatment modification as clinically indicated after discussion with the Sponsor's Medical Monitor. The frequency of bone scan after treatment on study in Phase 2 has been changed to be done as clinically indicated. Subjects who have relapsed after treatment for limited disease will be excluded for Phase 2 portion of the study. Additionally, the amendment also modified the statistical calculation for the Phase 2 portion of the study. The timing of the first two DSMB meetings has been modified.

SUMMARY OF CHANGES:

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

Synopsis	
Section 2.0	List of Abbreviations
Section 3.4	Clinical Background
Section 3.5	Dose Rationale
Section 5.0	Overall Study Design and Plan Description
Section 5.1	Phase 1b Portion
Section 5.5	Phase 2 Portion
Section 5.5.1	Blinded Treatment Phase
Section 6.2	Exclusion Criteria
Section 6.4	Subject Identification and Replacement of Subjects
Section 7.0	Treatment of Subjects
Section 7.1.1	Study Drug Administration
Section 7.3.1	Administration
Section 7.5	Dose Modifications or Delay for Treatment-Related Toxicities
Section 7.6	Anti-Emetics, Anti-diarrhea and Hematopoietic Supportive Care
Section 7.7	Concomitant and Prohibited Therapy
Section 8.2.2	Chemistry
Section 8.6	Pharmacokinetic Assessments
Section 11.1	Screening

Section 11.2	Treatment Visits
Section 11.2.2	Cycles 2-6 for Phase 1b and Cycles 2-4 for Phase 2
Section 11.2.2.1	Day 1 (± 1 day) of Cycles 2-6 for Phase 1b and Cycles 2 -4 for Phase 2
Section 11.2.2.2	D ay 2 of Cycles 2-6 for Phase 1b and Cycles 2 -4 for Phase 2
Section 11.2.2.3	Day 3 of Cycles 2-6 for Phase 1b and Cycles 2 -4 for Phase 2
Section 11.2.3	After Planned EP Treatment cycles
Section 11.2.4	Subsequent Cycles After Completion of Planned EP Cycles
Section 11.2.4.1	Day 1 (± 1 day) of Subsequent Cycles After Completion of Planned EP Cycles
Section 11.2.4.2	Anytime between Day 3 thru Day 14 of Cycle 5 and Cycle 7
Section 11.3	*Treatment Visits – Phase 2*
Section 13.1.2	Sample Size Justification – Phase 2
Section 13.2	Randomization and Blinding
Section 13.4.2	Analysis Set
Section 13.6.1	Progression Free Survival
Section 13.6.2	Response Rate (Best Overall Response)
Section 13.6.4	Overall Survival
Section 13.9	Termination Criteria
Section 13.11	Data Safety Monitory Board
Section 13.12	Interim Analysis
Section 16.6	Investigational Medicinal Product Accountability
Appendix A	Study Schema
Appendix B	Schedule of Assessments for Subjects in Phase 1B
Notes to Appendix B	
Appendix C	Schedule of Assessments for Subjects in Phase 2
Notes to Appendix C	
Appendix F	Sample Informed Consent – Phase 1b
Appendix G	Sample Informed Consent – Phase 2

AMENDMENT 6: 22 APRIL 2016

The following changes were made to the protocol. Italics in the text indicate new text.

RATIONALE

The protocol has been amended to de-prioritize the co-primary endpoint of determining PFS benefit by adding tarextumab to EP in first-line extensive stage small cell lung cancer patients with Notch 3 expression level into secondary endpoint. In addition to assessing the treatment effect by adding tarextumab to EP in first line extensive stage small cell lung cancer patients with Notch 3 expression, the treatment effect will be also explored in subjects with Hes1, Hey2, Hey1 and Hes6 expression. The required PFS events for the different analyses have been updated and other statistical sections have been updated accordingly. Clinical background section has been updated with emerging safety information and corresponding risk section of the consent has been updated. In addition, the USAN name of tarextumab has been added throughout the protocol as appropriate.

SUMMARY OF CHANGES:

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

Synopsis	
Section 3.4	Clinical Background
Section 4.1	Study Objectives
Section 13.1.2	Sample Size Justification – Phase 2
Section 13.3.2	Analysis Set
Section 13.5	Statistical Methods
Section 13.5.1	Progression-Free Survival
Section 13.5.4	Overall Survival
Section 13.5.6	Correlation of biomarkers with Efficacy Endpoints
Section 13.11	Analysis of PFS and OS Prior to the Final Analysis