CLINICAL STUDY PROTOCOL

Study Title:	A Two-Part, Open-Label, Randomized, Phase II/III Study of Dinutuximab and Irinotecan versus Irinotecan for Second Line Treatment of Subjects with Relapsed or Refractory Small Cell Lung Cancer
Investigational Product:	Dinutuximab injection, for intravenous use
Protocol Number:	DIV-SCLC-301
EudraCT Number:	2017-000758-20
Investigational New Drug Application:	IND 133,047
Sponsor:	United Therapeutics Corporation 55 TW Alexander Dr, P.O. Box 14186 Research Triangle Park, NC 27709 Telephone: (919) 485-8350
Contract Research Organization:	[redacted]
Protocol Date:	
Original	13 March 2017, Version 1.0
Amendment 1:	10 April 2017, Version 2.0
Amendment 2:	19 December 2017, Version 3.0

PROTOCOL APPROVAL SIGNATURE PAGE

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Approved by:

[redacted]

APPROVALS STATEMENT

This document is signed with electronic signatures at Precision Oncology and United Therapeutics Corporation. Electronic signatures made by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.

PROTOCOL ACCEPTANCE PAGE

Issue/Date: Protocol Number DIV-SCLC-301 / Amendment 2 / 19 December 2017

I have read this protocol for Study entitled:

A Two-Part, Open-Label, Randomized, Phase II/III Study of Dinutuximab and Irinotecan versus Irinotecan for Second Line Treatment of Subjects with Relapsed or Refractory Small Cell Lung Cancer

As principal investigator, I understand and agree to conduct this study as outlined herein.

_____

Principal Investigator Name (print)

_____ _____

Principal Investigator Signature *Date*

Signature on this page assures the Sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board (IRB)/Independent Ethics Committee (IEC) operates in accordance with the governing regulations, and that the investigator understands, and agrees to abide by, all governing regulatory obligations and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) while conducting this clinical investigation. Once signed, the original of this form should be detached from the protocol and returned to United Therapeutics or its designee (please retain a copy for your files).

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STUDY SYNOPSIS

Title of Study	A Two-Part, Open-Label, Randomized, Phase II/III Study of Dinutuximab and Irinotecan versus Irinotecan for Second Line Treatment of Subjects with Relapsed or Refractory Small Cell Lung Cancer
Study Design	Open-label, two-part, intrasubject dose-escalation, randomized
Study Objectives	The primary objective of this study is to compare overall survival (OS) in subjects treated with dinutuximab and irinotecan versus subjects treated with irinotecan alone as a second-line treatment for relapsed or refractory small cell lung cancer (SCLC). The secondary objectives of the study are: • To compare progression-free survival (PFS), objective response rate (ORR) (complete response [CR] + partial response [PR]), and clinical benefit rate (CR + PR + stable disease [SD]) in subjects treated with dinutuximab and irinotecan versus subjects treated with irinotecan alone. • To compare the safety of subjects treated with dinutuximab and irinotecan versus subjects treated with irinotecan alone. • To evaluate the pharmacokinetics (PK) of subjects treated with dinutuximab. • To compare OS, PFS, ORR, and clinical benefit rate (CBR) in subjects treated with dinutuximab and irinotecan versus subjects treated with topotecan alone. The exploratory objective of the study is to assess the relationship between selected biomarkers and survival of subjects treated with dinutuximab.
Eligibility Criteria	*Inclusion*: • Provide a signed informed consent form before any screening procedures. • Aged ≥18 years on the date of signing the informed consent form. • Have histologically or cytologically confirmed SCLC (undifferentiated small cell carcinoma arising in or consistent with lung cancer origin). • Documented (radiographic evidence of) relapse or disease progression during or after first-line platinum-based therapy (subjects refractory to initial platinum-based therapy are eligible). • No more than 1 prior regimen for SCLC. First-line platinum-based therapy followed by maintenance therapy is considered a single regimen provided there is no intervening disease progression. • Have no curative therapy available. • Have a life expectancy of at least 12 weeks. • Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. • Have adequate bone marrow function as assessed by the following laboratory test results: – Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L (erythropoietin or transfusion permitted). – Absolute neutrophil count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L

	(growth factors permitted). – Platelet count ≥100,000/mm^3 or ≥100 x 10^9/L (transfusions or thrombopoietic growth factors permitted). • Have creatinine clearance (CrCL) ≥30 mL/minute (using Cockcroft and Gault's formula) or serum creatinine ≤1.5 times below the upper limit of normal (ULN). • Have adequate hepatic function, as assessed by the following laboratory test results: – Total bilirubin ≤1.5 times the ULN. (Subjects with Gilbert's Syndrome or other benign congenital hyperbilirubinemia may be eligible at the Investigator's discretion in consultation with the Medical Monitor.). – Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 times ULN in subjects without liver metastases or ≤5.0 times ULN in subjects with liver metastases. • Women of reproductive potential must have a negative urine or serum beta human chorionic gonadotropin (β-HCG) pregnancy test obtained within 7 days prior to the first dose of study treatment (dinutuximab and/or chemotherapy). – Women not of reproductive potential are female subjects who are postmenopausal or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy). • Women of reproductive potential must agree to consistently use one form of highly effective contraception plus one additional form of contraception simultaneously or to practice complete abstinence from vaginal intercourse. The requirement for two forms of contraception or complete abstinence from vaginal intercourse applies from the time of informed consent until 90 days following the last dose of all study drugs. Male subjects who are sexually active with a woman of reproductive potential must agree to use a condom from the time of informed consent until 90 days following the last dose of all study drugs. The following are examples of highly effective and additional methods of contraception: Highly effective methods (must use one): • Hormonal associated with inhibition of ovulation (oral, injectable, implantable, intravaginal, transdermal) • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Tubal ligation • Vasectomy for partner Additional effective methods (must use one): • Male or female condom with or without spermicide • Cap, diaphragm or sponge with spermicide • Combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) *Exclusion*: • Candidate for re-treatment with original platinum-based regimen as second-line therapy. • Prior treatment with irinotecan, topotecan or dinutuximab.

	• Have active brain metastases. Subjects with brain metastases are allowed if they completed definitive brain therapy, are asymptomatic and radiologically stable, and if they are not currently receiving corticosteroids or radiation. Subjects in whom steroids are being tapered may be eligible with prior approval of the Medical Monitor. • Have mixed small-cell and non-small cell histologic features. • Have a previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study, except cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors (Ta and Tis [carcinoma in situ]) or any previous cancer curatively treated <3 years ago. • Have a history or current evidence of uncontrolled cardiovascular disease including but not limited to the following conditions: – Congestive heart failure of New York Heart Association (NYHA) grade 3 or greater. – Unstable angina (symptoms of angina at rest) or new-onset angina within 6 months. – Arterial thrombosis, deep vein thrombosis, or pulmonary embolism within 6 months. – Myocardial infarction or stroke within 6 months. – Pericarditis (any CTCAE v4.03 grade), pericardial effusion (CTCAE v4.03 Grade ≥2). • Have a history of atypical thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS). • Women who are pregnant or breast-feeding. • Have not recovered from prior surgery, significant trauma, systemic anticancer therapy (e.g., chemotherapy, biologic therapy, immunotherapy), radiation therapy or investigational therapy to Grade 1 or better toxicity prior to enrollment (Part 1) or randomization (Part 2). • Have had organ allograft or hematopoietic transplantation. • Known to be human immunodeficiency virus (HIV) positive. • Have an active infection requiring treatment or one that is clinically serious in the Investigator's opinion. • Have received a live vaccine within 6 months of enrollment (Part 1) or randomization (Part 2). • Exposure to strong CYP3A4 and/or UGT1A1 inhibitors and strong CYP3A4 inducers within 14 days of enrollment (Part 1) or randomization (Part 2). • Have any clinical condition that is considered unstable or might jeopardize the safety of the subject and / or influence the subject's compliance in the study.
Study Design and Treatment Plan	This study is an open-label randomized Phase II/III study of dinutuximab and irinotecan compared to irinotecan alone with an intrasubject dose-escalation lead-in phase in subjects with relapsed or refractory SCLC. The lead-in phase of the study (referred to as Part 1) enrolled 12 subjects with SCLC, meeting the enrollment target of approximately 10 subjects. In Part 1, dinutuximab is being administered at increasing doses, as tolerated,

	together with irinotecan at a dose of 350 mg/m^2 IV on Day 1 of each 21-day cycle. Subjects receive dinutuximab at a starting dose of 10 mg/m^2 IV, with increases administered in 2 mg/m^2 increments per cycle in subsequent cycles if maximal pain with prior dose is ≤Grade 1 or Grade 2/3 that in the view of the Investigator is adequately managed and the drug is otherwise tolerated. The maximum dose of dinutuximab that may be administered is 17.5 mg/m^2 (If this dose is reached, the last dose increment would be 1.5 mg/m^2.). Dinutuximab dose is to be decreased in 2 mg/m^2 decrements per cycle depending on the toxicity observed to as low as 8 mg/m^2. If a dose decrease from 17.5 mg/m^2 is required, the initial dose reduction should be 1.5 mg/m^2 (and 2 mg/m^2 for any subsequent decrements). The study safety review committee (SRC) met after the 12 subjects in Part 1 were exposed to irinotecan and dinutuximab for a mean of 3.2 cycles and recommended opening Part 2 at a starting dose of dinutuximab of 14 mg/m^2/day. The SRC reviewed additional data via a subsequent ad hoc meeting; at that time, 8 of the 12 subjects in Part 1 had received a dose of 16 mg/m^2/day or higher. The data at higher doses showed comparable safety and tolerability to data at lower doses (data on file), and thus the SRC recommended increasing the starting dose of dinutuximab for Part 2 to 16 mg/m^2/day. While enrollment in Part 1 is completed, dose escalation will continue in active subjects (per above), and subjects enrolled in Part 1 will remain on study treatment during the study until disease progression or intolerance. In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC will be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutiximab combination group and 92/topotecan group) to one of three groups: • Group A: Irinotecan; or • Group B: Dinutuximab + Irinotecan; or • Group C: Topotecan. Dosing will begin within 3 working days of randomization. Subjects randomized to Group A or Group B will receive irinotecan at a dose of 350 mg/m^2 on Day 1 of each cycle. Subjects randomized to Group B will also receive dinutuximab on Day 1 of each cycle beginning with a starting dose of 16 mg/m^2/day IV. Dose escalation and de-escalation for dinutuximab will occur as in Part 1. The maximum dose of dinutuximab that may be administered is 17.5 mg/m^2 (If this dose is reached, the dose increment would be 1.5 mg/m^2. If the dose is reduced from 17.5 mg/m^2, the initial dose decrement would be 1.5 mg/m^2 to 16 mg/m^2). Subjects randomized to Group C will receive topotecan 1.5 mg/m^2 IV for 5 consecutive days of each cycle.

	One cycle is 21 days in duration. There is a 2-day window around administration of study drugs on Day 1 of each cycle except for the first cycle (initial treatment should begin within 3 working days of enrollment or randomization). All subjects (Part 1 and Part 2) will be treated during the study until Response Evaluation Criteria in Solid Tumors (RECIST)-determined disease progression or intolerance. All subjects will be followed for disease progression even those discontinuing study drug for other reasons (e.g., intolerance). An end of treatment (EOT) visit will occur within approximately 30 days after the time the Investigator decides to discontinue all study drugs (dinutuximab and/or chemotherapy) or prior to the initiation of subsequent treatment, whichever occurs first. Immunogenicity follow-up will continue for subjects receiving dinutuximab for up to 16 weeks following the last dose of dinutuximab to assess anti-drug antibodies (ADA) and neutralizing antibodies (NAb). Monthly follow-up for survival will begin after the EOT visit and will continue until the subject has withdrawn consent, is lost to follow-up, has died, or until the Sponsor makes a decision to close the study. It is important that all subjects are followed for survival. No crossover between groups is allowed given OS is the primary endpoint.
Sample Size	Twelve subjects with relapsed or refractory SCLC were enrolled in Part 1 of the study. Approximately 460 subjects will be enrolled in Part 2 and randomized to one of three treatment groups (184 dinutuximab + irinotecan, 184 irinotecan, and 92 topotecan).
Withdrawal of Subjects	A subject may withdraw, or be withdrawn, from the study at any time. The most common reasons subjects are withdrawn from the study are: • Withdrawal of consent for further participation in the study. • Subject is lost to follow-up. • Study termination by the Sponsor. If a subject wishes to discontinue study treatment, the Investigator should explain to the subject the importance of remaining on study follow-up, or failing this of allowing routine follow-up data to be used for study purposes.
Study Procedures and Assessments	*Screening*: Written informed consent must be obtained before any protocol-specific screening tests or procedures may be conducted. The screening period for a particular subject commences when the subject undergoes the first study-specific screening assessment. After informed consent is obtained, the following screening assessments will be performed within 21 days before the planned day of enrollment (Part 1) or randomization (Part 2) unless otherwise stated. Laboratory tests for eligibility will be performed at a central laboratory. Local hematology and chemistry laboratory results cannot be used to confirm eligibility. CT, or magnetic resonance imaging (MRI) if judged clinically appropriate, performed (as described in the protocol) prior to informed consent may be used if within 28 days prior to enrollment (Part

	1) or randomization (Part 2). The method selected must be used consistently throughout the study. General • Demographics. • Medical history (including prior treatment for SCLC, prior surgery, history of tobacco use and other significant medical conditions). • Physical examination (including review of systems, height, weight, body surface area [BSA] using a standard formula), and ECOG status. • Neurologic assessment (Investigator's assessment at baseline of whether subject's mental status, coordination and gait, sensory function, motor function and vision [with consideration to corrective lenses as prescribed] are within the subject's normal limits). • Ophthalmology examination (including assessment of any vision problems and associated corrective measures, of pupils [size, shape, symmetry, response] and of any complaints regarding photophobia). The ophthalmology examination at screening is to be performed as part of the screening physical exam by the Investigator. The screening ophthalmology examination does not need to be performed by an ophthalmologist. However, if clinically significant deterioration in vision is noted during the course of the study, an ophthalmologist must be consulted. • Pain assessment (any pre-existing pain including locations and severity using the numeric 0-10 pain scale). • 12-lead electrocardiogram (ECG). • Vital signs (systolic and diastolic blood pressure, respiration, pulse, and oral temperature). • All ongoing medications. • Serious adverse events (SAEs) (and AEs based on local regulations) starting on the day of written informed consent (SAEs, and AEs based on local regulations, will be collected for screen-failed subjects up until the time they are deemed a screen-failure for the study). Laboratory • Hematology (complete blood count [CBC]). CBC machine differential is acceptable when ANC is $\geq$1,500/mm^3. Below 1,500/mm^3, the differential must be manually counted. • Chemistry (BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, lactate dehydrogenase [LDH], albumin, total protein, magnesium, alkaline phosphatase [ALP], AST, ALT, total bilirubin). • Pregnancy test: Women of reproductive potential must have a negative urine or serum β-HCG pregnancy test. Women not of reproductive potential are female subjects who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy). Hematology and chemistry will be analyzed by a central laboratory. Local hematology and chemistry laboratory results cannot be used to determine eligibility. Pregnancy test samples will be analyzed locally. Disease-Related • Disease assessments (CT or MRI of the chest/abdomen with contrast,

	with careful attention to the liver and adrenal and other locations as clinically indicated). • For subjects with a history of or medically suspected brain metastases, brain MRI (preferred) or brain CT with contrast. *Baseline*: • Repeat pregnancy test: Women of reproductive potential must have a negative urine or serum β-HCG pregnancy test obtained within 7 days prior to the first dose of study treatment (dinutuximab and/or chemotherapy). Women not of reproductive potential are female subjects who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy). • Archival tissue, if available, tested for programmed cell death ligand-1 (PD-L1). Test to be performed locally if assay is available. Prior test results are acceptable. • Blood sample for biomarker analysis. • Blood sample to analyze circulating tumor cells (CTC) (**Part 2, selected regions only)**. • *Optional sample for biomarker analysis (future exploratory research) for subjects who consent to participate*: o *Archival sample of tumor tissue that was fresh-frozen to analyze gangliosides and other biomarkers if available and taken for a reason not related to this protocol.* If the subject consents to provide an optional tissue sample for future exploratory research, the sample will be stored at the specialty laboratory (Precision Bioservices, Inc., Frederick, Maryland) for a maximum of 15 years. If samples are not used within this 15-year period, they will be destroyed. Samples may be also destroyed within this 15-year period. *During Treatment (Cycles 1 – 6 and beyond)*: The following routine assessments will be performed during treatment for all subjects except where noted. • Physical examination (including BSA calculation) and neurologic assessment on Day 1 (within 48 hours prior to Day 1) of every cycle. The focus of the neurologic assessment during treatment is on whether there is any clinically significant deterioration in the parameters (mental status, sensory function, etc.) since the last assessment. For Cycle 1, screening physical and neurologic assessment may be used if within 7 days prior to Day 1. • Vital signs are to be taken on Day 1 of every cycle within 1 hour (±30 minutes) prior to study drug administration. For subjects receiving dinutuximab, vital signs should be taken additionally 30 minutes (±10 minutes) into the infusion, at the end of the infusion (±30 minutes) and hourly (±30 minutes) after the infusion for a minimum of 1 hour, or longer if clinically indicated. • Hematology on Day 1 (within 48 hours prior to Day 1) and once between Days 8-15 (to measure ANC nadir) of every cycle (results must be available prior to study treatment administration); WBC must include

complete differential. As clinically indicated, an Investigator may consider additional collections during a treatment cycle. Hematology on Day 1 may be assessed within 24-48 hours in advance of Day 1.

- Chemistries on Day 1 (within 48 hours prior to Day 1) of every cycle (BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, ALP, AST, ALT, total bilirubin). Urea may be measured instead of BUN at the local laboratory.
- Serial blood samples for PK assessment during Cycle 1 at 10 time points **(Part 1 only)**:

Time points	Cycle 1	Post dose, hours (Day)								
	Pre-dose	2	6	24 (Day 2)	48 (Day 3)	72 (Day 4)	96 (Day 5)	192 (Day 8)	360 (Day 15)	528 (Day 22) before the next dose (Cycle 2 Day 1)
Windows	Anytime prior to dosing on the day of dosing	± 5 minutes		± 30 minutes				± 60 minutes		Anytime prior to the next dose on the day of the next dose

The time points for post dose samples start from the end of the infusion (e.g., 24 hours post dose = 24 hours after infusion end). Serial PK blood draws will be repeated with the <u>first</u> dose change (reduction or escalation). A validated assay will be used to measure concentration of dinutuximab. Details regarding sampling time points and procedures can be found in the lab manual.

- Sparse blood samples for population PK analysis during Cycle 1 at 2 time points and during Cycle 3 at 6 time points **(Part 2 Group B only)**:

Time points	Cycle 1	
	Pre-dose	Infusion end
Windows	Anytime prior to dosing on the day of dosing	Up to 10 minutes after end of infusion

Time points	Cycle 3		Post dose, hours (Day)			
	Pre-dose	Infusion end	24 (Day 2)	192 (Day 8)	360 (Day 15)	528 (Day 22) before the next dose (Cycle 4, Day 1)
Windows	Anytime prior to dosing on the day of dosing	Up to 10 minutes after end of infusion	± 30 minutes	± 60 minutes		Anytime prior to the next dose on the day of the next dose

The time points for post dose samples start from the end of the infusion (e.g., 24 hours post dose = 24 hours after infusion end). Details regarding sampling

	time points and procedures can be found in the lab manual. • Blood samples for the evaluation of ADA and NAb in plasma pre-dose on Day 1 of all cycles plus Day 8 (+/- 1 day) and Day 15 (+/- 1 day) of Cycle 1 **(Part 1 and Part 2 Group B only)**. Details regarding sampling time points and procedures can be found in the lab manual. • Blood sample for biomarker analysis. • Blood sample on Day 1 of every cycle to analyze CTC (**Part 2, selected regions only**). • Disease assessments (CT or MRI of the chest/abdomen with contrast, with careful attention to the liver and adrenal and other locations as clinically indicated) every 6 weeks (+/- 7-day window) from the date of enrollment (Part 1) or randomization (Part 2).* *Note: For subjects enrolled in Part 2, the timing of disease assessments should not be altered, even in the event of a dose delay or interruption in a cycle. This is very important to prevent or minimize evaluation-time bias. • For subjects with a history of or medically suspected brain metastases, brain MRI (preferred) or brain CT with contrast every 6 weeks (+/- 7-day window) from the date of enrollment (Part 1) or randomization Part 2) or as medically indicated. • AEs and concomitant medications (con meds) are to be assessed every cycle (The following information is required to be documented for each adverse event: date of onset, date of resolution, severity [NCI-CTCAE v4.03], the Investigator's opinion of the relationship of the event to the investigational product, and treatment required, if any.). Laboratory tests for safety during scheduled and unscheduled study visits will be performed at a central laboratory. Investigators may use local laboratory results for making real-time clinical decisions during the course of the study including managing subjects on study treatment and discontinuing study therapy due to toxicity. For AE reporting, the Investigator should report the highest NCI-CTCAE v4.03 grade if there is a difference in the reported value between contemporaneous local laboratory and central laboratory results. If the central laboratory value results in a higher grade than the local laboratory, local laboratory results may still be used for real-time clinical decision-making. *End of Treatment (EOT)/Safety*: The following assessments must be completed within approximately 30 days after the time the Investigator decides to discontinue all study drugs for the subject (dinutuximab and/or chemotherapy) or prior to the initiation of subsequent treatment, whichever occurs first. Any ongoing AEs/SAEs at the time of the EOT/safety visit should be followed as outlined in the AE section of the protocol. • ECOG performance status. • Status of ongoing AEs and con meds. • Hematology (including differential). • Chemistry (BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, ALP, AST, ALT, total bilirubin). • Blood samples for post-treatment immunogenicity (**Part 1 and Part 2**

	Group B only) **IF** EOT visit occurs within the time frame for the first evaluation (4 weeks [+/- 7 days] of completing dinutuximab). • Blood sample for biomarker analysis. • Blood sample to analyze CTC (**Part 2, selected regions only**). • Disease assessments (CT or MRI of the chest/abdomen with contrast, with careful attention to the liver and adrenal and other locations as clinically indicated) unless disease progression is previously documented during the study per RECIST. • Brain MRI (preferred) or brain CT with contrast for subjects with prior evidence of brain metastasis (at baseline) unless disease progression is previously documented during the study per RECIST. • Recording of planned subsequent anticancer treatment, if any. **Note:** All subjects should be followed for overall survival. Subjects enrolled in Part 2 who discontinue treatment prior to the documentation of disease progression should continue to be followed on the disease assessment schedule (every 6 weeks from the date of randomization [+/- 7 days]) until disease progression is documented radiographically per the protocol. At the EOT, further follow-up should be clarified with the subject (for OS, or for disease assessments if applicable) and any such consent for ongoing follow-up must be documented in both the source records and the electronic case report form (eCRF). Subject follow-up is critical to prevent or minimize informative censoring for assessment of OS and PFS, the study's primary endpoint and key secondary endpoint, respectively. *Immunogenicity Follow-Up (Part 1 and Part 2 Group B)*: Subjects who received dinutuximab will be followed for up to 16 weeks for immunogenicity following discontinuation of dinutuximab treatment. Blood samples will be collected 4, 8, 12 and 16 weeks (+/- 7 days) after the last dose of dinutuximab treatment. The 4-week visit may be omitted if immunogenicity assessment was performed at the EOT visit within the required time interval. *Survival Follow-Up*: Monthly (+/- 7 days) assessments of survival will be performed from the date of the EOT visit. Survival follow-up will continue until the planned number of events has been reached or until the Sponsor has stopped the study for any reason. Contacts can be made in person or by phone; the subject's primary care physician may be the contact should the subject be unavailable. If a subject does not return to the clinic for follow-up visits, at least 3 documented attempts, including one via mail that requires a signature (e.g., courier, certified), should be made to contact the subject before declaring a subject is lost to follow-up. If the subject is considered lost to follow-up, the date of death may be captured from public records. All subject contact will be documented in source documents. **It is critical that all subjects are followed for OS, the study's primary endpoint.**
Statistical Methods	The study will start with a cohort of approximately 10 subjects (Part 1) treated with dinutuximab (in combination with irinotecan) for at least 3 cycles at rising or decreasing doses, depending on pain and other toxicities, to select a safe dose for Part 2. Subjects in Part 1 will be followed for all

	efficacy/safety assessments, including OS, PFS and ORR. Data for this cohort will be summarized using descriptive statistics. In Part 2, 460 eligible subjects will be randomized in a 2:2:1 fashion to one of the following treatments: Group A: Irinotecan (N=184) Group B: Dinutuximab + Irinotecan (N=184) Group C: Topotecan (N=92) Randomization will be stratified by the subject's response to prior platinum therapy (relapse-free period < 3 months or ≥ 3 months). Although the study includes three treatment groups, the primary aim of the statistical analysis is to show that dinutuximab administered with irinotecan (Group B) is superior to irinotecan alone (Group A). All analyses regarding topotecan (Arm C) are exploratory. The primary efficacy analysis will compare Group B (Dinutuximab + Irinotecan) versus Group A (Irinotecan). Other pairwise treatment comparisons will be performed for exploratory purposes only. Statistical testing of the primary efficacy endpoint (OS) will evaluate superiority of Group B (Dinutuximab + Irinotecan) versus Group A (Irinotecan). A total of 306 deaths in these two groups will provide approximately 80% power to detect a hazard ratio (HR) of 0.725 or a 2.3 month gain in median OS (from 6 to 8.3 months); this calculation is based on a log-rank test (2-sided alpha=0.05). Results of secondary efficacy endpoints will be considered for potential labeling claims only if there is clear evidence of a survival benefit with the combination therapy versus irinotecan alone. A closed, hierarchical testing procedure will be used to control the overall false-positive rate at 5% (two-sided) for the primary comparison of Group B versus Group A. Secondary endpoints will be tested in the following sequence: PFS, ORR and CBR. Hypothesis testing will proceed in the above sequence and require statistically significant superiority for the dinutuximab regimen (Group B vs. Group A, with $p \leq 0.05$) in the first step before testing is allowed at the next step. Once the null hypothesis is not rejected, testing will stop and no further claims can be based on this or subsequent efficacy endpoints. Using this procedure, no alpha-adjustment is necessary for individual tests performed in the pre-specified sequence. Exploratory analyses will compare efficacy endpoints in Group B (Dinutuximab + Irinotecan) versus Group C (Topotecan). As above, hypothesis-testing will be performed in a fixed sequence to control the Type 1 error rate at 5% (two-sided) for this set of comparisons, beginning with OS and followed, in order, by PFS, ORR, and CBR.

1. INTRODUCTION

1.1. Background

Small cell lung cancer (SCLC) is a subtype of lung cancer with distinct clinical and histologic features. Of all lung cancers, it is the most aggressive, characterized by rapid growth and early dissemination to distant sites. In the United States, an estimated 31,000 new cases of SCLC were diagnosed in 2016.[1] In Europe, the incidence is roughly double that of the United States, with the highest incidence rates reported in Central and Eastern Europe.[2] At diagnosis, approximately 60-70% of patients with SCLC have clinically disseminated or extensive disease. Prognosis for these patients is exceedingly poor, with an estimated 5-year survival rate of only 2% following treatment with combination chemotherapy.[3] For patients with limited stage disease (disease that is limited to the ipsilateral hemithorax and regional lymph nodes), median survival is approximately 17 months, with 5-year survival rates of 12-15%.[4] Cigarette smoking is the strongest risk factor for the development of SCLC; more than 90% of patients with SCLC are current or past smokers.[5]

1.2. Initial Treatment of SCLC

Combination chemotherapy is the cornerstone treatment for both limited-stage and extensive-stage SCLC and is routinely recommended for patients with a good performance status.[3] For patients with limited-stage disease, cisplatin plus etoposide is most commonly given, often concurrently with radiation therapy.[6] With multimodality therapy, complete response (CR) rates of 50-60% can be achieved.[4,7] Patients with extensive disease are often treated with cisplatin or carboplatin in combination with either etoposide or irinotecan. CR rates of 10-20% are typically reported from trials of combination chemotherapy for extensive stage SCLC.[8] Because intracranial masses occur in more than half of patients with SCLC, prophylactic intracranial irradiation is recommended in patients with limited stage disease who achieve a response and for all patients who have had a complete resection (Category 1 - Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.).[9]

1.3. Relapsed and Refractory SCLC

Although SCLC is highly responsive to initial chemotherapy and radiotherapy, most patients relapse within one year of starting treatment.[3] Following failure of frontline therapy, patients are classified as having sensitive, resistant or refractory SCLC. Patients who achieved an initial treatment response and relapsed more than 3 months after completing frontline treatment are

considered to have sensitive disease while those who relapsed less than 3 months after frontline therapy are judged to have resistant disease. Patients whose disease progressed during first-line treatment are defined as refractory patients.

Second-line systemic therapy is primarily directed toward symptom control and improving quality of life and provides significant palliation for many SCLC patients. Prolonged survival and reduction in tumor burden may also be achieved in some patients.[10] The approach to second-line treatment takes into account initial response and the relapse-free interval. For patients whose disease relapsed more than 6 months after first-line treatment (sensitive disease, "late" relapse), reintroduction with the original or a novel platinum-based regimen may be considered.[11-13] For patients whose disease relapsed 3 to 6 months after completing frontline therapy (sensitive disease, early relapse) and for patients with resistant disease (relapse within 3 months), single-agent therapy with topotecan or irinotecan is typically offered.[9,14] There are no approved drugs in the United States for patients with refractory SCLC. For these patients, participation in a clinical trial is recommended.[14]

The outcome for patients with relapsed or refractory SCLC is poor. The most important factors affecting prognosis are performance status, tumor extent (i.e., limited versus extensive), and time to relapse after first-line therapy.[14] For patients with sensitive disease (relapse-free interval of more than 3 months), median survival ranges from 6 to 7.5 months and response rates of 25% can be achieved.[11,15] Among those with sensitive disease, patients with a poor performance status (PS 2) have shorter overall survival, while those with better performance status or a relapse-free interval greater than 6 months have slightly better outcomes.[16-17] For patients with resistant or refractory disease (relapse-free interval of less than 3 months or no response to frontline therapy), median survival is approximately 4 to 5 months and response to most agents or regimens is poor (≤10%).[9,11]

1.4. Topotecan as Second-Line Treatment for SCLC

Topotecan, a topoisomerase-I inhibitor, is the only drug approved in the United States for second-line treatment of SCLC; its indication is limited to patients with platinum-sensitive disease whose disease progressed at least 60 days after first-line chemotherapy (HYCAMTIN [topotecan] for injection U.S. prescribing information, 2015). The approval of IV topotecan was based on a randomized Phase III trial that showed similar response rates for topotecan compared to combination chemotherapy with cyclophosphamide, doxorubicin and vincristine.[15] Many

practicing oncologists have noted excessive toxicity with the standard regimen of 1.5 mg/m^2 of IV topotecan for 5 consecutive days,[9] prompting studies of alternate dosing regimens that are used in some clinical practices.[18]

1.5. Irinotecan as Second-Line Treatment for SCLC

Like topotecan, irinotecan is a specific inhibitor of topoisomerase I that works by inducing lethal DNA strand breaks in replicating cells. It is approved in the United States for the treatment of metastatic colorectal cancer (CRC), both in combination with 5-FU/leucovorin and as a single agent. Based on a finding of superior overall survival for irinotecan plus cisplatin (compared to cisplatin plus etoposide) in a Phase 3 first-line extensive stage study conducted in Japanese patients, irinotecan is approved for front-line use in SCLC in Japan.[19] In the setting of relapsed SCLC, irinotecan has been the subject of several Phase 2 studies showing good antitumor activity.[20] Based on these findings, irinotecan is recommended by the NCCN as one of the preferred single agents for second-line treatment of SCLC (For topotecan, irinotecan and other agents: Category 2A - Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.).[9] Additionally, NCCN guidelines recommend irinotecan plus either cisplatin or carboplatin as a possible first-line regimen. European Society of Medical Oncology (ESMO) guidelines[21] list irinotecan plus cisplatin as an alternative first-line regimen for those patients for whom etoposide is contraindicated.

A number of different dosing regimens of single-agent irinotecan have been evaluated for the treatment of second line SCLC including 100-125 mg/m^2 weekly and 350 mg/m^2 every 3 weeks.[20] In the setting of CRC, irinotecan monotherapy is approved in the United States http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020571s048lbl.pdf and elsewhere at a dose of 350 mg/m^2 on day 1 every 3 weeks and at a dose of 125 mg/m^2 weekly for four consecutive weeks followed by a two-week rest. A similar safety profile has been observed in the weekly-dosage schedule at the starting dose of 125 mg/m^2 compared to the every-3-week-dosage schedule. http://mri.cts-mrp.eu/download/NL_H_1326_001_FinalSPC.pdf

There are no published studies that demonstrate superiority of any single agent over another in second-line SCLC. In an effort to improve upon the outcomes seen with single-agent therapy, a recent randomized Phase 3 trial was conducted evaluating the combination of irinotecan, cisplatin and etoposide versus topotecan alone in relapsed-sensitive SCLC.[22] Survival was significantly

longer in patients receiving irinotecan combination therapy. This is the first time that any regimen has shown a survival benefit to topotecan alone in relapsed SCLC.[22]

1.6. Gangliosides

Gangliosides are a family of lipids known as sialic acid-bearing glycosphingolipids that were first described by the German scientist Ernest Klenk in 1942. Klenk proposed the term ganglioside because of the abundance of these molecules in ganglion cells of the brain.[23] Gangliosides have since been found in many tissues and organs throughout the body and have been suggested to be involved in the regulation of development and differentiation as recognition molecules or signal modulators.[24] Gangliosides function by recognizing specific molecules at the cell surface and by modulating the activities of proteins in the plasma membrane.[25]

In addition to playing important roles in many normal physiological processes, gangliosides also modulate transmembrane signaling essential for tumor cell growth, invasion, and metastasis.[26] Gangliosides differ in their nature and distribution between normal and cancer cells and among different types of cancer. Some gangliosides are highly expressed in tumor cells as well as healthy tissues while others show marked expression in tumor cells but very low levels of expression or no expression in normal cells.[27] One of the most extensively studied tumor-associated gangliosides or antigens is disialosyl ganglioside GD2.

1.7. Ganglioside GD2

GD2 represents a small fraction of the total amount of gangliosides on the surface of normal cells, with a level of expression that is several fold lower in comparison with other tumor associated gangliosides.[28] In normal tissues, GD2 expression has been shown to be primarily restricted to the central nervous system, peripheral nerves, and skin melanocytes.[29-32]

In tumors, the highest levels of GD2 expression have been observed on the cell surface of neuroblastomas, with a calculated mean antigen density of ~10^7 molecules per cell.[31,33] GD2 also is detected in most melanomas,[34] and is expressed in variety of other neuroectoderm-derived tumors and sarcomas including bone and soft-tissue sarcomas, brain tumors and small cell lung cancers.[35-36] While the function of GD2 is not completely understood, it is thought to be involved in the attachment of tumor cells to extracellular matrix proteins, suggesting that GD2 may play a significant role in the metastatic phenotype of these cells.[37]

Notably, GD2 was ranked 12th in priority among a list of 75 cancer antigens by the National Cancer Institute (NCI) project for prioritization of cancer antigens.[38]

1.8. Dinutuximab, A Monoclonal Antibody Directed at GD2

Because of the relatively tumor-selective expression combined with its presence on the cell surface, GD2 has been a target for tumor-specific antibody therapy over the past two decades.[39] Dinutuximab (formerly known as ch14.18) is a chimeric mouse/human monoclonal antibody (mAb)[40] composed of the variable region heavy and light chains of the murine mAb 14.18 and the human constant region genes for heavy chain immunoglobulin (Ig) G1 and light chain kappa. Dinutuximab binds to GD2 and induces tumor cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). In preclinical and early-phase clinical studies, dinutuximab showed promising activity against neuroblastoma,[41-43]leading to the conduct of a Phase 3 trial.[44]

The Phase 3 trial, led by the Children's Oncology Group (COG), was a multicenter, open-label, randomized trial. The primary endpoint was investigator-assessed event-free survival (EFS). Eligible patients had high-risk neuroblastoma and achieved at least a partial response to prior first-line multiagent, multimodality therapy. The trial randomized 226 patients (1:1) to either dinutuximab/13-cis-retinoic acid (RA) (dinutuximab/RA arm) or RA alone (RA alone arm). All patients received 6 cycles of treatment. In 5 of the 6 cycles, dinutuximab/RA was given in combination with alternating cytokines, granulocyte macrophage-colony stimulating factor (GM-CSF) and interleukin-2 (IL-2).[44] GM-CSF and IL-2 were added in an effort to augment ADCC.[45-47]

Demographic and baseline clinical characteristics were comparable between the two arms. Approximately 71% of the patients in the dinutuximab/RA arm and 77% of the patients in the RA alone arm completed planned treatment. The most common reason for premature discontinuation of study therapy was adverse reactions in the dinutuximab/RA arm (19%) and progressive disease in the RA alone arm (17%) (UNITUXIN® [dinutuximab] injection US prescribing information).

At an interim analysis, the data monitoring committee (DMC) determined that the study met the criteria for early stopping based on an improvement in EFS favoring dinutuximab: hazard ratio (HR) 0.57 (95% confidence interval [CI]: 0.37, 0.89); p=0.01 (UNITUXIN® [dinutuximab] injection US prescribing information). The median EFS in the dinutuximab/RA arm was not

reached (3.4 years to not reached) compared to 1.9 years (1.3 years to not reached) in the RA alone arm.

The most common (≥ 5%) serious (Grade 3 or 4) adverse drug reactions in the dinutuximab/RA group compared with the RA alone group were pain (51% vs. 6%), fever (40% vs. 6%), infection (sepsis) (16% vs. 9%), hypokalemia (37% vs. 2%), infusion reactions (25% vs. 1%), acute capillary leak syndrome (23% vs. 0%), and hypotension (16% vs. 0%) (UNITUXIN® [dinutuximab] injection US prescribing information). While GD2 is known to be expressed on neurons, the rate of CNS cortical symptoms was low (4%),[44] presumably due to the blood brain barrier to intravenous antibody therapy.[48] The toxic effects seen in the dinutuximab arm were primarily attributable to antibody binding to GD2 expressed on normal nerve cells, to cytokine-mediated capillary leak and to hypersensitivity reactions associated with dinutuximab or cytokines.[44] The reported adverse event (AE) profile of dinutuximab in the Phase 3 study was comparable to that reported in two other clinical (single-arm) studies of dinutuximab (UNITUXIN® [dinutuximab] injection US prescribing information).

Analysis of overall survival (OS) conducted 3 years following the EFS analysis documented an improvement in OS in the dinutuximab/RA arm compared to the arm with RA alone (HR 0.58 [95% CI: 0.37, 0.91]). The improvement in EFS and OS led to the approval of dinutuximab in the United States and Europe in 2015.[49-50] Dinutuximab was approved as an intravenous (IV) infusion administered at a daily dose of 17.5 mg/m^2 over 4 consecutive days for up to 5 cycles.

1.9. Clinical Experience with Dinutuximab in Adults with Melanoma or Sarcoma

In adults, data for dinutuximab comes from four studies of patients with malignant melanoma or sarcoma comprising a total of 90 patients. (Dinutuximab Investigator's Brochure)[46,51-53]These early clinical studies, carried out by individual academic investigators, evaluated the safety, dose and pharmacokinetic (PK) profile of dinutuximab, in single and multiple doses, and alone and in combination. The antibody's preliminary antitumor activity was also assessed. A wide range of doses was studied, ranging from as low as 2 mg/m^2/day[46] to as high as 60 mg/m^2/day, (Dinutuximab Investigator's Brochure) or 100 mg as a single, fixed dose.[51] Dinutuximab was evaluated as monotherapy[51] and in combination with GM-CSF,[52] IL-2,[46] and IL-2 plus the GD3 murine mAb R24.[53] The PK of dinutuximab, reported in one study, best fits a two-compartment model with a mean T ½α of 24 hours (± 1 hour) and a T½β of 181 hours (± 73 hours).[51] Pain was noted in all studies, most commonly in the abdomen and/or extremities. Two studies reported

objective responses,[46,53] including a PR and a CR at doses as low as 5.25 mg/m^2/day (equivalent to 7.5 mg/m^2/day of NCI-manufactured product).[46] Other studies reported stable disease as the best response to treatment.[51-52]

Additional information on the safety and activity of dinutuximab can be found in the Investigator's Brochure.

1.10. Dinutuximab Dose

Studies conducted for dinutuximab were largely performed in a chemotherapy-dominant era where maximum tolerated dose (MTD) was the benchmark for dosing.[54] With cytotoxic agents, MTD typically corresponds to the highest dose associated with an acceptable level of toxicity.[55] Targeted therapies, on the other hand, are typically dosed at the optimum biologic dose. The optimum biologic dose is a dose that reliably inhibits a drug target or achieves a target plasma concentration. In many cases, the optimum biologic dose is far below the MTD.[56]

In pediatric studies of dinutuximab, the response related to the dose of dinutuximab was generally not reported. In the registration-enabling study in pediatric patients with neuroblastoma,[44] dinutuximab was administered at a dose of 17.5 mg/m^2/day (equivalent to 25 mg/m^2/day of NCI-manufactured product). In studies of adult patients with cancer, doses of dinutuximab as low as 5.25 mg/m^2 (equivalent to 7.5 mg/m^2 of NCI-manufactured product) have been associated with antitumor activity.[46] While one study found there was no clear relationship between increase in pain and dose escalation,[57] others have suggested that the incidence and severity of pain may be in part related to the dose of anti-GD2 mAb treatment.[43,58] In a Phase I study of dinutuximab alone, little or no pain was reported with doses of 10-20 mg/m^2; however, at doses ≥50 mg/m^2 pain was severe requiring concomitant administration of a morphine drip.[43] Taking into consideration that little to no pain was reported with doses up to 14 mg/m^2 (equivalent to 20 mg/m^2 of NCI-manufactured product) in children,[43] it is possible that the optimum biologic dose is at or below this dose.

1.11. GD2 as a Target for SCLC Anti-GD2 Antibody Therapy

Like neuroblastoma, SCLC is of neural crest origin, and several studies have shown that human tumors derived from cells of neural crest origin express relatively large amounts of gangliosides on their surface. In SCLC, studies have shown that GD2 is a predominant ganglioside[59-60] and is expressed in SCLC cell lines[24,59-60] and tumors.[59-61] SCLC has also been found to differentially

express GD2 in comparison to non-small cell lung cancers,[24,59] and no significant levels of GD2 have been detected on normal tissues, including normal lung and skin tissue.[59,61] GD2 has also been shown to be involved in proliferation and invasion in SCLC cell lines. Importantly, successful *in vivo* detection of SCLC tumor sites with mAbs against GD2 has been reported,[61] and anti-GD2 mAbs have been shown to induce apoptosis of SCLC cells *in vitro* via activation of caspases.[24] These findings support GD2 as a target of chemoimmunotherapy in SCLC.[24]

1.12. Synergistic Activity of Anti-GD2 mAb Therapy and Chemotherapy

Yoshida and colleagues investigated the effects of anti-GD2 mAb therapy in combination with common chemotherapeutic agents in SCLC cell lines.[62] Chemosensitivity was significantly enhanced in the presence of anti-GD2 mAb, decreasing the drug needed for inhibitory concentration (IC)50 by approximately 2-8 fold; the greatest enhancement was seen with SN-38, the active metabolite of irinotecan (Table 1). Similarly, cytotoxicity was increased 27% to 68% over drug alone, with the most pronounced effects observed for the combination of cisplatin and anti-GD2 mAb (Table 2).

Table 1: Enhancement of Drug Sensitivity by Anti-GD2 mAb

Drug	IC50† (μM)		Enhancement of sensitivity (fold)
	Drug alone	Drug+Anti-GD2 mAb	
Cisplatin	86.66±4.16	18.66±8.08*	4.6
Doxorubicin	3.73±0.30	1.53±0.50*	2.4
Etoposide	171.6±36.8	43.66±10.06*	3.9
SN-38‡	10.66±3.05	1.36±0.37*	7.8
Paclitaxel	0.256±0.045	0.039±0.002*	6.6
Vinorelbine**	3.76±0.37	0.726±0.155*	5.2

†The IC50 was determined as the concentrations of drugs that showed 50% growth inhibition in MTT assay. Values are means ± SD of three independent experiments.
‡Active metabolite of irinotecan, a topoisomerase-1 inhibitor
*P<0.01
**Unit for vinorelbine is μg/mL.

Table 2: Enhancement of Drug Cytotoxicity by Anti-GD2 mAb

Drug	Survival rate (%)†		Enhancement of cytotoxicity (%)
	Drug alone	Drug+Anti-GD2 mAb	
Cisplatin	76.29±5.02	8.08±0.48	68.2
Doxorubicin	42.69±0.79	11.32±0.30	31.4
Etoposide	59.88±1.04	33.19±2.07	26.7
SN-38‡	56.92±2.35	21.88±1.80	35.0
Paclitaxel	82.9±5.50	43.00±5.00	39.9
Vinorelbine*	70.72±0.92	37.28±1.60	33.4

†Enhancement of cytotoxic effects of anticancer drugs by anti-GD2 mAb was calculated from growth inhibition curves. Enhancement of cytotoxicity = % survival by drug alone - % survival by drug plus anti-GD2 mAb at the point where the subtracted values were maximum for the individual drugs.
‡Active metabolite of irinotecan, a topoisomerase-1 inhibitor
*Unit for vinorelbine is μg/mL.

1.13. Clinical Activity of Dinutuximab and Irinotecan

Given the synergistic effect of dinutuximab and irinotecan *in vitro*, and non-overlapping toxicity of the two drugs, a randomized Phase 2 trial was undertaken by the COG to compare dinutuximab/GM-CSF versus temsirolimus in combination with irinotecan and temozolomide in children with relapsed, refractory or progressive neuroblastoma.[63] The study's primary endpoint was ORR, evaluated through a 2-stage sequential design. Treatment included dinutuximab 17.5 mg/m^2 IV Days 2-5 and irinotecan 50 mg/m^2 IV Days 1-5 of each 21-day cycle.

Stage 1 was completed following the enrollment of 18 and 17 patients into the temsirolimus and dinutuximab arms, respectively. The minimum of 3 responses was achieved to move to Stage 2. Objective responses were documented in 53% (9/17; 5 CR, 4 PR) of the dinutuximab-treated patients compared to 6% (1/18; 1 PR) of the temsirolimus-treated subjects. In seven of nine patients who responded to irinotecan–temozolomide–dinutuximab, best response was seen after only two cycles. One-year PFS also favored dinutuximab: 76.5% (95% CI 56.3-96.7) vs. 24.7% (95% CI 0.4-49.0).

The adverse events (AEs) observed were consistent with the expected AE profiles of dinutuximab, irinotecan and the other drugs under study (Table 3).[63] There were no obvious differences in the rate of Grade 3/4 AEs typically associated with irinotecan (diarrhea, myelosuppression) or with dinutuximab (pain, neuropathy, fever, electrolyte abnormalities) when compared to available data for either agent used alone. These safety findings strongly suggest that

the combination of dinutuximab and irinotecan does not result in potentiation of their respective toxicities. There were no reports of capillary leak syndrome in either arm. No treatment-related deaths occurred. Overall, the toxicities observed in the study were considered acceptable, with the observed benefit being seen to outweigh the risk for this patient population. Given the promising findings, the dinutuximab cohort will be expanded (N=50) to further assess activity and toxicities.[64]

Table 3: Treatment-Related AEs of Irinotecan-Dinutuximab Combination and Irinotecan-Temsirolimus Combination

	Irinotecan-Temsirolimus- Temozolomide (N=18)		*Irinotecan-Dinutuximab-* Temozolomide (N=16)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	6 (33%)	2 (11%)	4 (25%)	0
Thrombocytopenia	2 (11%)	3 (17%)	4 (25%)	0
Anemia	6 (33%)	0	4 (25%)	0
Fever and infection	2* (11%)	0	4† (25%)	0
Febrile neutropenia	3 (17%)	0	0	0
Capillary leak syndrome	0	0	0	0
Hypotension	0	0	2 (13%)	0
Hypoxia	0	0	3 (19%)	1 (6%)
Pain	1 (6%)	0	7 (44%)	0
Diarrhea	2 (11%)	0	1 (6%)	0
Vomiting	2 (11%)	0	3 (19%)	0
Mucositis	2 (11%)	0	0	0
Dehydration	3 (17%)	0	3 (19%)	0
Elevated creatinine	0	0	0	1 (6%)
Increased bilirubin	1 (6%)	0	0	0
Hyponatremia	0	0	3 (19%)	0
Hypokalemia	3 (17%)	1 (6%)	6 (38%)	0
Increased alanine aminotransferase	5 (28%)	0	1 (6%)	0
Peripheral motor neuropathy	0	0	1 (6%)‡	0

Note: One patient in the dinutuximab arm did not receive treatment and therefore is not included in the safety population.
*Both patients had bacteremia. †Two of these patients had Grade 3 or 4 fever during the time period in which the patient was receiving dinutuximab. The other two had documented infections including bacteremia and urinary tract infection.
‡Peripheral motor neuropathy occurred on day 6 of cycle 6 and returned to baseline within 6 weeks of onset.

1.14. Study Rationale

This study is a two-part, open-label, randomized Phase II/III study of dinutuximab and irinotecan versus irinotecan alone in subjects with relapsed or refractory SCLC. SCLC was selected based on the scientific evidence for GD2 as a therapeutic target[24,59-61] and the profound unmet need that patients with this disease have for effective therapy.[9,11,15] Dinutuximab will be evaluated without

IL-2 or GM-CSF due to lack of persuasive evidence that these agents are needed[52,63] and the associated risks of added toxicity,[44] particularly in an adult population. Dosing for dinutuximab will be individualized given that pain, the most common toxicity of dinutuximab, is highly subjective and variable from patient to patient.

Part 1 of the study is designed to assess the safety, tolerability and PK of dinutuximab when administered in combination with irinotecan and to confirm the starting dose of dinutuximab for Part 2. The Part 1 starting dose of 10 mg/m^2/day was selected based on prior studies of dinutuximab suggesting that doses as low as 5.25 mg/m^2/day have antitumor activity,[46] and in children, little to no pain was reported with doses up to 14 mg/m^2/day.[43] The maximum dose of 17.5 mg/m^2/day was selected based on the approved daily dose of dinutuximab in children with high-risk neuroblastoma. The irinotecan dose of 350 mg/m^2 is consistent with the dose evaluated in second-line SCLC and the approved dose of irinotecan as monotherapy for CRC given on an every 3-week basis. Administering dinutuximab on the same schedule as irinotecan is intended to minimize subject burden.

After approximately 10 subjects in Part 1 have completed three 21-day cycles of therapy, Part 2 of the study commences with approval of the safety review committee (SRC) (Section 12.7). Part 2 of the study is designed to assess the contribution of effect of dinutuximab to irinotecan, a standard of care agent for second-line treatment of SCLC. The combination group builds upon the preclinical evidence showing that anti-GD2 mAbs act synergistically with a number of chemotherapeutic agents including irinotecan.[62] Additionally, it is supported by recent clinical evidence showing promising activity of irinotecan and dinutuximab in children with neuroblastoma,[63] and in the setting of SCLC, evidence suggesting that irinotecan in combination may be more effective than single-agent therapy.[22] The topotecan group is included given it is the only currently approved agent for second-line treatment of (relapsed-sensitive) SCLC. The dose and schedule for topotecan (1.5 mg/m^2 for 5 consecutive days of every 21-day cycle) is the approved dose and schedule for SCLC. Evaluation of the effect of the combination group against the topotecan alone group is relegated to a secondary objective. Owing to the poor prognosis of patients with relapsed and refractory SCLC, OS is the primary outcome measure of interest. The study findings are intended to support registration of dinutuximab (in combination with irinotecan) if warranted.

1.15. Summary of Clinical Safety from Part 1 of the DIV-SCLC-301 Study

The SRC for the DIV-SCLC-301 study met to review the safety and tolerability data entered into the electronic data capture (EDC) system for Part 1 of the study. At the time of the data cutoff, 12 subjects with SCLC had been exposed to dinutuximab and irinotecan for a mean of 3.2 cycles (range: 2-5 cycles). The maximum dose of dinutuximab administered was 16 mg/m^2 and three subjects had data entered into the EDC at this dose level. The median infusion time for dinutuximab during Cycle 1 was 2 hours and 30 minutes (interquartile range [IQR]: 2 hours and 27 minutes, 3 hours and 4 minutes). The median time for subsequent infusions of dinutuximab was 1 hour and 8 minutes (IQR: 1 hour and 0 minutes, 1 hour and 30 minutes). Subjects received a mean dose of 22.8 mg of dinutuximab (range: 15-35 mg) and 649.2 mg of irinotecan (range: 420-777 mg). Dose reductions were not required for dinutuximab at any time; two subjects required a dose reduction in irinotecan. Table 4 presents total drug exposure by cycle for dinutuximab and irinotecan.

Table 4: Summary of Dinutuximab and Irinotecan Exposure (Part 1)

Cycle	Mean (Min, Max) Dinutuximab Dose (mg)	Mean (Min, Max) Irinotecan Dose (mg)	No. of Subjects (%)
Cycle 1	19.0 (15, 22.2)	664.8 (525, 777)	12 (100)
Cycle 2	21.4 (15.3, 26)	644.8 (420, 777)	12 (100)
Cycle 3	25.9 (21, 30)	649.6 (420, 777)	9 (75)
Cycle 4	28.3 (24.2, 31)	587 (420, 760)	4 (33.3)
Cycle 5	35.04	760	1 (8.3)

A total of 105 treatment-emergent AEs (TEAEs) were reported for the 12 subjects during Part 1 to the last data cutoff for the SRC. Diarrhea (75% of subjects), back pain (58.3%), nausea (41.7%), and vomiting (33.3%) were the most commonly reported AEs by preferred term.

Nine serious adverse events (SAEs) for five subjects were reported: hypercalcemia, community acquired pneumonia, Clostridium difficile (C. diff) colitis, peripheral arterial occlusive disease, bronchitis, acute respiratory failure, elevated creatinine, clinical deterioration and sepsis (with pancytopenia). Overall, the SAEs that were reported were representative of the background disease in this population and do not reflect a change in the safety profile of dinutuximab in SCLC patients.

Pain was reported in 8 of the 12 subjects and in 15 of 38 (39%) treatment cycles. Mild pain (Grade 1) was most often reported: Grade 1 (82.7% of pain reports), Grade 2 (3.4%) and Grade 3 (13.8%). The median duration of pain was <1 day (IQR: <1 day, <1 day) with most cases resolving within hours of completing the infusion. Opioid analgesics were administered either as premedication or as treatment for pain in 4 subjects and in a minority of treatment cycles (21% of cycles). Pain was commonly managed through conservative measures consisting of decreasing the dinutuximab infusion rate, briefly interrupting the infusion (<30 minutes) and/or administering non-steroidal anti-inflammatory drugs (NSAIDs). Reports of pain in the neck, lower and upper extremities, abdomen, back and pelvis/hip were documented in the EDC. Three subjects reported chest pain and/or pressure during the dinutuximab infusion in cycles 1, 2, 4 and 5. The chest pain/pressure was determined to be non-cardiac in etiology. Pain did not result in any treatment discontinuations and has not required long-term management.

Nine subjects experienced diarrhea. According to the Investigators' assessments, seven events of diarrhea were possibly or probably related to irinotecan, two events were possibly or probably related to irinotecan and dinutuximab, two events were not related to either drug and one event had no causality noted. Diarrhea events lasted a median of 4 days (IQR: 1.5 days, 7 days). Overall, 91.7% of diarrhea reported was graded a CTCAE Grade 1 and 8.3% was graded a CTCAE Grade 2.

The data reviewed at the time of the data cutoff did not demonstrate any safety signals or otherwise trends based upon dosing, infusion rates or number of cycles. Dose levels of 16 mg/m^2 were tolerated and no unanticipated AEs were reported. No suspected unexpected serious adverse reactions were reported. The SRC concluded that Part 2 of the study should open at a starting dose of dinutuximab of 14 mg/m^2 and no safety modifications to the protocol were required for Part 2.

The SRC reviewed additional data via a subsequent ad hoc meeting; at that time, 8 of the 12 subjects in Part 1 had received a dose of 16 mg/m^2/day or higher. The data at higher doses showed comparable safety and tolerability to the data at lower doses (data on file), and thus the SRC recommended increasing the starting dose of dinutuximab for Part 2 to 16 mg/m^2/day.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to compare OS in subjects treated with dinutuximab and irinotecan versus subjects treated with irinotecan alone as a second-line treatment for relapsed or refractory SCLC.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To compare progression-free survival (PFS), objective response rate (ORR) (complete response [CR] + partial response [PR]) and clinical benefit rate (CR + PR + stable disease [SD]) in subjects treated with dinutuximab and irinotecan versus subjects treated with irinotecan alone.
- To compare the safety of subjects treated with dinutuximab and irinotecan versus subjects treated with irinotecan alone.
- To evaluate the pharmacokinetics of subjects treated with dinutuximab.
- To compare OS, PFS, ORR, and clinical benefit rate (CBR) in subjects treated with dinutuximab and irinotecan versus subjects treated with topotecan alone.

2.3. Exploratory Objectives

The exploratory objective of the study is to assess the relationship between selected biomarkers and survival of subjects treated with dinutuximab.

3. ELIGIBILITY CRITERIA

3.1. Inclusion Criteria

Subjects must meet all of the following criteria:

3.1.1. Provide a signed informed consent form before any screening procedures.

3.1.2. Aged ≥18 years on the date of signing the informed consent form.

3.1.3. Have histologically or cytologically confirmed SCLC (undifferentiated small cell carcinoma arising in or consistent with lung cancer origin).

3.1.4. Documented (radiographic evidence of) relapse or disease progression during or after first-line platinum-based therapy (subjects refractory to initial platinum-based therapy are eligible).

3.1.5. No more than 1 prior regimen for SCLC. First-line platinum-based therapy followed by maintenance therapy is considered a single regimen provided there is no intervening disease progression.

3.1.6. Have no curative therapy available.

3.1.7. Have a life expectancy of at least 12 weeks.

3.1.8. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

3.1.9. Have adequate bone marrow function as assessed by the following laboratory test results:

- Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L (erythropoietin or transfusion permitted).
- Absolute neutrophil count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L (growth factors permitted).
- Platelet count ≥100,000/mm^3 or ≥100 x 10^9/L (transfusions or thrombopoietic growth factors permitted).

3.1.10. Have calculated creatinine clearance (CrCL) ≥30 mL/minute (using Cockcroft and Gault's formula) or serum creatinine ≤1.5 times below the ULN.

3.1.11. Have adequate hepatic function, as assessed by the following laboratory test results:

- Total bilirubin ≤1.5 times the ULN. (Subjects with Gilbert's Syndrome or other benign congenital hyperbilirubinemia may be eligible at the investigator's discretion in consultation with the Medical Monitor.)

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 times ULN in subjects without liver metastases or ≤5.0 times ULN in subjects with liver metastases.

3.1.12. Women of reproductive potential must have a negative urine or serum beta human chorionic gonadotropin (β-HCG) pregnancy test obtained within 7 days prior to the first dose of study treatment (dinutuximab and/or chemotherapy)

- Women not of reproductive potential are female subjects who are postmenopausal or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy).

3.1.13. Women of reproductive potential must agree to consistently use one form of highly effective contraception plus one additional form of contraception simultaneously or to practice complete abstinence from vaginal intercourse. The requirement for two forms of contraception or complete abstinence from vaginal intercourse applies from the time of informed consent until 90 days following the last dose of all study drugs. Male subjects who are sexually active with a female of reproductive potential must agree to use a condom from the time of informed consent until 90 days following the last dose of all study drugs.

The following are examples of highly effective and additional methods of contraception:

Highly effective methods (must use one):
- Hormonal associated with inhibition of ovulation (oral, injectable, implantable, intravaginal, transdermal)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Tubal ligation
- Vasectomy for partner

Additional effective methods (must use one):
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)

3.2. Exclusion Criteria

Subjects are excluded if they meet any of the following criteria:

3.2.1. Candidate for re-treatment with original platinum-based regimen as second-line therapy.

3.2.2. Prior treatment with irinotecan, topotecan or dinutuximab.

3.2.3. Have active brain metastases. Subjects with brain metastases are allowed if they completed definitive brain therapy, are asymptomatic and radiologically stable, and if they are not currently receiving corticosteroids or radiation. Subjects in whom steroids are being tapered may be eligible with prior approval of the Medical Monitor.

3.2.4. Have mixed small-cell and non-small-cell histologic features.

3.2.5. Have a previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study, except cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors (Ta and Tis [carcinoma in situ]) or any previous cancer curatively treated <3 years ago.

3.2.6. Have a history or current evidence of uncontrolled cardiovascular disease including but not limited to the following conditions:

- Congestive heart failure of New York Heart Association (NYHA) grade 3 or greater.
- Unstable angina (symptoms of angina at rest) or new-onset angina within 6 months.
- Arterial thrombosis, deep vein thrombosis, or pulmonary embolism within 6 months.
- Myocardial infarction or stroke within 6 months.
- Pericarditis (any CTCAE v.4.03 grade), pericardial effusion (CTCAE v4.03 Grade ≥2).

3.2.7. Have a history of atypical thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS).

3.2.8. Women who are pregnant or breast-feeding.

3.2.9. Have not recovered from prior surgery, significant trauma, systemic anticancer therapy (e.g., chemotherapy, biologic therapy, immunotherapy), radiation therapy or investigational therapy to Grade 1 or better toxicity prior to enrollment (Part 1) or randomization (Part 2).

3.2.10. Have had organ allograft or hematopoietic transplantation.

3.2.11. Known to be human immunodeficiency virus (HIV) positive.

3.2.12. Have an active infection requiring treatment or one that is clinically serious in the Investigator's opinion.

3.2.13. Have received a live vaccine within 6 months of enrollment (Part 1) or randomization (Part 2).

3.2.14. Exposure to strong CYP3A4 and/or UGT1A1 inhibitors and strong CYP3A4 inducers within 14 days of enrollment (Part 1) or randomization (Part 2).

3.2.15. Have any clinical condition that is considered unstable or might jeopardize the safety of the subject and / or influence the subject's compliance in the study.

4. ENROLLMENT AND RANDOMIZATION PROCEDURES

Eligible and consented subjects will be enrolled in the study. In Part 1, each subject will receive dinutuximab in combination with irinotecan and will start treatment within 3 working days of enrollment. Subjects participating in Part 2 of the study will be randomized in an open-label fashion using a 2:2:1 ratio to one of three treatment groups and will begin treatment within 3 working days of randomization. Randomization will be performed using a web-based randomization and product inventory control (RPIC) system provided by a third-party vendor. Specific procedures for randomization through RPIC are contained in the study procedures manual.

5. EXPERIMENTAL PLAN

5.1. Study Design and Treatment Plan

This study is an open-label randomized Phase II/III study of dinutuximab and irinotecan compared to irinotecan alone with an intrasubject dose-escalation lead-in phase in subjects with relapsed or refractory SCLC.

The lead-in phase of the study (referred to as Part 1) enrolled 12 subjects with SCLC, meeting the enrollment target of approximately 10 subjects. In Part 1, dinutuximab is being administered at increasing doses, as tolerated, together with irinotecan at a dose of 350 mg/m^2 IV on Day 1 of each 21-day cycle. Subjects receive dinutuximab at a starting dose of 10 mg/m^2 IV, with increases administered in 2 mg/m^2 increments per cycle in subsequent cycles if maximal pain with the prior dose is ≤Grade 1 or Grade 2/3 that in the view of the Investigator is adequately managed and the drug is otherwise tolerated. The maximum dose of dinutuximab that may be administered is 17.5 mg/m^2 (If this dose is reached, the dose increment would be 1.5 mg/m^2.). Dinutuximab dose is to be decreased in 2 mg/m^2 decrements per cycle depending on the toxicity observed to as low as 8 mg/m^2. If a dose decrease from 17.5 mg/m^2 is required, the initial dose reduction should be 1.5 mg/m^2 (and 2 mg/m^2 for any subsequent decrements) (See Section 6.7).

The study SRC met after the 12 subjects in Part 1 had been exposed to irinotecan and dinutuximab for a mean of 3.2 cycles and recommended opening Part 2 at a starting dose of dinutuximab of 14 mg/m^2/day. The SRC reviewed additional data via a subsequent ad hoc meeting; at that time, 8 of the 12 subjects in Part 1 had received a dose of 16 mg/m^2/day or higher. The data at higher doses showed comparable safety and tolerability to the data at lower doses (data on file), and thus the SRC recommended increasing the starting dose of dinutuximab for Part 2 to 16 mg/m^2/day. While enrollment in Part 1 is completed, dose escalation will continue in active subjects (per above), and subjects enrolled in Part 1 will remain on study treatment during the study until disease progression or intolerance.

In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC will be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutiximab combination group and 92/topotecan group) to one of three groups:

- Group A: Irinotecan; or

- Group B: Dinutuximab + Irinotecan; or
- Group C: Topotecan.

Subjects randomized to Group A or Group B will receive irinotecan at a dose of 350 mg/m^2 on Day 1 of each cycle.

Subjects randomized to Group B will also receive dinutuximab on Day 1 of each cycle beginning with a starting dose of 16 mg/m^2 IV. Dose escalation and de-escalation for dinutuximab will occur as in Part 1. The maximum dose of dinutuximab that may be administered is 17.5 mg/m^2 (If this dose is reached, the last dose increment would be 1.5 mg/m^2. If the dose is reduced from 17.5 mg/m^2, the initial dose decrement would be 1.5 mg/m^2 to 16 mg/m^2.).

Subjects randomized to Group C will receive topotecan 1.5 mg/m^2 IV for 5 consecutive days of each cycle.

One cycle is 21 days in duration.

There is a 2-day window around administration of study drugs on Day 1 of each cycle except for the first cycle (initial treatment should begin within 3 working days of enrollment or randomization). All subjects (Part 1 and Part 2) will be treated during the study until Response Evaluation Criteria in Solid Tumors (RECIST)-determined disease progression or intolerance. All subjects will be followed for disease progression even those discontinuing study drug for other reasons (e.g., intolerance).

An end of treatment (EOT) visit will occur within approximately 30 days after the time the Investigator decides to discontinue all study drugs (dinutuximab and/or chemotherapy) or prior to the initiation of subsequent treatment, whichever occurs first.

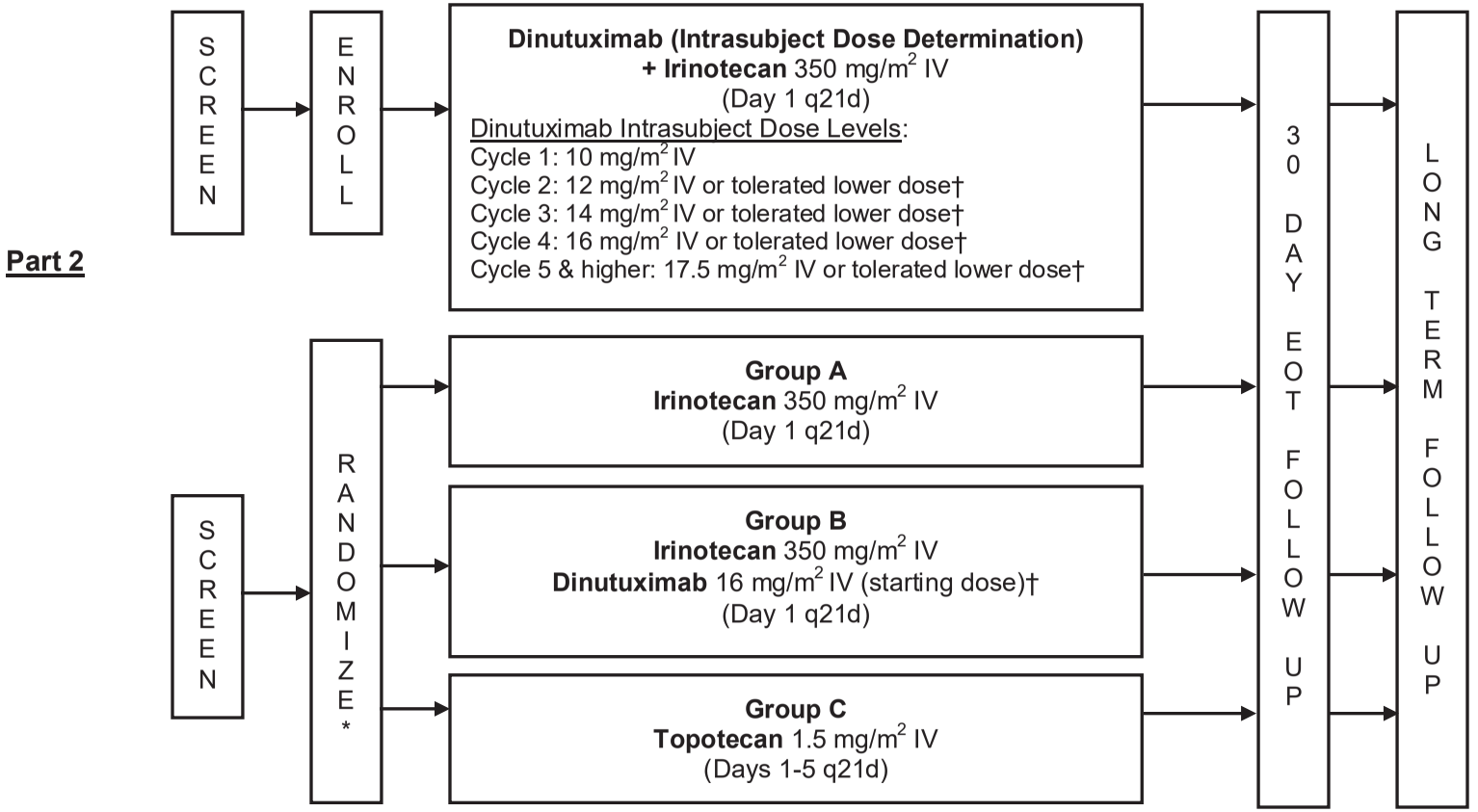
Immunogenicity follow-up will continue for subjects receiving dinutuximab for up to 16 weeks following the last dose of dinutuximab to assess anti-drug antibodies (ADA) and neutralizing antibodies (NAb).

Monthly follow-up for survival will begin after the EOT visit and will continue until the subject has withdrawn consent, is lost to follow-up, has died, or until the Sponsor makes a decision to close the study. It is important that all subjects are followed for survival.

No crossover between groups is allowed given OS is the primary endpoint.

See Figure 1 for study schema.

Figure 1. Study Schema



One cycle = every 21 days (q21d).
†Dose will be escalated if maximal pain with the prior dose is ≤Grade 1 or Grade 2/3 that in the view of the Investigator is adequately managed and the drug is otherwise tolerated up to a maximum dose of 17.5 mg/m^2 IV (If this dose is reached, the dose increment would be 1.5 mg/m^2.). Dose will be de-escalated in 2 mg/m^2 decrements for toxicity to as low as 8 mg/m^2/cycle per Section 6.7. If the dose is reduced from 17.5 mg/m^2, the initial dose decrement would be 1.5 mg/m^2 (to 16 mg/m^2).
*2:2:1 ratio (184/Group A, 184/Group B and 92/Group C); randomization will be stratified by relapse-free interval (<3 months, ≥3 months).
Treatment continues during the study until disease progression or intolerable toxicity.

5.2. Number of Centers

Approximately 200 centers will participate in this study globally.

5.3. Number of Subjects

Twelve subjects with relapsed or refractory SCLC were enrolled in Part 1 of the study and an additional 460 subjects will be enrolled in Part 2 and randomized to one of three treatment groups (184 dinutuximab combination group, 184 irinotecan group, 92 topotecan group).

5.4. Estimated Study Duration

The study enrollment period is expected to be approximately 10 months for Part 2. Assuming uniform enrollment over 10 months, the requisite number of death events for Part 2 is expected to occur after a follow-up period of 14 months from the last patient enrolled.

Monitoring of survival will continue until 306 deaths are documented in Groups A and B combined. This cut-off point will define the end of the study for the purpose of statistical analysis and report preparation. Events observed in ongoing patients under follow-up at this time will be included in a subsequent safety update.

6. STUDY TREATMENT

6.1. Dinutuximab Pretreatment (Part 1 and Group B of Part 2)

Dinutuximab will be given on Day 1 (+/- 2 days) of each 21-day cycle. Dinutuximab for injection will be provided by United Therapeutics free of charge for subjects enrolled in Part 1 and randomized to Group B in Part 2 of the study. Ordering information will be provided within the pharmacy manual that will be provided at the start of the study.

Prior to each dinutuximab dose, subjects must receive IV hydration in addition to premedication with antihistamines and antipyretics. From Cycle 2 onwards, premedication with opioid analgesics (morphine or morphine equivalent) may be considered, if in the judgment of the investigator pain is experienced in a prior cycle necessitating use of such medications, as allowed per institutional guidelines. For subjects on opioid medications for pre-existing pain, Medical History should be indicated as the reason for concomitant medication use on the electronic case report form (eCRF). If an opioid is also given as a premedication for possible dinutuximab-

related pain, an additional use should be indicated on the concomitant medication page and premedication should be selected as the category (i.e., two entries with distinct indications).

Subjects must be monitored closely for signs and symptoms of infusion reactions during and following the completion of each dinutuximab infusion in a setting where appropriate medical resources for the treatment of severe infusion reactions are available.

Subjects in Part 1 will be monitored for 4 hours after completion of each dinutuximab infusion. Subjects enrolled in Part 2 Group B will be monitored for 4 hours after completion of each infusion for the first 2 cycles, after which the observation time may decrease to 1 hour or duration deemed clinically necessary by the Investigator (if greater than 1 hour). After each dose increase, subjects should be carefully monitored for tumor lysis syndrome, according to the clinical judgment of the Investigator.

Intravenous Hydration

- Administer appropriate IV fluids of at least 1 liter one hour prior to initiating each dinutuximab infusion. A volume of less than 1 liter may be administered in subjects at risk for fluid overload, per Investigator discretion. IV hydration may be started during the irinotecan infusion beginning at Cycle 2 when the wait period of 1 hour between the end of the irinotecan infusion and the start of the dinutuximab infusion is no longer required.

Antihistamines and Antipyretics

- Administer an antihistamine such as diphenhydramine (suggested starting dose 50 mg) prior to initiation of dinutuximab and as needed and tolerated during the dinutuximab infusion. Investigators may use their judgment in determining the route (e.g., oral, IV) and dose of antihistamines. If antihistamines are given before the irinotecan infusion, the dose may be halved when antihistamines are given again before the dinutuximab infusion (e.g., 25 mg of diphenhydramine before irinotecan and 25 mg before dinutuximab infusions).

- Administer acetaminophen (suggested starting dose 1,000 mg) approximately 20 minutes prior to each dinutuximab infusion and every 4 to 6 hours as needed for fever or pain. Administer ibuprofen (600-800 mg per dose, not to exceed 3,200 mg in 24 hours) or other NSAID as needed for control of persistent fever or pain.

Opioid Analgesics

- If pain is experienced in a prior cycle necessitating the use of opioid analgesics, subjects may be given opioid analgesics (morphine sulfate or morphine equivalent such as hydrocodone, hydromorphone, oxycodone) as premedication, as allowed per institutional guidelines. Investigators may use their judgment in determining the route (e.g., oral, subcutaneous) and dose of opioid medications. In determining the dose, consideration should be given to whether the subject is currently receiving opioids for pre-existing pain or is opioid naïve.

Other

- For premedications due to ***prior*** hypersensitivity reaction to dinutuximab, see Section 6.7.3.

6.2. Dinutuximab Preparation and Administration

Preparation

- Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the outer carton. DO NOT FREEZE OR SHAKE vials.
- Inspect visually for particulate matter and discoloration prior to administration. Do not administer dinutuximab and discard the single-use vial if the solution is cloudy, has pronounced discoloration, or contains particulate matter.
- Aseptically withdraw the required volume of dinutuximab from the single-use vial and inject into a 100 mL bag of 0.9% Sodium Chloride Injection, USP. Mix by gentle inversion. Do not shake. Discard unused contents of the vial.
- Store the diluted dinutuximab solution under refrigeration (2°C to 8° C). Initiate infusion within 4 hours of preparation.
- Discard diluted dinutuximab solution 24 hours after preparation.

Administration

- Administer dinutuximab as a diluted intravenous infusion only. **Do not administer dinutuximab as an intravenous push or bolus.**

- For the first infusion, dinutuximab should be administered over approximately 2 hours, as tolerated. For subsequent infusions, the rate may be increased to attain a 1-hour infusion time, as tolerated.

- If pain is experienced during dinutuximab administration, initial management should consist of conservative measures such as a brief interruption in the infusion (for a maximum of 30 minutes) or decrease in the infusion rate. For pain occurring during or after the infusion, NSAIDs or other non-opioid pain medications may be administered. Additional management of pain, if required, should consist of opioid analgesics and/or medications to treat neuropathic pain (e.g., gabapentin, pregabalin, duloxetine, venlafaxine). See Section 6.7.2 for further details regarding management of pain.

- Dose and infusion rate at the start, and any increases or decreases, must be recorded in the eCRF.

For subjects randomized to Group B (dinutuximab and irinotecan), there must be a 1-hour (±15 minutes) wait time between the end of irinotecan infusion and the start of dinutuximab infusion for the first infusion. After the first infusion, the 1-hour wait time between irinotecan and dinutuximab infusions is no longer required.

6.3. Irinotecan Administration (Part 2: Group A and Group B only)

Irinotecan will be given on Day 1 (+/- 2 days) of each 21-day cycle at a dose of 350 mg/m^2. Irinotecan is commercially available and should be prepared according to the manufacturer's instructions. Investigators should use the locally approved package insert/summary of product characteristics for additional information such as safety issues, adverse reactions, and storage information. Investigators are strongly encouraged to use anti-emetics other than corticosteroids. If corticosteroids are used, they should be used at the lowest dose and for the shortest period of time judged clinically necessary.

6.4. Topotecan Administration (Part 2: Group C only)

Topotecan will be given for 5 consecutive days beginning with Day 1 (+/- 2 days) of each 21-day cycle at a dose of 1.5 mg/m^2. Topotecan is commercially available and should be prepared according to the manufacturer's instructions. Investigators should use the locally approved

package insert/summary of product characteristics for additional information such as safety issues, adverse reactions, and storage information.

A summary of the treatment schedule and dosing can be found in Table 5.

Table 5: Summary of Treatment Schedule and Dosing

Part 1:

	Cycles†					
	1	2	3	4	5	≥6
	Days (Day 1 +/- 2 day window)					
	1	1	1	1	1	1
Irinotecan						
Treatment	X	X	X	X	X	X
Dose mg/m^2	350	350	350	350	350	350
	1 hour (±15 minutes) wait time between end of irinotecan infusion and start of dinutuximab infusion for the 1st infusion					
Dinutuximab						
Pretreatment:						
IV hydration	X	X	X	X	X	X
Antihistamines	X	X	X	X	X	X
Antipyretics	X	X	X	X	X	X
Treatment	X	X	X	X	X	X
Dose mg/m^2	10	12*^	14*^	16*^	17.5*^	17.5*^

†Each cycle is 21 days.
*Dose escalation should occur in 2 mg/m^2 increments per cycle if maximal pain with prior dose is ≤Grade 1 or Grade 2/3 that in the view of the Investigator is adequately managed and the drug is otherwise tolerated. The maximum dose is 17.5 mg/m^2 (If this dose is reached, the last dose increment would be 1.5 mg/m^2.).
Dose de-escalation should occur in 2 mg/m^2 decrements if toxicity is observed to as low as 8 mg/m^2/cycle (See Section 6.7). If the dose is reduced from 17.5 mg/m^2, the initial dose decrement would be 1.5 mg/m^2 (to 16 mg/m^2).
^Or tolerated lower dose.
Treatment should continue during the study until RECIST disease progression or intolerable toxicity. See Section 6.7 and Section 6.9 for treatment modifications for dinutuximab and irinotecan, respectively.

Part 2 can be found on the following page.

Part 2:

	Cycles†																								
	1					2					3					4					5					≥6				
	Days (Day 1 +/- 2 day window)																												
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Groups A & B **Irinotecan** Treatment	X					X					X					X					X					X				
Dose mg/m^2	350					350					350					350					350					350				
Group B only# **Dinutuximab** *Pretreatment:*	*1 hour (±15 mins) wait time between end of irinotecan infusion and start of dinutuximab infusion for 1st infusion*																												
IV hydration	X					X					X					X					X					X				
Antihistamines	X					X					X					X					X					X				
Antipyretics	X					X					X					X					X					X				
Dinutuximab Treatment	X					X					X					X					X					X				
Dose mg/m^2	16					17.5*^					17.5*^					17.5*^					17.5*^					17.5*^				
Group C only **Topotecan** Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose mg/m^2	<-------1.5------->					<-------1.5------->					<-------1.5------->					<-------1.5------->					<-------1.5------->					<-------1.5------->				

†Each cycle is 21 days.
#After the first infusion, the 1-hour wait time between the end of irinotecan infusion and the start of dinutuximab is no longer required.
*Dose escalation should occur if maximal pain with prior dose is ≤Grade 1 or Grade 2/3 that in the view of the Investigator is adequately managed, and the drug is otherwise tolerated. The maximum dose is 17.5 mg/m^2 (If this dose is reached, the dose increment would be 1.5 mg/m^2.).
^Or tolerated lower dose.
Dose de-escalation should occur in 2 mg/m^2 decrements if toxicity is observed to as low as 8 mg/m^2/cycle (See Section 6.7). The dose decrement from 17.5 mg/m^2 is 1.5 mg/m^2 (to 16 mg/m^2).
Treatment should continue during the study until RECIST disease progression or intolerable toxicity. Dose modifications can be found in the following sections: dinutuximab (Section 6.7), irinotecan (Section 6.9), and topotecan (Section 6.10).

6.5. Duration of Therapy

It is intended that subjects will be treated until radiologically determined progressive disease per RECIST v1.1 or unacceptable study drug-related toxicity. However, a subject may discontinue study treatment at any other time. Reasons for discontinuing study treatment include, but are not limited to the following:

- Documented disease progression (radiographically) per RECIST.
- Clinical deterioration sufficient to prevent further radiological assessment.
- Extraordinary medical circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, study treatment should be discontinued.
- Pregnancy.
- A study drug related adverse event, prior to disease progression, which in the opinion of the Investigator precludes further treatment with all study drugs.
- Subject requests to stop further treatment or withdraws consent for the study.
- Development of an intercurrent medical condition or need for concomitant therapy that precludes further treatment with all study drugs.

Discontinuing study treatment is not the same as withdrawing consent to be in the study. Subjects discontinuing study treatment must continue with all ongoing protocol requirements, as detailed in Section 8, unless they have withdrawn consent for further follow-up.

6.6. Treatment Delays and Termination due to Toxicity (Irinotecan + Dinutuximab)

For subjects randomized to Group B, irinotecan and dinutuximab are intended to be given on the same day of each cycle (Day 1 ±2 days). A cycle for the combination may be delayed up to 7 days due to unresolved toxicity of one drug or the other. In this case, the cycle for irinotecan and dinutuximab would be shifted by up to 7 days. If there is unresolved toxicity for irinotecan resulting in a treatment delay of >7 days, subjects should continue with dinutuximab alone for that cycle and irinotecan should be omitted until the next cycle. Conversely, if there is unresolved toxicity for dinutuximab resulting in a treatment delay of >7 days, subjects should

continue with irinotecan alone for that cycle and dinutuximab should be omitted until the next cycle. Treatment delays of >7 days should be discussed with the Medical Monitor.

Subjects should continue with dinutuximab alone on schedule if irinotecan is terminated for toxicity. If dinutuximab is terminated for toxicity, irinotecan should continue on schedule. In some cases, coincident toxicities may occur resulting in delay or termination of both dinutuximab and irinotecan.

6.7. Treatment Modifications for Dinutuximab

Adverse reactions to dinutuximab should be managed by infusion interruptions, infusion rate reductions, dose reductions, or permanent discontinuation of dinutuximab.

6.7.1. Dose Reduction Levels for Dinutuximab

	Dinutuximab Dose Levels		
	0	-1	-2
Dinutuximab (mg/m^2)	16*	14	12

*Part 2 starting dose
Subsequent doses may be adjusted in 2 mg/m^2 decrements per cycle depending upon individual subject tolerance to as low as 8 mg/m^2/day (Part 1 and Part 2).

6.7.2. Pain

In general, pain should be managed initially through conservative measures (brief interruption in infusion, decrease in the infusion rate and/or use of NSAIDs or other non-opioid pain medications). Opioid analgesics may also be given. Dose reductions should be undertaken in subsequent cycles (as required - see below), after these measures have been implemented.

Pain Severity (NCI CTCAE v4.03)		**Dinutuximab Treatment Modification**
Grade 1	Mild pain	Interrupt infusion for a maximum of 30 minutes, or decrease the infusion rate, and/or administer NSAIDs or other non-opiate pain medication, as needed. The dose of dinutuximab should be increased in subsequent cycle(s) per Table 5.
Grade 2	Moderate pain; limiting instrumental activities of daily living (ADL)	Interrupt infusion for a maximum of 30 minutes, or decrease the infusion rate, and/or administer NSAIDs or other non-opiate pain medication. Administer opioid analgesics (morphine sulfate or morphine equivalent such as hydrocodone, hydromorphone, oxycodone). Consider use of medications used to treat neuropathic pain (e.g., gabapentin, pregabalin, duloxetine, venlafaxine). If Grade 2 pain is adequately managed, the dose of dinutuximab should be increased in subsequent cycle(s) per Table 5. If Grade 2 pain is not adequately managed, the dose should be maintained in the next cycle and opioid analgesics should be given as premedication as allowed per institutional guidelines. If Grade 2 pain is not adequately managed in the next cycle despite maintaining the dose, opioid premedication and/or the measures noted above, the dose should be decreased by 1 dose level in subsequent cycle(s) per Table 5.
Grade 3	Severe pain; limiting self care ADL	Interrupt infusion for a maximum of 30 minutes, or decrease the infusion rate, and/or administer NSAIDs or other non-opiate pain medication. Administer opioid analgesics (morphine sulfate or morphine equivalent such as hydrocodone, hydromorphone, oxycodone). Consider use of medications used to treat neuropathic pain (e.g., gabapentin, pregabalin, duloxetine, venlafaxine). If Grade 3 pain is adequately managed, the dose of dinutuximab should be increased in subsequent cycle(s) per Table 5. If Grade 3 pain is not adequately managed, the dose should be maintained in the next cycle and opioid analgesics should be

	given as premedication as allowed per institutional guidelines. If Grade 3 pain is not adequately managed in the next cycle despite maintaining the dose, opioid premedication and/or the measures noted above, the dose should be decreased by 1 dose level in subsequent cycle(s) per Table 5. **If Grade 3 pain recurs in a subsequent cycle despite a one-time dose reduction, consideration should be given to discontinuing dinutuximab.** **Permanently discontinue dinutuximab for Grade 3 pain unresponsive to maximum supportive measures.**
See Section 6.7.4. for treatment modifications for neuropathy.	

6.7.3. Infusion-Related Reactions

Infusion Reactions Severity (NCI CTCAE v4.03)*		**Dinutuximab Treatment Modification**
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated (e.g., transient flushing or rash, drug fever <38°C)	Decrease dinutuximab infusion rate by 50% and monitor closely for any worsening.
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, opioid analgesics, IV fluids); prophylactic medications indicated for ≤24 hrs (e.g., rash, flushing, urticaria, dyspnea, drug fever ≥38°C)	Interrupt dinutuximab infusion, administer appropriate therapy (e.g., antihistamines, NSAIDs, IV fluids, steroids, and then restart the dinutuximab infusion with a decrease in the infusion rate of 50% and monitor closely for any worsening. Premedicate in all future cycles with: • Dexamethasone 20 mg PO administered approximately 12 and 6 hours before dinutuximab, • Diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to dinutuximab, and • Cimetidine 300 mg or ranitidine 50 mg IV 30 to 60 minutes before dinutuximab infusion. • If re-starting dinutuximab infusion results in grade 2 or higher toxicity, stop infusion (and record infused dose). Reduce dose of dinutuximab by 1 dose level in next cycle.
Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema, hypotension)	Immediately stop the dinutuximab infusion and disconnect infusion tubing from the subject. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, IV fluids, vasopressor agents, oxygen, etc., as medically indicated. Permanently discontinue dinutuximab. (If standard practice and risk-benefit in the judgment of the Investigator warrants continued treatment, administering dinutuximab in future cycles can be considered only if additional precautions (re. premedications and infusion rate) are followed and after consultation with and approval of the Medical Monitor.)
Grade 4	Life-threatening consequences; urgent intervention indicated	Immediately stop the dinutuximab infusion and disconnect infusion tubing from the subject.

	(e.g., event characterized by rapid onset, often within minutes, of airway obstruction [bronchospasm, stridor, hoarseness], urticaria, and/or hypotension	Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, IV fluids, vasopressor agents, oxygen, etc., as medically indicated. Permanently discontinue dinutuximab.
*Grades are per NCI CTCAE v4.03. Examples of signs and symptoms are provided in addition to aid diagnosis.		

6.7.4. Neuropathy

Peripheral sensory neuropathy

Peripheral sensory neuropathy is a disorder characterized by inflammation or degeneration of the peripheral sensory nerves.

Peripheral Neuropathy Severity (NCI CTCAE v4.03)		**Dinutuximab Treatment Modification**
Grade 1	Asymptomatic; loss of deep tendon reflexes or paresthesia	Decrease dinutuximab infusion rate by 25% and monitor closely for any worsening. Administer non-opiate pain medication, as needed. Morphine and medications to treat neuropathic pain may also be considered (see below).
Grade 2	Moderate symptoms; limiting instrumental ADL	Decrease dinutuximab infusion rate by 50% and monitor closely for any worsening. Administer opioid analgesics (morphine sulfate or morphine equivalent such as hydrocodone, hydromorphone, oxycodone). Consider use of medications used to treat neuropathic pain (e.g., gabapentin, pregabalin, duloxetine, venlafaxine). Once symptoms resolve to <Grade 2, gradually increase dinutuximab infusion rate as tolerated. Reduce dose of dinutuximab by 1 dose level in next cycle. Once maximal symptoms per cycle have resolved <Grade 2, the dose of dinutuximab should be increased in subsequent cycle(s) per Table 5.
Grade 3	Severe symptoms; limiting self care ADL	Hold dinutuximab until resolution. Administer opioid analgesics per above. Morphine drip may also be considered. Reduce dose of dinutuximab by 2 dose levels in next cycle. Once maximal symptoms per cycle have resolved <Grade 2, the dose of dinutuximab should be increased in subsequent cycle(s) per Table 5. **Permanently discontinue dinutuximab in subjects with Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks.**
Grade 4	Life-threatening consequences; urgent intervention indicated	Permanently discontinue dinutuximab immediately upon awareness.

Peripheral motor neuropathy

Peripheral motor neuropathy is a disorder characterized by inflammation or degeneration of the peripheral motor nerves.

Motor Neuropathy Severity (NCI CTCAE v4.03)		**Dinutuximab Treatment Modification**
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Hold dinutuximab until resolution (Grade 0). **Notify Medical Monitor immediately.** **Permanently discontinue dinutuximab in subjects with Grade 1 motor neuropathy that does not resolve within 2 weeks.**
Grade 2	Moderate symptoms; limiting instrumental ADL	Permanently discontinue dinutuximab immediately upon awareness.
Grade 3	Severe symptoms; limiting self care ADL; assistive device indicated	Permanently discontinue dinutuximab immediately upon awareness.
Grade 4	Life-threatening consequences; urgent intervention indicated	Permanently discontinue dinutuximab immediately upon awareness.

Transverse Myelitis

Transverse myelitis is a disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence. **Discontinue dinutuximab immediately if transverse myelitis is suspected and contact the Medical Monitor.**

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Reversible Posterior Leukoencephalopathy Syndrome (also known as Posterior Reversible Encephalopathy Syndrome, RPLS or PRES) is a disorder characterized by severe headache, hypertension, visual changes, lethargy and/or seizure.

RPLS Severity (NCI CTCAE v4.03)		**Dinutuximab Treatment Modification**
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Hold dinutuximab until resolution (Grade 0). **Notify the Medical Monitor immediately.**
Grade 2	Moderate symptoms; limiting instrumental ADL	Permanently discontinue dinutuximab immediately upon awareness. Immediately notify the Medical Monitor.
Grade 3	Severe symptoms; very abnormal imaging studies; limiting self-care ADL	Permanently discontinue dinutuximab immediately upon awareness. Immediately notify the Medical Monitor.
Grade 4	Life-threatening consequences; urgent intervention indicated	Permanently discontinue dinutuximab immediately upon awareness. Immediately notify the Medical Monitor.

6.7.5. Clinical Tumor Lysis Syndrome (TLS)

Clinical TLS is present when laboratory TLS is accompanied by an increased creatinine level and a constellation of clinical signs and symptoms including any symptoms of hypocalcemia, such as anorexia, vomiting, cramps, seizures, spasms, altered mental status, and muscle tetany and symptoms of hyperkalemia, such as weakness and paralysis.

Clinical TLS	**Dinutuximab Treatment Modification**
Onset of reaction	Hold dinutuximab until resolution (Grade 0). Institute cardiac rhythm monitoring, fluids as clinically indicated, and serial laboratory monitoring per institutional standard. Correct electrolyte abnormalities, monitor renal function and fluid balance. Administer therapeutic (rasburicase or other approved uric acid-lowering agent) and supportive care, including dialysis, as clinically indicated. **Note: There is a potential for immunogenic interaction between rasburicase and dinutuximab.**
After resolution	In next cycle, resume dinutuximab treatment at an infusion rate that is 50% of the previous rate. Gradually increase the infusion rate as tolerated.

6.7.6. Hypotension Requiring Medical Intervention

Hypotension requiring medical attention refers to symptomatic hypotension.

Symptomatic Hypotension	Dinutuximab Treatment Modification
Onset of reaction	Interrupt dinutuximab infusion. Institute clinic standard treatment.
After resolution	Resume dinutuximab infusion at 50% of the previous rate. If blood pressure remains stable, gradually increase the infusion rate as tolerated.

6.7.7. Severe Systemic Infection or Sepsis

Severe Systemic Infection	Dinutuximab Treatment Modification
Onset of reaction	Discontinue dinutuximab until resolution of infection, and then proceed with subsequent cycles of therapy.

6.7.8. Neurologic Disorders of the Eye

Neurologic disorders of the eye include dilated pupil with sluggish light reflex or other visual disturbances.

Neurologic Eye Disorders	Dinutuximab Treatment Modification
Onset of reaction	Interrupt dinutuximab infusion until resolution (Grade 0). **Notify Medical Monitor immediately if clinically significant deterioration in vision is observed. Consult with ophthalmologist to examine the subject's eyes and document retinal, optic nerve and visual testing results.**
After resolution	Reduce dinutuximab **dose** by 50%.
First recurrence or if accompanied by visual impairment	Permanently discontinue dinutuximab.

6.8. Treatment Modifications for Irinotecan and Topotecan

The following sections are general guidelines regarding dose modifications for irinotecan and topotecan based on U.S. prescribing information for these drugs. Investigators should use their best judgment in determining dose modifications per their standard clinical practice.

6.9. Treatment Modifications for Irinotecan

Adverse reactions to irinotecan should be managed by dose reductions or permanent discontinuation of irinotecan. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the subject has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.

6.9.1. Dose Reduction Levels for Irinotecan

	Irinotecan Dose Levels		
	0	-1	-2
Irinotecan (mg/m^2)	350	300	250
Subsequent doses may be adjusted as low as 200 mg/m^2 in 50 mg/m^2 decrements depending upon individual subject tolerance.			

6.9.2. Irinotecan Dose Reduction for Diarrhea

A new cycle of irinotecan should not begin until treatment-related diarrhea is fully resolved.

Diarrhea Severity (NCI CTCAE v4.03)		**Irinotecan Treatment Modification Next Cycle**
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Maintain dose level
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Maintain dose level
Grade 3	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Reduce by 1 dose level (50 mg/m^2)
Grade 4	Life-threatening consequences; urgent intervention indicated	Reduce by 1 dose level (50 mg/m^2)

6.9.3. Irinotecan Dose Reduction for Neutropenia

A new cycle of irinotecan should not begin until the granulocyte count has recovered to ≥1500/mm^3. For *neutropenic fever*, reduce dose by 1 dose level (50 mg/m^2) in subsequent cycle.

Neutrophil Count Decreased	**Irinotecan Treatment Modification**

Severity (NCI CTCAE v4.03)		**Next Cycle**
Grade 1	<LLN – 1500/mm^3	Maintain dose level
Grade 2	<1500 to 1000/mm^3	Maintain dose level
Grade 3	<1000 to 500/mm^3	Reduce by 1 dose level (50 mg/m^2)
Grade 4	<500/mm^3	Reduce by 1 dose level (50 mg/m^2)

LLN= lower limit of normal

6.9.4. Irinotecan Dose Reduction for Other Hematologic Toxicities

Dose modifications for leucopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above. A new cycle of irinotecan should not begin until the platelet count has recovered to ≥100,000/mm^3.

6.9.5. Dose Reduction for Other Nonhematologic Toxicities (Excluding Alopecia, Anorexia and Asthenia)

Other Nonhematologic toxicities	**Irinotecan Treatment Modification**
Severity (NCI CTCAE v4.03)	**Next Cycle**
Grade 1	Maintain dose level
Grade 2	Reduce by 1 dose level (50 mg/m^2)
Grade 3	Reduce by 1 dose level (50 mg/m^2)
Grade 4	Reduce by 1 dose level (50 mg/m^2)

6.10. Dose Modifications for Topotecan

Adverse reactions to topotecan should be managed by dose reductions or permanent discontinuation of topotecan.

6.10.1. Dose Reduction Levels for Topotecan

	Topotecan Dose Levels		
	0	-1	-2
Topotecan (mg/m^2)	1.5	1.25	1.0

6.10.2. Topotecan Dose Reduction for Hematologic Toxicities

Topotecan can cause severe myelosuppression and should only be administered to subjects with baseline neutrophil counts ≥1,500 cells/mm^3 and platelet counts ≥100,000 cells/mm^3. Subjects should not be treated with subsequent courses of topotecan until neutrophils recover to >1,000 cells/mm^3, platelets recover to >100,000 cells/mm^3, and hemoglobin levels recover to 9.0 g/dL (with transfusion if necessary).

Reduce dose of topotecan by 1 level if:

- Neutrophil counts of less than 500 cells/mm^3, or administer granulocyte-colony stimulating factor (G-CSF) starting no sooner than 24 hours following the last dose of topotecan.
- Platelet counts less than 25,000 cells/mm^3 during previous cycle.

6.11. Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications must be recorded on the subject's eCRF for all enrolled/randomized subjects from the start of screening to approximately 30 days following the last dose of study treatment (dinutuximab and/or chemotherapy) or initiation of new anticancer therapy, whichever occurs first.

6.11.1. Optional and Allowed Concomitant Medications

Subjects may receive antiemetics, antidiarrheal agents, and antibiotics as necessary. Subjects receiving corticosteroids for emesis prophylaxis should receive the lowest dose and for the shortest period of time according to clinical judgment. The use of growth factors and

erythropoietin stimulating agents is allowed as per American Society of Clinical Oncology/ESMO/NCCN Guidelines. Subjects may receive red blood cell (RBC) transfusions or platelet transfusions if clinically indicated in accordance with institutional guidelines. Palliative radiation for pain management is permitted with the prior approval of the Medical Monitor.

6.11.2. Excluded Concomitant Medications

The following concomitant medications are not allowed during the study:

- Strong CYP3A4 and/or UGT1A1 inhibitors including ketoconazole, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole, atazanavir, gemfibrozil, and indinavir **(Applies only to subjects receiving irinotecan)**.
- Strong CYP3A4 enzyme-inducing anticonvulsants including phenytoin, phenobarbital, carbamazepine, St. John's wort, rifampin and rifabutin **(Applies only to subjects receiving irinotecan)**.
- Granulocyte macrophage colony stimulating factor (GM-CSF). **G-CSF is permitted.**
- Marketed or investigational anticancer therapeutic or immunotherapy or radiation.
- Other investigational agents.
- Vaccination with a live vaccine. Subjects should avoid contact for up to 2 weeks with anyone who has had a live vaccine.

7. WITHDRAWAL OF SUBJECTS

A subject may withdraw, or be withdrawn, from the study at any time. The most common reasons subjects are withdrawn from the study are:

- Withdrawal of consent for further participation in the study.
- Subject is lost to follow up.
- Study termination by the Sponsor.

The reasons for study treatment discontinuation are noted in Section 6.5. If a subject wishes to discontinue study treatment, the Investigator should explain to the subject the importance of remaining on study follow-up, or failing this of allowing routine follow-up data to be used for study purposes. **It is critical that all subjects are followed for the study endpoints of OS and PFS.**

8. STUDY PROCEDURES AND ASSESSMENTS

A summary of study procedures and assessments can be found in Table 6.

8.1. Screening

Written informed consent must be obtained before any protocol-specific screening tests or procedures may be conducted. The screening period for a particular subject commences when the subject undergoes the first study-specific screening assessment. After informed consent is obtained, the following screening assessments will be performed within 21 days before the planned day of enrollment (Part 1) or randomization (Part 2) unless otherwise stated. Laboratory tests for eligibility will be performed at a central laboratory. Local hematology and chemistry laboratory results cannot be used to confirm eligibility. CT, or magnetic resonance imaging (MRI) if judged clinically appropriate, performed (as described in the protocol) prior to informed consent may be used if within 28 days prior to enrollment (Part 1) or randomization (Part 2). The method selected (CT or MRI) must be used consistently throughout the study.

General

- Demographics.
- Medical history (including prior treatment for SCLC, prior surgery, history of tobacco use and other significant medical conditions).
- Physical examination (including review of systems, height, weight, body surface area [BSA] using a standard formula), and ECOG status.
- Neurologic assessment (Investigator's assessment at baseline of whether the subject's mental status, coordination and gait, sensory function, motor function and vision [with consideration to corrective lenses as prescribed] are within the subject's normal limits.).

- Ophthalmology examination (including assessment of any vision problems and associated corrective measures, of pupils [size, shape, symmetry, response] and of any complaints regarding photophobia). The ophthalmology examination at screening is to be performed as part of the screening physical exam by the Investigator. The screening ophthalmology examination does not need to be performed by an ophthalmologist. However, if clinically significant deterioration in vision is noted during the course of the study, an ophthalmologist must be consulted, per Section 6.7.8.

- Pain assessment (any pre-existing pain including locations and severity using the numeric 0-10 pain scale [Appendix A]).

- 12-lead electrocardiogram (ECG).

- Vital signs (systolic and diastolic blood pressure, respiration, pulse, and oral temperature).

- All ongoing medications.

- SAEs (and AEs based on local regulations) starting on the day of written informed consent (SAEs, and AEs based on local regulations, will be collected for screen-failed subjects up until the time they are deemed a screen-failure for the study).

Laboratory

- Hematology (complete blood count [CBC]). CBC machine differential is acceptable when ANC is ≥1,500/mm^3. Below 1,500/mm^3, the differential must be manually counted.

- Chemistry (BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, lactate dehydrogenase [LDH], albumin, total protein, magnesium, alkaline phosphatase [ALP], AST, ALT, total bilirubin).

- Pregnancy test: Women of reproductive potential must have a negative urine or serum β-HCG pregnancy test. Women not of reproductive potential are female subjects who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).

Hematology and chemistry will be analyzed by a central laboratory to confirm eligibility. Local hematology and chemistry laboratory results cannot be used to determine eligibility. Pregnancy test samples will be analyzed locally.

Disease-Related

- Disease assessments (CT or MRI of the chest/abdomen with contrast, with careful attention to the liver and adrenal and other locations as clinically indicated).
- For subjects with a history of or medically suspected brain metastases, brain MRI (preferred) or brain CT with contrast.

8.2. Baseline

- Repeat pregnancy test: Women of reproductive potential must have a negative urine or serum β-HCG pregnancy test obtained within 7 days prior to the first dose of study treatment (dinutuximab and/or chemotherapy). Women not of reproductive potential are female subjects who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).
- Archival tissue, if available, tested for programmed cell death ligand-1 (PD-L1). Test to be performed locally if assay is available. Prior test results are acceptable.
- Blood sample for biomarker analysis.
- Blood sample to analyze circulating tumor cells (CTC) (**Part 2, selected regions only**).
- *Optional sample for biomarker analysis (future exploratory research) for subjects who consent to participate*:
    - *Archival sample of tumor tissue that was fresh-frozen to analyze gangliosides and other biomarkers if available and taken for a reason not related to this protocol.*

  If the subject consents to provide an optional tissue sample for future exploratory research, the sample will be stored at the specialty laboratory (Precision Bioservices, Inc., Frederick, Maryland) for a maximum of 15 years. If samples are not used within this 15-year period, they will be destroyed. Samples may also be destroyed within this 15-year period.

8.3. During Treatment (Cycles 1 – 6 and beyond)

The following routine assessments will be performed during treatment for all subjects except where noted.

- Physical examination (including BSA calculation) and neurologic assessment on Day 1 (within 48 hours prior to Day 1) of every cycle. The focus of the neurologic assessment during treatment is on whether there is any clinically significant deterioration in the parameters (mental status, sensory function, etc.) since the last assessment. For Cycle 1, screening physical and neurologic assessment may be used if within 7 days prior to Day 1.

- Vital signs are to be taken on Day 1 of every cycle within 1 hour (±30 minutes) prior to study drug administration. For subjects receiving dinutuximab, vital signs should be taken additionally 30 minutes (±10 minutes) into the infusion, at the end of the infusion (±30 minutes) and hourly (±30 minutes) after the infusion for a minimum of 1 hour, or longer if clinically indicated.

- Hematology on Day 1 (within 48 hours prior to Day 1) and once between Days 8-15 (to measure ANC nadir) of every cycle (results must be available prior to study treatment administration); WBC must include complete differential. As clinically indicated, an Investigator may consider additional collections during the treatment cycle.

- Chemistries on Day 1 (within 48 hours prior to Day 1) of every cycle (BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, ALP, AST, ALT, total bilirubin). Urea may be measured instead of BUN at the local laboratory.

- Serial blood samples for PK assessment during Cycle 1 at 10 time points **(Part 1 only)**:

Time points	Cycle 1	Post dose, hours (Day)								
	Pre-dose	2	6	24 (Day 2)	48 (Day 3)	72 (Day 4)	96 (Day 5)	192 (Day 8)	360 (Day 15)	528 (Day 22) before the next dose (Cycle 2 Day 1)
Windows	Anytime prior to dosing on the day of dosing	± 5 minutes		± 30 minutes				± 60 minutes		Anytime prior to the next dose on the day of the next dose

The time points for post dose samples start from the end of the infusion (e.g., 24 hours post dose = 24 hours after infusion end). Serial PK blood draws will be repeated with the first dose change (reduction or escalation). A validated assay will be used to measure concentration of dinutuximab. Details regarding sampling time points and procedures can be found in the lab manual.

- Sparse blood samples for population PK analysis during Cycle 1 at 2 time points and during Cycle 3 at 6 time points **(Part 2 Group B only)**:

Time points	Cycle 1	
	Pre-dose	Infusion end
Windows	Anytime prior to dosing on the day of dosing	Up to 10 minutes after the end of the infusion

Time points	Cycle 3		Post dose, hours (Day)			
	Pre-dose	Infusion end	24 (Day 2)	192 (Day 8)	360 (Day 15)	528 (Day 22) before the next dose (Cycle 4, Day 1)
Windows	Anytime prior to dosing on the day of dosing	Up to 10 minutes after the end of the infusion	± 30 minutes	± 60 minutes		Anytime prior to the next dose on the day of the next dose

The time points for post dose samples start from the end of the infusion (e.g., 24 hours post dose = 24 hours after infusion end). Details regarding sampling time points and procedures can be found in the lab manual.

- Blood samples for the evaluation of ADA and NAb in plasma pre-dose on Day 1 of all cycles plus Day 8 (+/- 1 day) and Day 15 (+/- 1 day) of Cycle 1 **(Part 1 and Part 2 Group B only)**. Details regarding sampling time points and procedures can be found in the lab manual.

- Blood sample for biomarker analysis.

- Blood sample on Day 1 of every cycle to analyze CTC (**Part 2, selected regions only**).

- Disease assessments (CT or MRI of the chest/abdomen with contrast, with careful attention to the liver and adrenal and other locations as clinically indicated) every 6 weeks (+/- 7-day window) from the date of enrollment (Part 1) or randomization (Part 2).*

*Note: For subjects enrolled in Part 2, the timing of disease assessments should not be altered, even in the event of a dose delay or interruption in a cycle. This is very important to prevent or minimize evaluation-time bias.

- For subjects with a history of or medically suspected brain metastases, brain MRI (preferred) or brain CT with contrast every 6 weeks (+/- 7-day window) from the date of enrollment (Part 1) or randomization Part 2) or as medically indicated.

- AEs and concomitant medications (con meds) are to be assessed every cycle (The following information is required to be documented for each AE: date of onset, date of resolution, severity [NCI-CTCAE v4.03], the Investigator's opinion of the relationship of the event to the investigational product, and treatment required, if any.).

Laboratory tests for safety during scheduled and unscheduled study visits will be performed at a central laboratory. Investigators may use local laboratory results for making real-time clinical decisions during the course of the study including managing subjects on study treatment and discontinuing study therapy due to toxicity. For AE reporting, the Investigator should report the highest NCI-CTCAE v4.03 grade if there is a difference in the reported value between contemporaneous local laboratory and central laboratory results. If the central laboratory value results in a higher grade than the local laboratory, local laboratory results may still be used for real-time clinical decision-making.

8.4. EOT/Safety Visit

The following assessments must be completed within approximately 30 days after the time the Investigator decides to discontinue all study drugs for the subject (dinutuximab and/or chemotherapy) or prior to the initiation of subsequent treatment, whichever occurs first. Any ongoing AEs/SAEs at the time of the EOT/safety visit should be followed as outlined in Section 9.2.

- ECOG performance status.

- Status of ongoing AEs and con meds.

- Hematology (including differential).

- Chemistry (BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, ALP, AST, ALT, total bilirubin).

- Blood samples for post-treatment immunogenicity (**Part 1 and Part 2 Group B only**) **IF** EOT visit occurs within the time frame for the first evaluation (4 weeks [+/- 7 days] of completing dinutuximab) (See Section 8.5).
- Blood sample for biomarker analysis.
- Blood sample to analyze CTC **(Part 2, selected regions only)**.
- Disease assessments (CT or MRI of the chest/abdomen with contrast, with careful attention to the liver and adrenal and other locations as clinically indicated) unless disease progression is previously documented during the study per RECIST.
- Brain MRI (preferred) or brain CT with contrast for subjects with prior evidence of brain metastasis (at baseline) unless disease progression is previously documented during the study per RECIST.
- Recording of planned subsequent anticancer treatment, if any.

Note: All subjects should be followed for overall survival. Subjects enrolled in Part 2 who discontinue treatment prior to the documentation of disease progression should continue to be followed on the disease assessment schedule (every 6 weeks from the date of randomization [+/- 7 days]) until disease progression is documented radiographically per the protocol. At the EOT, further follow-up should be clarified with the subject (for OS, or for disease assessments if applicable) and any such consent for ongoing follow-up must be documented in both the source records and the eCRF. Subject follow-up is critical to prevent or minimize informative censoring for assessment of OS and PFS, the study's primary endpoint and key secondary endpoint, respectively.

8.5. Immunogenicity Follow-Up (Subjects in Part 1 and Part 2 Group B)

Subjects who received dinutuximab will be followed for up to 16 weeks for immunogenicity following discontinuation of dinutuximab treatment. Blood samples will be collected 4, 8, 12 and 16 weeks (+/- 7 days) after the last dose of dinutuximab treatment. The 4-week visit may be omitted if immunogenicity assessment was performed at the EOT visit within the required time interval.

8.6. Survival Follow-Up

Monthly (+/- 7 days) assessments of survival will be performed from the date of the EOT visit. Survival follow-up will continue until the planned number of events has been reached or until the Sponsor has stopped the study for any reason. Contacts can be made in person or by phone; the subject's primary care physician may be the contact should the subject be unavailable. If a subject does not return to the clinic for follow-up visits, at least 3 documented attempts, including one via mail requiring a signature (e.g., courier, certified), should be made to contact the subject before declaring a subject is lost to follow-up. If the subject is considered lost to follow-up, the date of death may be captured from public records. All subject contact will be documented in source documents. **It is critical that all subjects are followed for OS, the study's primary endpoint.**

Table 6: Summary of Study Assessments

Assessment[i]	Screening (21 days)[ii]	Baseline (Before 1st dose)	Treatment		Disease assessments	Long-Term Follow-Up
			Cycles 1-6 & beyond[iii]	End of Treatment[iv]	Every 6 weeks[v]	
Demographics, medical history	X					
Physical exam,[vi] neurologic assessment	X[vii]		X[viii,ix]			
Ophthalmology exam[x]	X					
Pain assessment	X[xi]					
ECOG performance status	X			X		
12-lead ECG	X					
Vital signs	X		X[xii]			
AEs[xiii] and con meds	X		X	X		
Hematology[xiv]	X[xv]		X[xvi]	X		
Chemistry[xvii]	X[xviii]		X[xix]	X		
B-HCG pregnancy test	X	X[xx]				
CT or MRI chest/abdomen with contrast[xxi]	X[xxii]			X[xxiii]	X	
Brain MRI (preferred) or brain CT with contrast if history of or medically suspected brain metastases	X			X[xxiv]	X	
Blood sample for biomarker analysis		X	X	X		
Blood sample for CTC (Part 2, selected regions only)		X	X	X		
PD-L1 test results[xxv]		X				
Optional biomarker tissue sample[xxvi]		X				
PK (dinutuximab)			X[xxvii, xxviii]			
Immunogenicity (dinutuximab)			X[xxix]	X[xxx]		X[xxxi]
Recording of subsequent treatment				X		

Assessment[i]	Screening (21 days)[ii]	Baseline (Before 1st dose)	Treatment		Disease assessments	Long-Term Follow-Up
			Cycles 1-6 & beyond[iii]	End of Treatment[iv]	Every 6 weeks[v]	
Survival						X[xxxii]

[i] Written informed consent must be obtained before any protocol-specific assessments may be conducted.
[ii] Screening assessments will be performed within 21 days before the planned day of enrollment (Part 1) or randomization (Part 2) unless otherwise stated.
[iii] All assessments should be performed on Day 1 of each cycle unless otherwise noted.
[iv] Within approximately 30 days after the time the Investigator decides to discontinue all study treatment or prior to subsequent treatment, whichever is earlier. Follow-up will continue on subjects with ongoing AEs/SAEs at the EOT/safety visit (See Section 9.2).
[v] From the date of enrollment (Part 1) or randomization (Part 2) until documented disease progression per the protocol. Tumor response and progression are defined by RECIST v1.1 (Appendix C). Subjects enrolled in Part 2 who discontinue treatment before disease progression should be followed on the disease assessment schedule until RECIST disease progression is documented.
[vi] Physical examination includes review of systems, height, weight, and BSA using a standard formula.
[vii] Neurologic assessment at screening consists of the Investigator's assessment at baseline of whether the subject's mental status, coordination and gait, sensory function, motor function and vision (with consideration to corrective lenses) are within normal limits for the subject.
[viii] During treatment, neurologic assessment focuses on whether there is any clinically significant deterioration in any of the parameters since the last assessment.
[ix] Physical and neurologic examinations are to be performed on Day 1 (within 48 hours prior to Day 1) of every cycle. For Cycle 1, screening physical and neurologic assessment may be used if within 7 days of Day 1.
[x] Including assessment of any vision problems and associated corrective measures, of pupils [size, shape, symmetry, response] and of any complaints regarding photophobia. Ophthalmology exam at screening is to be performed by the Investigator as part of the screening physical exam.
[xi] Any pre-existing pain including locations and severity using the numeric 0-10 pain scale (Appendix A).
[xii] Vital signs: systolic and diastolic blood pressure, respiration, pulse, and oral temperature. Vital signs should be taken within 1 hour (±30 minutes) of study drug administration. Additionally, for subjects receiving dinutuximab, vital signs should be taken 30 minutes (±10 minutes) into the infusion, at the end of the infusion (±30 minutes) and hourly (±30 minutes) post-dinutuximab infusion for a minimum of 1 hour, or longer if clinically indicated.
[xiii] SAEs (and AEs based on local regulations) will be collected starting on the day of written informed consent (SAEs, and AEs based on local regulations, will be collected for screen-failed subjects up until the time they are deemed a screen-failure for the study). AEs will be collected for all enrolled subjects beginning with first dose of study medication. For AE reporting, the Investigator should report the highest NCI-CTCAE v4.03 grade if there is a difference in the reported value between contemporaneous local laboratory and central laboratory results. If the central laboratory value results in a higher grade than the local laboratory, local laboratory results may still be used for real-time clinical decision-making.
[xiv] CBC. CBC machine differential is acceptable when ANC is ≥1,500/mm^3. Below 1,500/mm^3, the differential must be manually counted.
[xv] Central laboratory results must be used to determine eligibility.
[xvi] Day 1 (within 48 hours prior to Day 1) and once between Days 8-15 of every cycle to measure ANC nadir. Local laboratory results may be used during the course of the study for real-time clinical decision-making.
[xvii] BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, ALP, AST, ALT, total bilirubin. Urea may be measured instead of BUN at the local laboratory.
[xviii] Central laboratory results must be used to determine eligibility.
[xix] Day 1 (within 48 hours prior to Day 1) of every cycle. Local laboratory results may be used during the course of the study for real-time clinical decision-making.
[xx] Women of reproductive potential must have a negative urine or serum β-HCG pregnancy test obtained within 7 days prior to the first dose of study treatment (dinutuximab and/or chemotherapy).
[xxi] With careful attention to the liver and adrenal and other locations as clinically indicated.

[xxii] CT or MRI performed (as described in the protocol) prior to informed consent may be used if within 28 days prior to enrollment (Part 1) or randomization (Part 2). The method selected must be used consistently throughout the study.
[xxiii] CT or MRI of chest/abdomen with contrast does not need to be performed during the EOT visit if disease progression was previously documented during the study per RECIST.
[xxiv] Brain MRI or brain CT with contrast does not need to be performed during the EOT visit for subjects with prior evidence of brain metastasis if disease progression was previously documented during the study per RECIST.
[xxv] Archival tissue, if available, tested for PD-L1. Test to be performed locally if assay is available. Prior test results are acceptable.
[xxvi] For subjects who consent, an archival sample of tumor tissue that was fresh frozen if available and taken for a reason not related to this protocol will be provided.
[xxvii] Serial blood samples for PK assessment will be collected for all subjects in Part 1 (only). Samples will be taken during Cycle 1 at 10 time points: pre-dose (anytime prior to dosing on the day of dosing), 2 hours (± 5 minutes), 6 hours (± 5 minutes), 24 hours (± 30 minutes) (Day 2), 48 hours (± 30 minutes) (Day 3), 72 hours (± 30 minutes) (Day 4), 96 hours (± 30 minutes) (Day 5), 192 hours (± 60 minutes) (Day 8), 360 hours (± 60 minutes) (Day 15), and 528 hours (Day 22) (anytime prior to the next dose on the day of the next dose (Cycle 2, Day 1). Serial PK blood draws will be repeated with initial dose change (escalation or de-escalation).
[xxviii] Sparse blood samples for population PK analysis will be collected from subjects in Part 2 Group B (only). Samples will be taken during Cycle 1 at 2 time points: pre-dose (anytime prior to dosing on the day of dosing) and infusion end (up to 10 minutes after the end of the infusion), and again during Cycle 3 at 6 time points: pre-dose (within 1 hour of dosing start), end of the infusion (up to 10 minutes after the end of the infusion), 24 hours (± 30 minutes) (Day 2), 192 hours (± 60 minutes) (Day 8), 360 hours (± 60 minutes) (Day 15), and 528 hours (Day 22) (anytime prior to the next dose on the day of the next dose, Cycle 4, Day 1).
[xxix] Blood samples for the evaluation of ADA and NAb in plasma will be collected pre-dose on Day 1 of all cycles plus Day 8 (+/- 1 day) and Day 15 (+/- 1 day) of Cycle 1 (Part 1 and Part 2 Group B only).
[xxx] Blood samples for post-treatment immunogenicity (Part 1 and Part 2 Group B only) **IF** EOT visit occurs within the time frame for the first evaluation (4 weeks [+/- 7 days] of completing dinutuximab (See Section 8.5).
[xxxi] Subjects who received dinutuximab will be followed for up to 16 weeks for immunogenicity following discontinuation of dinutuximab treatment. Blood samples will be collected 4, 8, 12 and 16 weeks (+/- 7 days) after the last dose of dinutuximab treatment. The 4-week visit may be omitted if immunogenicity assessment was performed at the EOT visit within the required time interval.
[xxxii] Assessments for survival will be performed monthly (+/- 7 days) from date of the EOT visit until the planned number of survival events has been reached or the Sponsor has stopped the study for any reason. Contacts can be made in person or by phone. The subject's primary care physician may be the contact should the subject be unavailable.

9. ADVERSE EVENT REPORTING

All AEs/SAEs that occur while the subject is participating in the study will be recorded as instructed in this protocol (Section 9.2).

9.1. Definitions

9.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the use of the medicinal product.

An AE may include:

- An intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance.
- Worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures (e.g., exacerbation of a pre-existing illness following the start of the study or an increase in the frequency or intensity of a pre-existing episodic event or condition).

Thus, no causal relationship with the study drug is implied by the use of the term "adverse event".

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); however, the condition for which the surgery is required may be an adverse event.
- Planned surgical measures permitted by the study protocol and the condition(s) leading to these measures are not adverse events.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions).

Signs and symptoms clearly associated with disease progression should not be recorded as AEs unless judged by the Investigator to be atypical or accelerated or if the Investigator considers the sign or symptom to be caused by the study drug. If there is any uncertainty regarding causality, the event should be recorded as an AE or SAE as appropriate.

9.1.2. Serious Adverse Event

An SAE is an AE which results in any of the following:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Results in a medically important event or reaction

Life-threatening in this context refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered SAEs, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

9.2. Documentation of Adverse Events

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE such as onset and cessation date and times, severity (see definitions in NCI-CTCAE v4.03), relationship to study drug, and outcome is also to be documented in the eCRF (see Appendix B for definitions). Where possible, AEs should be recorded using standard medical terminology. If several signs or symptoms are clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the eCRF page, not the individual signs and symptoms.

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final visit. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than 30 days after completion of the final visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The eCRF pages should be updated with any new or additional information as appropriate.

Fatal events that occur after 30 days from the last dose of study drug will be entered into the EDC as events for the primary endpoint analysis and do not need to be reported to UT GDS unless the Investigator believes the event to be related to study drug.

9.3. Pregnancy

If a subject becomes pregnant during participation in this clinical study, site staff must notify the Sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Notification Form and submitting via fax or e-mail to United Therapeutics (UT) Global Drug Safety (GDS) by e-mail or fax [redacted] UT GDS will follow-up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse. Infants should be followed for a minimum of 8 weeks and all findings should be reported to the Sponsor. Pregnancy becomes an AE/SAE if there is an abnormal outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring.

All study participants should be instructed to contact the Investigator immediately if they suspect they or their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

9.4. Reporting Responsibilities of the Investigator

All SAEs, regardless of expectedness or causality, must be reported to UT GDS by e-mail or fax [redacted] within 24 hours of awareness. A completed SAE Notification Form, along with any relevant hospital records and autopsy reports should be sent to UT GDS. A follow-up SAE Notification Form must be forwarded to UT GDS within 24 hours of the receipt of any new / updated information. The Investigator must also promptly notify the IRB or IEC of the SAE, including any follow-up information, in accordance with applicable national regulations and guidelines set forth by the IRB or IEC.

9.5. Safety Reports

In accordance with US Food and Drug Administration (FDA), European, and national regulations, the Sponsor will notify the US FDA, other competent authorities, and all participating Investigators of any AE that is considered to be possibly attributable to study drug and is both serious and unexpected. The Investigator must report these AEs to their IRB or EC in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

10. STATISTICAL METHODOLOGY

This section briefly describes the statistical methods to be used for the analysis of this study. The Statistical Analysis Plan (SAP) will provide more details regarding the data-handling conventions and methods to be used. The SAP will be finalized before locking the database.

10.1. General Statistical Considerations

The study will start with a cohort of approximately 10 subjects (Part 1) treated with dinutuximab (in combination with irinotecan) for at least 3 cycles at rising or decreasing doses, depending on pain and other toxicities, to select a safe dose for Part 2. Subjects in Part 1 will be followed for all efficacy/safety assessments, including OS, PFS and ORR. Data for this cohort will be summarized using descriptive statistics.

In Part 2, eligible subjects will be randomized in a 2:2:1 fashion to one of the following treatments:

Group A: Irinotecan
Group B: Dinutuximab + Irinotecan

Group C: Topotecan

Randomization will be stratified by the subject's response to prior platinum therapy (relapse-free period < 3 months or ≥ 3 months).

Although the study includes three treatment groups, the primary aim of the statistical analysis is to show that dinutuximab administered with irinotecan (Group B) is superior to irinotecan alone (Group A). All analyses regarding topotecan (Group C) are exploratory.

Treatment Comparisons and Hierarchy of Significance Tests

The primary efficacy analysis will compare Group B (Dinutuximab + Irinotecan) versus Group A (Irinotecan). Other pairwise treatment comparisons will be performed for exploratory purposes only.

Statistical testing of the primary efficacy endpoint (OS) will evaluate superiority of Group B (Dinutuximab + Irinotecan) versus Group A (Irinotecan); the test will be performed at the two-sided 5% significance. Results of secondary efficacy endpoints will be considered for potential labeling claims only if there is clear evidence of a survival benefit with the combination therapy versus irinotecan alone. A closed, hierarchical testing procedure will be used to control the overall false-positive rate at 5% (two-sided) for the primary comparison of Group B versus Group A. Secondary endpoints will be tested in the following sequence: PFS, ORR and CBR.

Hypothesis testing will proceed in the above sequence and require statistically significant superiority for the dinutuximab regimen (Group B vs. Group A, with $p \leq 0.05$) in the first step before testing is allowed at the next step. Once the null hypothesis is not rejected, testing will stop and no further claims can be based on this or subsequent efficacy endpoints. Using this procedure, no alpha-adjustment is necessary for individual tests performed in the pre-specified sequence.

Exploratory analyses will compare efficacy endpoints in Group B (Dinutuximab + Irinotecan) versus Group C (Topotecan). As above, hypothesis-testing will be performed in a fixed sequence to control the Type 1 error rate at 5% (two-sided) for this set of comparisons, beginning with OS and followed, in order, by PFS, ORR, and CBR.

10.2. Sample size and power

Twelve subjects were enrolled in Part 1. This sample size was not based on statistical power calculations. It is considered adequate to judge the safety of the combination of dinutuximab and irinotecan, two approved products with known and distinct toxicities.

Power calculations for the randomized portion of the study (Part 2) were based on the primary efficacy objective: to demonstrate significantly longer OS with combination therapy (dinutuximab + irinotecan) vs. irinotecan alone. A 2:2:1 randomization scheme was chosen to increase exposure to dinutuximab and to maximize statistical power for the primary efficacy comparison (dinutuximab combination vs. irinotecan). A total 306 deaths in these two groups will provide approximately 80% power to detect a HR of 0.725 or a 2.3 month gain in median OS (from 6 to 8.3 months); this calculation is based on a log-rank test (2-sided alpha=0.05). If at least 82 deaths occur in the topotecan group, the power will be approximately 65% to detect the same hazard ratio of 0.725, or a 2.3-month gain in median OS (6 to 8.3 months) with the combination versus topotecan alone (a secondary objective). Overall, a total of approximately 460 subjects (184 each in dinutuximab combination and single-agent irinotecan groups and 92 in the topotecan group) is expected to yield the requisite number of deaths assuming uniform enrollment over 10 months and a follow-up period of 14 months after the last patient is enrolled. The OS rate will be tracked by the DMC and, if less frequent than anticipated, additional subjects may be enrolled to maintain original power specifications for the primary efficacy comparison.

Any decision to extend enrollment will be based on the total number of deaths observed, not on the basis of the observed hazard ratio or other unblinded efficacy data. There is no plan to re-estimate the sample size in any manner that would affect the Type 1 error rate.

10.3. Endpoints

The primary efficacy endpoint is OS.

Secondary efficacy endpoints are, in order of clinical importance: PFS, ORR, and CBR.

Safety will be evaluated based on the following:

- Adverse events
- Physical exam

- Concomitant medication usage
- Vital signs
- Clinical laboratory evaluations

10.4. Analysis populations

The following analysis sets will be used in the study:

- **Safety Analysis Set:** All subjects who receive at least one dose of any study medication (even a partial dose), grouped by actual treatment received. The Safety population will be used to evaluate safety and treatment compliance/administration.
- **Intent to Treat (ITT) Analysis Set:** All subjects randomized in Part 2 of the study, as assigned to treatment. The ITT population will serve as the primary population for evaluating all efficacy endpoints and subject characteristics. Sensitivity analyses will use populations that may exclude some members of the ITT population (e.g., those who received no study medication or those who had major protocol violations).
- **Pharmacokinetic Analysis Set:** All subjects with at least one post-dose dinutuximab concentration measurement.
- **Pharmacodynamic Biomarker Analysis Set:** All subjects who receive the first dose of dinutuximab and have at least one evaluable post-dose sample.

Data for Part 1 of this study will consist primarily of data listings and summary data displays. All efficacy analyses will be based on the ITT set. Demographic and other baseline characteristic information will be summarized for the Safety and ITT Analysis Sets. Unless noted otherwise, safety data will be summarized separately for Part 1 and Part 2.

10.5. Subject disposition

Enrollment will be tabulated by investigator and overall for each treatment group. The disposition of all randomized subjects will be summarized according their status at the time of analysis, including the number of subjects who discontinue study treatment prematurely or withdraw from the study completely. The summary will include reasons for discontinuing study treatment or withdrawing from the study as recorded on the eCRF. Additionally, tables or data listings will identify any subjects who were randomized into the study but did not meet all of the inclusion

criteria, met any exclusion criterion, or experienced a major protocol violation (as defined in the statistical analysis plan) during the study.

10.6. Demographic and Baseline Characteristics

The following baseline data will be used to describe the study population:

- Subject demographics
- Medical/surgical history
- Baseline disease characteristics
- Prior cancer therapy

Baseline measurements are defined as the last measurement collected prior to randomization. Descriptive statistics will be used to summarize subject demographics (including age, race, sex, ethnicity, smoking status, height, weight, and body surface area) and baseline disease characteristics (e.g., time since initial diagnosis, performance status, extent of disease, number of prior cancer treatment regimens, best response to prior therapy) for each treatment group. These summary tables will be provided for the ITT and Safety populations. The 3 treatment groups will be compared using chi-square tests for categorical data and analysis of variance (ANOVA) for continuous data. Any significant imbalances detected among the treatment groups will be considered in the analysis.

10.7. Prior and Concomitant Medications (Non-Cancer-Related)

The WHO Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior medications will be defined as medications taken within 30 days prior to the screening visit that were stopped before the first dose of study medication. Concomitant medications will be defined as any medication taken during the study between the date of the first dose of study medication and the date of the EOT visit.

By-subject data listings will be presented for prior medications and concomitant medications. In addition, concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classes and preferred term (PT) using frequency counts and percentages by treatment group. For summaries of concomitant medications, subjects who take the same medication (in terms of PT) more than once will be counted only once for that medication.

10.8. Treatment Exposure

Extent of exposure for each subject will be calculated as the number of days from the date of the first dose of study medication to the date of the last dose taken, inclusive. Extent of exposure, total number of cycles initiated, and total number of doses administered will be summarized for each treatment group using descriptive statistics (n, mean, median, SD, minimum, and maximum) based on the Safety Analysis Set.

For each treatment administered, infusion start and stop times, the volume infused, and reasons for any dose reductions or interruptions will be listed for each subject. The number of subjects requiring dose reductions or interruptions will be summarized descriptively by treatment group. Subjects who permanently discontinue study treatment will be summarized descriptively by treatment group and reason for discontinuation as recorded in the eCRFs.

10.9. Efficacy Analysis

10.9.1. OS

OS will be derived as: (date of death – date of randomization) + 1. Subjects who are alive or permanently lost to follow-up at the cut-off date for the analysis will be censored at the last date the subject was known to be alive.

The primary analysis of OS will be performed using a stratified log-rank test (two-sided, alpha=0.05) to evaluate the difference between survival curves for the dinutuximab combination group versus the irinotecan group (primary comparison). Stratification will be based on the same factor used for randomization (relapse-free period during prior platinum treatment < 3 months vs. ≥ 3 months). Similarly, the stratified log-rank test will be used to compare OS for the dinutuximab combination group versus the topotecan group (exploratory comparison).

Median OS in each treatment group and the corresponding 2-sided 95% confidence interval (CI) will be estimated using the Kaplan-Meier method. Kaplan-Meier estimates of OS distributions will be plotted over time for each treatment group. The hazard ratio and its 95% CIs will be used to summarize the difference in OS distributions.

Sensitivity analyses for the OS endpoint will include an analysis of the subjects in the ITT group who were fully protocol compliant and received at least 80% of the assigned dose of each study

drug. Alternative censoring rules will also be considered to evaluate the robustness of findings to assumptions about dates of death in subjects lost to follow-up.

Cox proportional hazards model will be used to explore the potential impact of stratification factors and other baseline covariates on the primary OS endpoint. The potential influence of the following factors will be examined: age, gender, ethnicity, geographic region of enrolling site, ECOG status, duration of prior response to platinum, ganglioside and PD-L1 expression, and years since diagnosis. Candidate covariates for the multivariate model will be selected using a backward selection process and only variables significant at a 10% level will be considered for the final multivariate model.

10.9.2. PFS

PFS will be defined as the time from the date of randomization to the date of first documentation of tumor progression or death from any cause, whichever occurs first. Tumor response assessments will be performed using RECIST version 1.1 (Appendix C).

PFS will be evaluated using the stratified log-rank test, as described for OS, with specific conventions for censoring. PFS data will be censored on the date of the last tumor assessment documenting absence of PD for subjects who 1) are given anti-tumor treatment other than the study treatment prior to observing objective tumor progression; 2) are removed from the study prior to documentation of RECIST confirmed tumor progression; 3) are ongoing and do not have objective tumor progression at the time of the analysis.

Subjects with no post-baseline tumor assessments will be censored on the date of randomization. Death or disease progression that occurs after more than one missed visit will be censored on the day following the date of the last tumor assessment.

10.9.3. CBR

The CBR is defined as the proportion of subjects with either a CR or PR, or SD, relative to the number of subjects in the treatment group. Subjects missing post-baseline results will be considered non-responders.

10.9.4. Best Overall Response (BOR)

The BOR is the best response recorded from the start of study treatment until the end of tumor follow-up prior to the start of any post treatment cancer therapy. The number and percentage of subjects in each BOR category (i.e., CR, PR, SD, PD, and unevaluable) will be summarized by treatment group.

10.9.5. ORR

ORR is the percentage of subjects with BOR of either CR or PR. The rates will be presented along with two-sided 95% exact confidence intervals. The 95% CIs will be derived using the Clopper-Pearson method.

10.9.6. Other efficacy outcomes:

The study analysis will also compare treatment groups based on the following additional efficacy outcomes, with tumor response defined by RECIST criteria (version 1.1):

- Time to Response (TTR), defined as the time interval between the date of randomization and the date of first documented CR or PR.
- Duration of response (DOR), defined as the time interval between the date of first PR or CR and the subsequent first date of documented disease progression, as determined by radiological assessment using RECIST criteria (version 1.1).

Binary endpoints (ORR and CBR) will be analyzed using stratified Cochran-Mantel-Haenszel chi-square tests, with two-tailed alpha=0.05. Rates will be presented for each treatment group along with corresponding 95% confidence intervals. Subjects with no post-baseline tumor assessments or who die, experience PD, drop out, or receive anti-tumor therapy other than study treatment prior to reaching the endpoint will be considered non-responders. Response will be defined by RECIST criteria (version 1.1) as evaluated by radiological assessment.

For duration of response, subjects who do not experience disease progression, who do not die, or who are lost to follow-up will be censored on the last date of radiological tumor assessment. Duration of ORR for subjects who achieve a PR and then a CR will be calculated starting from the date of the PR. Duration of response will be derived as (earliest date of progression or death)

– (date of first documented objective response) + 1. Duration of response will be summarized descriptively for each treatment group using Kaplan-Meier methods, as appropriate.

10.10. Safety Analyses

Safety data, including AEs, SAEs, vital signs, clinical laboratory evaluations, and treatment discontinuation due to toxicity, will be summarized descriptively. Univariate descriptive statistics, including mean, standard deviation, median, and range will be presented for continuous variables. Frequency tables will be used to present categorical data. All summaries will be prepared for the Safety Analysis Set. For each safety parameter, the last assessment made before the first dose of study treatment will be used as baseline for all analyses of that safety parameter.

10.10.1.Toxicities - Part 1

Toxicities reported during Part 1 (intrasubject dose escalation) will be listed for individual subjects and summarized by dinutuximab dose at time of onset. Pain severity scores and detailed pain medication log will also be listed by dinutuximab dose, cycle, and time since start of infusion and will be submitted with the Clinical Study Report.

10.10.2.Adverse Events

AEs will be coded using the current version of the Medical Dictionary for Regulatory Terms (MedDRA). TEAEs will be grouped and tabulated by the MedDRA System Organ Class (SOC) and Preferred Term (PT). An AE that starts or increases in severity after the first dose of study medication will be considered a TEAE. Severity of the AEs will be graded according to the NCI CTCAE Version 4.03. TEAEs will be summarized by treatment group, severity, and relationship to study drug. The number and percentage of subjects experiencing at least one TEAE will be displayed by SOC and PT in each treatment group for the Safety Analysis Set.

Additional summary tables will be generated for grade 3 or higher TEAEs, TEAEs considered related to study medication (possibly + probably + related), TEAEs by severity and relationship, deaths, SAEs, and TEAES leading to treatment discontinuation.

A by-subject AE data listing will present each AE verbatim term, SOC, PT, onset date/day relative to start of study treatment, severity, outcome, and relationship to study treatment. Separate listings will be generated for deaths, SAEs, and AEs leading to treatment

discontinuation. The listing of deaths will include the date and cause of death, number of days from randomization, and number of days from last dose of study treatment.

10.10.3.Concomitant Medications (Cancer-Related)

Pain medications and other treatments administered to prevent or alleviate pain and infusion reactions (including drugs initiated during the infusion period) will be recorded in the eCRF and summarized separately for each treatment group. The number and percentage of subjects in each treatment group requiring analgesics and other medications for infusion-related adverse reactions will be summarized by ATC code. All concomitant medications, including name of drug, indication, dose, frequency, mode of administration, and start/stop day relative to start of treatment, will be listed by subject.

10.10.4.Clinical Laboratory Parameters

Hematology and blood chemistry data will be graded according to NCI CTCAE v4.03. The frequencies of the worst severity grade observed will be displayed for each parameter. Laboratory data will also be summarized descriptively based on observed values at each scheduled visit and the change from baseline values at each post-baseline visit. Baseline is defined as the last evaluation prior to the first dose of study drug. In addition, the maximum and minimum values during treatment will be presented. Shift tables from baseline to the worst post-baseline values will be provided for laboratory parameters that have NCI-CTCAE v4.03 toxicity grades. Both scheduled and unscheduled post-baseline values during the treatment period will be considered. Additionally, the number and percentage of subjects in each treatment group experiencing at least one Grade 3 or 4 event will be tabulated for each NCI CTCAE gradable laboratory test. All clinical laboratory data will be listed by subject and will be structured to permit review of the data over time relative to the start of treatment. Values outside the normal ranges will be flagged and toxicity grades will be displayed for relevant parameters.

10.10.5.Vital Signs

Vital sign measurements will be summarized at each infusion, by treatment, using descriptive statistics (mean, standard deviation, median, minimum, and maximum); change from baseline values will be presented for each time point for the Safety Analysis Set. A by-subject data listing of all vital sign data will be generated.

10.10.6.Physical Examinations

Information on physical examinations will be listed by subject. Clinically significant post-baseline physical examination findings will be reported as AEs.

10.11. Interim Data Monitoring

An independent DMC will review accumulating safety data at scheduled intervals during Part 2 of the study, with attention focused on the percentage of subjects with SAEs, AEs of particular concern (see Section 12.8), Grade 3 or 4 toxicities, and any Grade 5 toxicity considered at least possibly related to study treatment. Excess risk will be determined according to the lower 97.5% exact lower confidence bound on the difference between incidence rates for Group B (dinutuximab + irinotecan) minus Group A (irinotecan alone); a lower bound >0% will be flagged as a possible reason to stop the trial. Incidence calculations will depend on the respective numerators and denominators at the time of each interim look. Wilson scores method will be used to calculate confidence limits.

In addition to safety monitoring, the DMC will review risk-benefit based on investigator-assessed tumor response rates and consider stopping the study early if trends are unfavorable. A short-term endpoint, ORR, will be used for futility assessment because it is an objective measure of anti-tumor activity and a potential early marker of efficacy for dinutuximab.

Futility will be evaluated when tumor assessments are available for a sufficient number of subjects in Groups A and B (corresponding to the second and third pre-specified DMC safety reviews as outlined in Section 12.8). Futility will be based on interim ORR values and the resulting conditional power (CP). Based on historical data for irinotecan (ORR=20%), the final sample size provides 80% power to detect an odds ratio of 2.0 for the group proportions, using a chi-square test at the 5% significance level. This hypothesized treatment effect sets the target for the final test statistic (the “alternative” hypothesis) to evaluate the trajectory of the interim test statistic. The DMC will use CP values to judge the likelihood that the completed trial will demonstrate significantly higher ORR in Group B (dinutuximab + irinotecan) versus Group A (irinotecan alone).

The methodology for conditional power estimation is described in Proschan, Lan and Wittes (2006).[65] CP is the conditional probability of rejecting the null hypothesis at the end of the study, conditional on the interim findings. It will be calculated under 2 different assumptions:

- the current trend continues
- the hypothesized treatment effect (odds ratio of 2.0) will be observed.

The CP value under each assumption will be considered together with safety data and any survival trends as a basis for the DMC's recommendation to continue or stop study enrollment. If CP is less than 20% under either assumption, the DMC may recommend trial closure. The DMC charter will provide detailed methodology and guidelines for early recommendations.

No formal interim analysis of OS is planned. However, the number and causes of death in each treatment group will be reviewed by the DMC from a safety perspective. Mortality rates will also be assessed using confidence bounds as described above. A lower limit >0% would be grounds for stopping the study due to elevated mortality risk associated with dinutuximab.

The planned approach to interim data monitoring will not impact the Type I error rate for the primary efficacy analysis because there is no possibility of stopping for efficacy. Any decision to stop the study would be based on safety issues or futility (the absence of an efficacy signal for tumor response), not a positive effect on survival.

10.12. Pharmacokinetic Analysis

Individual plasma concentrations of dinutuximab at each sampling time point will be presented in listings. Post dose time points start from the end of the infusion. Descriptive summary statistics of plasma concentrations including means, geometric means, ranges, standard deviations, and coefficient of variation will be presented.

PK parameters will be derived using non-compartmental analysis with the software program Phoenix® WinNonlin® (version 15.3 or higher). Actual sampling times will be used to calculate PK parameters in this study. The plasma PK parameters will include the following: area under the concentration versus time curve (AUC), maximum concentration (C_{max}), minimum serum concentration (C_{min}), T_{max}, half-life ($t_{1/2}$), volume of distribution (V_d), clearance (CL).

Individual plasma concentrations at each sampling time point for dinutuximab will be presented in listings. Descriptive summary statistics of plasma concentrations including means, geometric means, ranges, standard deviations, and coefficient of variation will be presented. Individual and mean concentrations versus time will be plotted on linear and semi-logarithmic scales. Dose proportionality will be assessed as appropriate.

The dinutuximab PK profile will be further characterized by nonlinear mixed-effects modeling with NONMEM® version 7.2 (ICON Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation method with interaction (FOCE-I). One, two, and three-compartment models with zero-order infusion and first-order elimination will be explored during the structural model development. Models will be evaluated based on the likelihood objective function value (OFV) provided by NONMEM, graphical evaluation, and precision of the parameter estimates (relative standard error).

The population PK model will assess covariate effects on dinutuximab concentrations. A two-step approach will be used for covariate identification. In the first step, covariates will be screened on a univariate basis. Only covariates that show a significant ($p < 0.05$) effect on the estimated PK parameters and have a meaningful clinical explanation will be carried through to the second step. The second step will use a stepwise, backward elimination process, with $p < 0.05$ to retain each covariate in the final model.

Potential covariates will include patient demographics (sex, age, baseline body weight, race), baseline laboratory measurements (liver and kidney function and hematology parameters), level of ganglioside expression, and immunogenicity variables (presence of ADA and NAb).

The final population PK model will yield individual exposure variables (C_{max}, AUC) for use in conducting exposure-response analyses. Multiple logistic regression will be used to assess exposure-response relationships between dinutuximab PK parameters, efficacy (tumor response), and safety (NCI-CTCAE v4.03 grade ≥3 AEs). The effects of dinutuximab exposure levels on PFS and OS will be explored using Cox proportional hazards models and Kaplan-Meier plots.

Further details of the population PK and exposure-response analysis, including specific data-handling and model-fitting procedures, will be addressed in a separate analysis plan. Methods will be performed in compliance with relevant FDA guidance documents: Population Pharmacokinetics (1999) and Exposure-Response Relationships-Study Design, Data Analysis, and Regulatory Applications (2003).

10.13. Pharmacodynamic Analyses

Pharmacodynamic data will be summarized using descriptive statistics. Change from baseline values of PD measurements may be used as PD markers to explore PK/PD, PD-efficacy, and PD-safety relationships, as appropriate.

A PK/PD statistical plan will be developed to describe analytic models and procedures to be used for exploratory PD analysis.

10.14. Analysis of Immunogenicity Data

The number and percentage of subjects with a test in the ADA confirmatory assay or neutralizing antibody assay will be presented at each visit and overall for subjects exposed to dinutuximab. Titers will be reported if applicable. Additionally, a summary of subjects who experience an infusion reaction and have a positive ADA test in the ADA confirmatory and neutralizing antibody assays (i.e., any dose of dinutuximab), will be presented. All immunogenicity data will be listed by subject. Immunogenicity may be reported for ADA positive status (such as persistent positive, neutralizing positive, only last sample positive, baseline positive and other positive) and ADA negative status, relative to baseline. The relationship between PK and positive ADA test results and AEs will be explored as appropriate.

Methods to explore the effects of immunogenicity on safety, efficacy, PK, and biomarkers will be provided in the PK/PD statistical plan.

10.15. Procedures for Missing, Unused and Spurious Data

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

10.16. Rules for Excluding Subjects from Analysis

All dosed subjects will be included in the safety analyses unless otherwise specified. The Sponsor will determine whether any subjects or any individual values belonging to a subject will be excluded from any efficacy evaluations should any relevant protocol violation be considered to have a negative impact on the scientific integrity and interpretation of the study results. The reason(s) for any exclusion will be described in the report.

10.17. Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

11. OBLIGATIONS OF PRINCIPAL INVESTIGATOR

The Investigator will conduct the study in accordance with Title 21 of the Code of Federal Regulations §§ 50, 56, and 312, the ICH E6 Guideline, and any applicable regulatory requirements. To ensure compliance, the Investigator agrees, by written consent to the protocol, to fully cooperate with compliance checks by allowing access to all documentation by authorized individuals. See Appendix D for listing of Investigator responsibilities.

12. STUDY ADMINISTRATION

12.1. Regulatory and Ethical Considerations

12.1.1. Regulatory Authority Approval

The Sponsor of the study will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

12.1.2. Ethical Conduct of the Study

This study will be conducted in accordance with GCP, ICH guidelines as well as all applicable regulatory requirements. The Investigator is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential study subjects are reviewed and approved by the appropriate IRB/IEC prior to the enrollment of any subjects.

12.1.3. Informed Consent

Informed consent will be obtained before the subject can participate in the study and before any study specific procedures are conducted. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

12.1.4. Investigator Reporting Requirements to the IRB

The Investigator is responsible for reporting SAEs to the IRB, in accordance with all applicable regulations. Furthermore, the Investigator may be required to provide safety updates on the conduct of the study at his or her site and notification of study closure to the IRB (when applicable).

12.1.5. Protocol Amendments and Study Termination

All protocol amendments must receive IRB/IEC approval before implementation, except where necessary to eliminate an immediate hazard to subjects. The Investigator or designee must send a copy of the approval letter from the IRB/IEC, along with the revised ICF, to Sponsor or designee. Both Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Investigator or designee should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Sponsor or designee.

12.2. Study Monitoring

The study will be monitored in accordance with GCP and ICH guidelines. Study monitors will contact the site prior to enrollment to review the protocol and study procedures with the site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on such considerations as enrollment rate, completion of data, numbers of reported SAEs, and subject retention rate. The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

Upon completion of the study, the monitor will conduct a final visit to account for and return any remaining study drug, address any final paperwork and to confirm all final data.

12.3. Archival of Records

Following closure of the study, the Investigator must maintain all site study records in a safe and secure location for at least the minimum retention time as dictated by institutional requirements or local laws or regulations.

12.4. Publications

The Sponsor recognizes the importance of communicating medical study data and therefore encourages publication of study results in scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between Sponsor and the institution of the Investigator.

12.5. Financial Disclosure

Prior to beginning the study, the Investigator at each site must provide to Sponsor or designee, a fully executed and signed US FDA Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators and research coordinators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of subjects in this study.

12.6. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, an independent quality assurance audit may be arranged. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and the institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

Additionally, metrics will be established around critical protocol requirements (i.e., subjects meeting eligibility criteria; proper scheduling and conduct of tumor assessments; subject retention for survival and disease follow-up) and timeliness of data entry. Adherence to these metrics will be reviewed throughout the course of the study.

12.7. Safety Review Committee

An SRC will be established whose role is to closely monitor safety during Part 1 of the study. After the first 10 subjects complete three cycles (or sooner if recommended by the SRC) of dinutuximab and irinotecan treatment, the SRC will perform a safety review of these treated subjects and make recommendations to the Sponsor to move to Part 2 of the study based on parameters outlined in the SRC Charter. The SRC will evaluate all available safety data including but not limited to AEs, clinical assessment changes in physical and neurologic examinations, pain score assessments, vital signs, and laboratory parameters as well as available PK data. A summary of the preliminary safety data from Part 1 will be available after approximately 10 subjects have completed three cycles of therapy. These safety data will be submitted to regulatory authorities or other bodies, as required, prior to commencing Part 2 of the study.

12.8. Independent Data Monitoring Committee

An independent DMC will be established to ensure safe and ethical conduct of the study. The DMC will operate independently of the Sponsor and clinical investigators. A Charter based on the FDA guideline will guide the operation of the DMC. The Charter will indicate the safety and efficacy parameters that the DMC wishes to review. The DMC will have access to unblinded data for ongoing safety review and for the futility analysis.

DMC members will be provided summary tables of safety data (i.e., AE and SAE data) with a focus on AEs of particular concern for dinutuximab:

- Severe non-hematologic toxicities including allergic reactions (anaphylaxis),
- Severe neuropathic pain unresponsive to treatment,
- Prolonged motor weakness > 2 wks duration,
- Acute grade 4 vascular leak syndrome, and
- Grade 3 visual toxicity.

Because many types of AEs cannot be anticipated prior to a large-scale study, the DMC will be provided with interim summaries by treatment group of AEs observed, not limited to those specified in advance. The DMC will review safety and efficacy data at predefined intervals. The first review will occur after 15% of subjects randomized to Group B (dinutuximab + irinotecan) and Group A (irinotecan alone) (approximately 30/group) have completed at least 1 cycle of treatment. Subsequent reviews will occur when 25% (approximately 50/group), 50% (approximately 90/group) and 75% (approximately 140/group) of subjects randomized to Group B and Group A have completed at least 1 cycle of treatment. There may be a need for extra meetings when there is concern about potential emerging safety problems, or when important new information external to the trial arises.

The DMC will be provided with a comparison of AE rates in each treatment group. Concerns about the extent and type of AEs observed may lead to early termination of the trial when the DMC judges that the potential benefits of the intervention are unlikely to outweigh the risks. In other cases, the DMC may recommend measures short of termination that might reduce the risk of AEs. Statistical considerations for early stopping when the data are trending in the direction of harm can be found in Section 10.11.

The primary goal of the DMC will be to ensure that the study is being performed without any major safety concerns, with a reasonable balance between risk and benefit. The DMC will make a recommendation, as defined by the Charter, to continue the study as designed, terminate the study, continue the study with major or minor modifications, or temporarily suspend enrollment until some uncertainty is resolved.

13. CONFIDENTIALITY

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician. The Investigator/Institution will permit direct access to source data and documents by Sponsor, its designee, the FDA, and other applicable regulatory authorities. The access may consist of study-related monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

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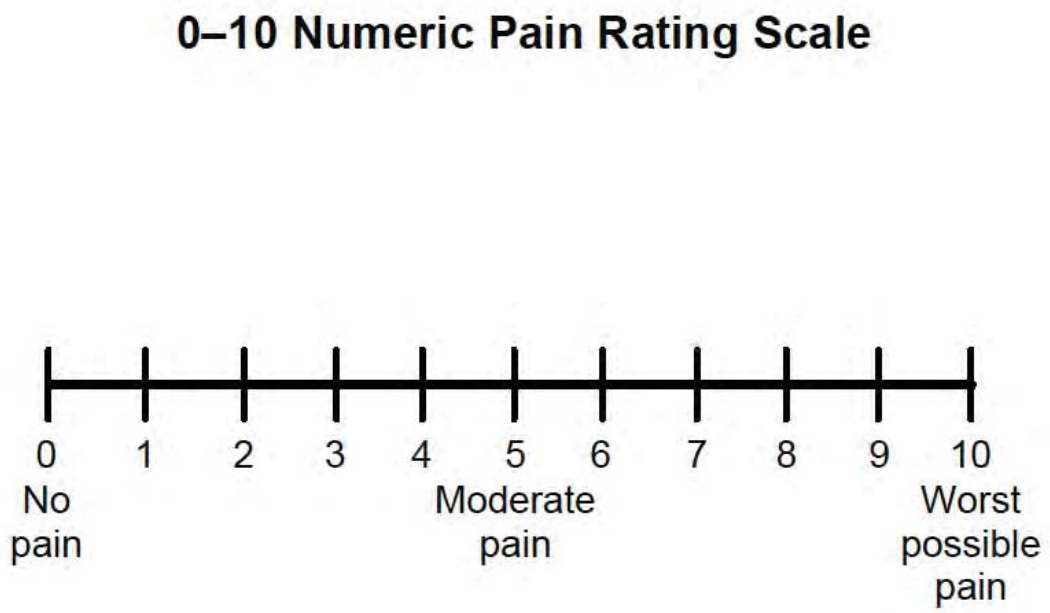
APPENDIX A: 0-10 NUMERIC PAIN RATING SCALE



The Pain Rating Scale is adapted from McCaffery M, Pasero C. Pain: Clinical Manual, 2nd ed., 1999: p. 67, Mosby, Inc.

APPENDIX B: GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

The Investigator or a designated member of his/her staff will probe each subject for any AEs that may have occurred. The Investigator should always ask the same question when conducting the verbal probe in order to ensure uniformity between subjects. The Investigator should ask:

"How are you doing (feeling)?"

Based on the subject's response to this question, the Investigator should ask additional questions relevant to the specific complaint such as:

"How severe is/was the symptom?"

"How often did the symptom occur?"

"How long did the symptom last?"

It is the Investigator's responsibility to review the results of all diagnostic and laboratory tests as they become available and ascertain if there is a clinically significant change from Baseline. If the results are determined to be a clinically significant change from Baseline, this should be reported as an AE. The Investigator may repeat the diagnostic procedure or laboratory test or request additional tests to verify the results of the original tests. When possible, a diagnosis associated with the abnormality should be used as the reported AE.

Using provided definitions, the Investigator will then:

(1) rate the intensity and seriousness of the AE, (2) estimate the causality of the AE to study drug, and (3) note actions taken to counteract the AE.

Definitions of Seriousness, Causality, Action Taken, and Outcome

Adverse Event Grade Assessment

The investigator will grade the severity of AEs experienced by the subjects according to the criteria set forth in the Nation Cancer Institute's Common Toxicity Criteria for Adverse Events Version 4.03. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity of, and to analyze and interpret, all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4 = Life-threatening consequences; urgent intervention indicate.

Grade 5 = Death related to AE

SERIOUSNESS

A serious AE is one that represents an actual or potential significant hazard. This includes, but is not limited to, an event that is fatal, life-threatening, permanently or severely disabling, requires or prolongs inpatient hospitalization*, is a congenital abnormality (offspring of subject) or is medically significant (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

*Hospitalizations that would not be considered SAEs include those for:

- Routine treatment or monitoring of the study indication not associated with any deterioration in condition (e.g., hospitalization for a routine RHC).
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition (e.g., pre-planned operation which does not lead to further complications etc.).
- Treatment of an emergency, in an outpatient setting for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

CAUSALITY

An estimate of causality between a specified AE and the study drug is made by the Investigator. Several factors should be considered when determining causality. These factors include temporal relationship and response to withdrawal or reintroduction of the study drug.

Definitions of the causality categories are as follows:

- NOT RELATED – There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, or concurrent disease and the SAE, or any of the following:
    - An event that precedes the first administration of study drug
    - An event for which the cause is clearly related to an external event
    - Temporal relationship to study drug is atypical
    - Is readily explained by an intercurrent illness AND has an expected level of severity, duration and resolution
    - An alternative explanation (concomitant drug, intercurrent illness) is likely
- POSSIBLE – There is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear, study drug administration was not modified in response to the SAE, or any of the following:
    - Has a reasonable temporal relationship to study drug
    - The event has a plausible biological link to the activity of the study drug
    - Is unlikely to be related to an intercurrent illness or has an unexpected degree of severity, duration or complication

- PROBABLE – There is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge - the event resolves or improves with modification of study drug administration. Rechallenge (the original study drug was restarted) is not required, or any of the following:
    - Has a reasonable temporal relationship to study drug
    - The event has a plausible biologic link to the activity of the study drug
    - Not readily explained by an intercurrent illness
    - Not readily explained by external event
    - Improves on discontinuation of study drug
    - If study drug has been discontinued, may recur or reintroduction of study drug

ACTION TAKEN
STUDY DRUG DOSE MODIFICATION*

- Dose Not Changed – The dose of the study drug was not changed
- Infusion Rate Decreased – The rate of study drug infusion was decreased
- Dose Decreased – The dose of study drug was decreased
- Dose Delayed – The dose of study drug was delayed but eventually administered
- Dose Skipped/Missed – The dose of study drug was not administered
- Drug Interrupted – Administration of the study drug was stopped temporarily
- Drug Withdrawn – Administration of the study drug was stopped permanently and not restarted
- Unknown – Changes to the administration of the study drug cannot be determined
- Not Applicable

*NOTE: Only the last study drug action should be recorded in the eCRF. For example, if the study drug is withdrawn and then the decision is made to restart, the dose modification of "Drug interrupted" should be reported on the SAE form.

OUTCOME

- Fatal – The study subject died.
- Not Recovered/Not Resolved – The AE was ongoing at the time of death or at the time the subject was lost to follow up.
- Recovered/Resolved – The AE resolved.
- Recovered/Resolved with Sequelae – The AE is considered resolved however there is residual sequelae. Some events do not return to baseline, such as metastasis or progression of disease; however, once these events are determined by the Investigator to be stable or chronic, the Investigator may consider the event to be resolved or resolved with sequelae.
- Recovering/Resolving – The AE is improving but is not yet completely recovered/resolved.
- Unknown – The outcome of the AE cannot be determined.

APPENDIX C: RECIST v1.1

Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1

1. Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below.

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

2. Disease Parameters

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

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

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next

largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

3. Methods for Evaluation of Disease

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

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

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

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

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

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

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

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based

on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

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

MIBG (meta-iodobenzylguanidine). The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

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

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

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

4. Response Criteria

a. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute

increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

b. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

c. Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

d. Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**

CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

5. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

APPENDIX D: INVESTIGATOR RESPONSIBILITIES

In accordance with ICH E6/GCP guidelines and FDA Form 1572, the Investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and IRB/IEC review and approval in 21 CFR Part 56 are met.
- He or she will report to the Sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments.
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.