STATISTICAL ANALYSIS PLAN

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

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STATISTICAL ANALYSIS PLAN APPROVAL PAGE

Approved by:

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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.

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List of Abbreviations

Abbreviation or Acronym	Definition
ADA	anti-drug antibodies
AE	adverse event
ATC	anatomical therapeutic chemical
BMI	body mass index
BOR	best overall response
BSA	Body surface area
CBR	clinical benefit rate
CP	conditional power
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ICF	informed consent form
ICH	International Conference on Harmonization
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
NAb	neutralizing antibodies
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response

Abbreviation or Acronym	Definition
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	rest of world
RPIC	randomization and product inventory control
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SOC	System Organ Class
SRC	safety review committee
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) was developed after review of United Therapeutic Corporation (UTC) Study Protocol DIV-SCLC-301 (Amendment 2, dated 19-December-2017) and the associated electronic case report form (eCRF). The SAP contains definitions of analysis sets, derived variables, and statistical methods to be used for the analysis and reporting of all efficacy and safety data collected for these subjects. The statistical considerations in this SAP supersede those identified in the protocol; where considerations are substantially different, they will be identified as such in this document. Protocol amendment(s), if required, will not necessitate an amendment to the SAP unless they have an impact on the statistical analysis methodology. This SAP was developed and finalized prior to any unblinding of the clinical database for Protocol DIV-SCLC-301. Exploratory analyses of pharmacokinetics (PK), immunogenicity, and pharmacodynamics data will be covered by separate analysis plans. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the Clinical Study Report (CSR).

The SAP was written in accordance with recommendations outlined in the International Conference on Harmonisation (ICH) E9[1] Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the most recent ICH E3[2] Guideline, entitled "Guidance for Industry: Structure and Content of Clinical Study Reports."

2 OBJECTIVES

2.1 Primary Objective

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).

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 OVERALL 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.

At the time of Amendment 2, the lead-in phase of the study (referred to as Part 1) had 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 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). Subjects enrolled in Part 1 will remain on study treatment until objective disease progression or intolerance.

The study safety review committee (SRC) met after 12 subjects in Part 1 were exposed to irinotecan and dinutuximab for a mean of 3.2 cycles and initially recommended opening Part 2 at a starting dose of dinutuximab of 14 mg/m^2/day. At the next meeting, the SRC reviewed additional safety data (after 8 of 12 subjects in Part 1 had received 16 mg/m^2/day) and voted to increase the starting dose to 16 mg/m^2/day.

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

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

- 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.

Subjects randomized to Group C will receive topotecan 1.5 mg/m^2 IV for the first 5 consecutive days of each 21-day cycle.

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 until 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 approximately 30 days after the last administration of all study drugs (dinutuximab and/or chemotherapy) or prior to the initiation of subsequent treatment (whichever occurs first).

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

Follow-up for survival 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 is allowed given OS is the primary endpoint.

3.1 Changes in the conduct of the study or planned analyses

Not applicable.

4 STATISTICAL METHODOLOGY

4.1 General Statistical Considerations

Data from subjects enrolled in Part 1 will primarily be displayed in listing format and simple statistics summaries. Part 2 data will be summarized in tables according to the treatment groups: Dinutuximab + Irinotecan, Irinotecan, and Topotecan. Unless otherwise specified, Part 1 data will be summarized in the same table as Part 2, but will not be included in any inferential analyses.

Descriptive statistics (n, mean, standard deviation [Std Dev], median, minimum [min], and maximum [max]) for continuous variables, and frequency distributions and percentages for discrete variables will be utilized. In general, the baseline measurement for Part 1 subjects is defined as the last measurement collected prior to the first dose of study treatment. For Part 2 subjects, baseline is defined as the last measurement obtained prior to the date of randomization.

All tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Version 9.4 or higher.

4.2 Determination of Sample Size

The sample size for Part 1 (approximately 10 subjects) was not based on statistical power calculations. It is considered adequate from a clinical perspective 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 subject is enrolled. The mortality rate will be tracked by the Data Monitoring Committee (DMC) and, if lower 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.

4.3 Analysis Data Sets

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. This set will serve as the basis for the evaluation of all safety data, as well as demographic and baseline disease characteristics, prior cancer therapy, study drug exposure, and dose modifications. Unless noted otherwise, safety data will be summarized or listed separately for Part 1 and Part 2.

Intent to Treat (ITT) Analysis Set: All subjects randomized in Part 2 of the study, as assigned to treatment. The ITT population is the primary population for the analysis of Overall Survival (OS) and will also be used to evaluate all secondary efficacy endpoints and subject characteristics.

Modified Intent to Treat (mITT) Analysis Set: All subjects who were randomized and received at least one dose of the study drug in Part 2 of the study, as assigned to treatment. The mITT population is the primary population for the sensitivity analysis of Overall Survival (OS) and all secondary efficacy endpoints.

Efficacy Evaluable: All subjects randomized in Part 2 of the study who have measurable disease at baseline, receive any amount of the assigned study treatment, and have at least one evaluable post-baseline tumor assessment. Subjects with measurable disease must have at least one measurable lesion. Measurable lesions are defined (according to RECIST) as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20

mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. Together with the ITT population, the Efficacy Evaluable group will be used to evaluate ORR and other tumor response endpoints.

Per Protocol Population: All subjects randomized in Part 2 of the study who satisfy the following criteria:

1) Completed at least 2 cycles of the assigned treatment
2) Qualified for the study based on SCLC diagnosis and prior therapies (i.e., met protocol inclusion criteria 3.1.3, 3.1.4, 3.1.5; did not meet exclusion criterion 3.2.2)
3) Received at least 80% of the prescribed study drug (i.e., their average dose during the treatment period was at least 80% of the planned dose).

This population will be used for sensitivity analysis of the primary efficacy endpoint.

4.4 Disposition of Subjects

The disposition of all randomized subjects will be summarized according their status at the time of analysis. This information will include: the number of subjects randomized, treated, discontinued from treatment, discontinued from the study, and continuing in follow-up. The summary will include reasons for discontinuing study treatment or withdrawing from the study as recorded on the eCRF.

Additionally, 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 during the study.

4.5 Protocol Deviations and Violations

Subjects with major protocol deviations/violations will be listed by treatment group. Protocol deviations will be identified via clinical review based on aspects of study conduct that include (but are not limited to): (1) eligibility criteria; (2) treatment compliance; (3) subject safety; (4) efficacy assessment deviation. Protocol deviations/violations will be closely monitored during the execution of the study and the specific set of protocol deviations/violations that merit consideration in the statistical analysis will be finalized before database lock.

4.6 Demographic and Other Baseline Characteristics

All demographic and baseline characteristics will be summarized for the ITT, mITT, and safety analysis sets using descriptive statistics. The following baseline data will be summarized to describe the study population:

- Demographic and Baseline Characteristics (including age, sex, race/ethnicity, performance status, region of enrollment, tobacco use, height, weight, and body surface area)
- Cancer History and Baseline Pain (e.g., SCLC stage at initial diagnosis, time since initial diagnosis, time since relapse/progression, best response to prior therapy, and pre-existing pain assessment) for each treatment group.
- Tumor Burden at screening visit, defined by:
    - Size of target lesions - sum of recorded diameters for all target lesions
    - Number of non-target lesions (1, 2-3 vs. > 3)
    - Number of involved sites (1, 2-3 vs. > 3) – distinct locations of target and non-target lesions

The 3 treatment groups in Part 2 will be compared using chi-square tests for categorical data and F-test from analysis of variance (ANOVA) for continuous data. Any significant imbalances detected among the treatment groups will be considered in the analysis.

4.6.1 Medical and Surgical History

Medical history data will be coded using the Medical Dictionary of Regulatory Activities (MedDRA), version 20.0 (or higher), and listed by subject.

4.7 Prior/Concomitant Treatment

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 30 days after the date of the last dose (dinutuximab and/or chemotherapy).

4.7.1 Prior Cancer Therapy

The best response to prior cancer therapy and the duration of response to prior first-line platinum therapy (classified as < 3 months or ≥ 3 months) will be summarized by frequency table (i.e., number and percentage of subjects in each category). The type of therapies, details of the administration, and best response to each regimen will be listed for each subject.

4.7.2 Concomitant Treatments

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, version September 2016 (or higher).

The number and percentage of subjects taking concomitant medications during the treatment period will be summarized by anatomical therapeutic chemical (ATC) and preferred term (PT). Although a subject may have taken the same medication multiple times, the subject is counted only once within an ATC classification. The same subject may contribute to two or more preferred terms in the same ATC classification.

4.8 Study Drug Exposure

4.8.1 Exposure

A frequency table will display the number (%) of patients in each treatment group according to the total number of cycles initiated, as of the cut-off date for analysis. Duration of treatment 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. Duration of treatment, total number of doses administered, cumulative dose, dose intensity, and relative dose intensity will be summarized for each treatment group and each treatment using descriptive statistics (n, mean, median, SD, inter-quartiles, minimum, and maximum) based on the Safety Analysis Set.

For Part 2 subjects, methods for calculating cumulative actual dose, cumulative planned dose, dose intensity, and relative dose intensity for each medication are as follows:

- Cumulative actual dose (mg/m^2): Sum of {Starting dose level for each cycle};
- Cumulative planned dose (mg/m^2): Sum of {Planned dose level for each cycle}, i.e.;
    - Dinutuximab – (Number of cycles that should have been initiated between the first dose date and the last dose date – 1) x 17.5 + 16, if number of cycles ≥2; otherwise, 16 mg/m^2 if number of cycles = 1;
    - Irinotecan – (Number of cycles that should have been initiated between the first dose date and the last dose date) x 350;
    - Topotecan – (Number of cycles that should have been initiated between the first dose date and the last dose date) x 1.5 x 5;
- Dose intensity (mg/m^2/day): Cumulative actual dose / (Last dose date – first dose date + 21);

- Relative dose intensity (%): Dose intensity / {Cumulative planned dose / [(Number of cycles that should have been initiated between the first dose date and the last dose date) x 21]} x 100.

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 a dose modification (reduction, delay or interruption) will be summarized descriptively by treatment group.

4.9 Efficacy Analysis

A closed, hierarchical testing procedure will be used to control the overall false-positive rate at 5% (two-sided) for the primary comparison of dinutuximab + irinotecan versus irinotecan. The primary efficacy endpoint (Overall Survival) will be tested first and, if it achieves statistical significance, the secondary endpoints will be tested in the following sequence: PFS, ORR and CBR. All the analyses described below will be performed for the purpose of displaying summary statistics, but once the first in the sequence of tests yields a p-value that exceeds 0.05, the nominal p-value for this and subsequent endpoints in the series will be declared non-significant.

4.9.1 Overall Survival (OS)

OS is defined as duration of time from the date of randomization to the date of the subject's death from any cause. 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 in the ITT set 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. Stratification will be based on the same factor used for randomization, i.e., the subject's response to prior platinum therapy (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 (an exploratory analysis, not part of the hierarchical procedure described above).

Median OS in each treatment group and the corresponding 2-sided 95% confidence interval (CI) will be estimated using the Kaplan-Meier method (Brookmeyer[3], 1982). Kaplan-Meier curves for OS distributions will be plotted over time for each treatment group.

In addition, two-sided 95% CIs for the OS rate for each treatment will be constructed at pre-specified time intervals (i.e., 6 months, 12 months, …, etc.), using the log-log transformation methodology of Kalbfleisch and Prentice (Kalbfleisch[4], 1980) where the estimated variance of $\log(-\log(\hat{S}(t))$ is:

$$\tau^2(t) = \sigma^2[\hat{S}(t)\log(\hat{S}(t))]^2$$

The 100 x (1-α)% CI for S(t) is given by:

$$\left[\hat{S}(t)\right]^{\exp(Z_{\alpha/2}\tau(t))} \le S(t) \le \left[\hat{S}(t)\right]^{\exp(-Z_{\alpha/2}\tau(t))}$$

Note that the stratified log-rank test will be used for evaluating the treatment difference. The Kaplan-Meir plots as well as the summary statistics for median OS and the OS rate will be derived from analyses without adjusting for the stratification factor.

The treatment effect of the dinutuximab combination on OS, as compared to irinotecan, will be estimated by the hazard ratio and its 95% CI; the Cox proportional hazards model will be used for this analysis, stratified by the subject's response to prior platinum therapy. Similarly, the hazard ratio and 95% CI comparing the dinutuximab combination group and the topotecan group will be provided.

Sensitivity analyses for the OS endpoint will include an analysis of subjects in the mITT and Per Protocol populations (as defined above). An additional sensitivity analysis will be performed that considers ITT subjects who were lost to follow as having died on their last follow-up date.

In addition, 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, geographic region of enrolling site, ECOG status, duration of prior response to platinum, PD-L1 status (if available), 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.

4.9.2 Progression-Free Survival (PFS)

PFS is 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 Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.

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 objective tumor progression; 3) are ongoing and do not have objective tumor progression at the time of the analysis. Death or disease progression that occurs after more than one missed visit (i.e., 12 weeks) will be censored on the date of the last tumor assessment prior to the first missed visit. Subjects with no post-baseline tumor assessments will be censored on the date of randomization.

4.9.3 Overall Response Rate (ORR)

ORR is the percentage of subjects with best overall response (BOR) of either CR or PR. Subjects with no post-baseline results will be considered non-responders. ORR will be calculated by treatment group for ITT and Efficacy Evaluable subjects. Both confirmed and unconfirmed CR/PR will be tabulated. The rates will be presented along with two-sided 95% exact confidence intervals. The 95% CIs will be derived using the Clopper-Pearson method. This method is commonly used in the literature for reporting tumor response rates and is conservative, providing no less than 95% coverage probability even for small N.

4.9.4 Clinical Benefit Rate (CBR)

The CBR is the percentage of subjects with either a CR or PR, or SD. The rates and the exact 95% CIs will be provided for each treatment group. Subjects with no post-baseline tumor assessments will be considered to have achieved no clinical benefit. Subjects will be classified as having stable disease if assessed as SD (or better) at least 6 weeks after first dose date.

Binary endpoints (ORR and CBR) will be analyzed using stratified Cochran-Mantel-Haenszel chi-square tests, with two-tailed alpha=0.05. Odds ratios will be presented along with corresponding 95% confidence intervals.

4.9.5 Other Efficacy Outcomes

Treatment groups will also be compared on the basis of the following additional efficacy outcomes, with tumor response defined by RECIST criteria (version 1.1):

Best Overall Response (BOR)

The BOR is the best response observed from the start of study treatment until the last assessment of tumor response recorded during follow-up or the start of any post treatment cancer therapy (whichever is sooner), taking into account any requirement for confirmation (i.e., at least 4 weeks apart). The number and percentage of subjects in each BOR category (i.e., CR, PR, SD, PD, and unevaluable) will be summarized by treatment group. Subjects with unconfirmed CR or PR assessments will be categorized separately. The table will include a category for subjects who died or discontinued the study due to disease progression prior to the first tumor assessment, as well as ongoing subjects without a tumor assessment prior to the data cut-off date for analysis. Subjects will be classified as having stable disease if assessed as SD (or better) at least 6 weeks after first dose date.

Data listings will display target lesion measurements and non-target lesion response assessments at each timepoint, together with the level of tumor response assigned by the investigator.

Time to Response (TTR)

The TTR is defined as the time interval between the date of randomization and the date of first documented CR or PR. CR or PR requires confirmation at least 4 weeks apart. Once it is confirmed, the first documented CR or PR will be considered as the start of the response. TTR will be descriptively summarized for subjects who responded.

Duration of response (DOR)

The DOR is defined as the time interval between the date of first documented PR or CR and the subsequent first date of disease progression as determined by radiological assessment using RECIST criteria (version 1.1) or death.

Subjects who do not experience disease progression and have not died will be censored on the date of their last tumor assessment. Disease progression that occurs after more than one missed visit (i.e., 12 weeks) will be censored on the date of the last tumor assessment prior to the first

missed visit. For OS, the death date will be used as an event time, no matter how many prior visits were missed.

DOR 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.

4.9.6 Subgroup Analysis

For exploratory purposes, the analysis of OS will be performed within subgroups of subjects in the ITT Analysis Set defined by the following criteria. The same method used for the analysis of the primary efficacy endpoint (OS) will be applied except that the stratification factor will not be included in the analysis of the prior platinum response subgroups.

- Prior Platinum Response (relapse-free < 3 months vs. ≥ 3 months)
- Age Group (< 65 years vs. ≥ 65 years)
- Sex (male vs. female)
- Geographic Region (North America/Europe/Asia-Pacific)
- Baseline Tumor Burden (Lowest, Middle, Highest Tertile)
- GD2 expression (positive vs. negative)

In addition, the impact of steroid use on the treatment effect of dinutuximab will be explored.

4.10 Safety Analysis

4.10.1 Adverse Events – Part 1

Toxicities reported during Part 1 (intrasubject dose escalation) will be listed for individual subjects by dinutuximab dose at time of onset. Pain severity scores will also be listed by dinutuximab dose, cycle, and time since start of infusion.

4.10.2 Adverse Events – Part 2

AEs will be coded using MedDRA Version 20.0 or higher. Treatment-emergent AEs (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 and up

until 30 days after the last dose will be considered a TEAE. Severity of the AEs will be graded according to the NCI CTCAE Version 4.03.

All safety summaries will be generated for the Safety Analysis Set.

A safety overview table will present the number (%) of subjects in each treatment group with events in the following categories:

- Any TEAEs
- Treatment-Related TEAEs
- Grade ≥3 TEAEs
- Grade ≥3 Treatment-Related TEAEs
- Treatment-Emergent Serious Adverse Events (SAEs)
- Treatment-Related SAEs
- Grade ≥3 SAEs
- Grade ≥3 Treatment-Related SAEs
- TEAEs leading to Discontinuation of Study Treatment
- TEAEs leading to Reduction in Dose of Study Treatment
- Fatal TEAEs
- Fatal Treatment-Related TEAEs

For these events, the difference between incidence rates for Group B (dinutuximab + irinotecan) minus Group A (irinotecan) will be presented, together with its 2-sided 95% confidence interval calculated using the Wilson score method. A lower bound > zero may indicate excess risk in the dinutuximab group. The Wilson score method will be used to calculate 95% confidence intervals to ensure actual coverage closest to the nominal level.

The number and percentage of subjects experiencing TEAEs will also be summarized by SOC and PT. The following tables will be generated:

- Overall TEAEs
- Dinutuximab-Related TEAEs
- Irinotecan/Topotecan-Related TEAEs
- Grade ≥3 TEAEs,
- Dinutuximab-Related Grade ≥3 TEAEs
- Irinotecan/Topotecan-Related Grade ≥3 TEAEs
- TEAEs leading to discontinuation of Dinutuximab

- TEAEs leading to discontinuation of Irinotecan/Topotecan
- TEAEs leading to dose reduction of Dinutuximab
- TEAEs leading to dose reduction of Irinotecan/Topotecan
- Treatment-emergent SAEs
- Treatment-emergent SAEs related to Dinutuximab
- Treatment-emergent SAEs related to Irinotecan/Topotecan
- TEAEs with an outcome of death
- TEAEs by Maximum Grade
- TEAEs of special interest

Adverse events of special interest are defined as:

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

By-subject data listings of AEs will provide the 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 all AEs (regardless of treatment emergence), Grade ≥3 AEs, all treatment-related AEs, all SAEs, AEs that lead to discontinuation of any study treatment, AEs with a fatal outcome, and all deaths. 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.

4.10.3 Pain Medications and Infusion Related Reaction Medications

Pain medications and other treatments administered to prevent or alleviate pain and infusion reactions (including drugs initiated during the infusion period) will be summarized separately for each treatment group. The number and percentage of subjects in each treatment group 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 study treatment, will be listed by subject.

4.10.4 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. 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.

Serology testing was not mandatory and discontinued during the study. Serology data collected will be included in the database, but will not be presented in data listings for the CSR.

4.10.5 Vital Signs

Vital sign measurements will be summarized at each infusion, by treatment, using descriptive statistics; change from baseline values will be presented for each timepoint for the Safety Analysis Set. Summary statistics by treatment group will be based on vital sign assessments obtained prior to the first dose of each cycle. Clinically significant post-baseline vital sign findings will be reported as AEs. A by-subject data listing of all vital sign data will be generated.

4.10.6 Physical Examinations

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

Neurological assessments will be tabulated using shift tables to categorize subjects according to the change from baseline evaluation to each post baseline visit (Normal, Abnormal – not

clinically significant, Abnormal – clinically significant), for each item in the assessment scale (e.g., mental status, coordination and gait, …, etc.), by treatment group.

4.10.7 ECOG Performance Status

ECOG performance status scores will be summarized by treatment group. Frequency counts and percentages for the EOT assessment will be presented.

5 INTERIM DATA MONITORING

An independent DMC will review accumulating safety data at scheduled intervals during Part 2 of the study. Attention will focus on the percentage of subjects with SAEs, AEs of special interest, fatal events, and Grade 3 or 4 toxicities, with the severity and relationship to study medication(s) taken into consideration. Details regarding DMC member roles, the frequency of DMC meetings, contents of safety reports, and procedural aspects of DMC meetings will be described in the DMC charter. Excess risk will be determined according to the lower 97.5% lower confidence bound on the difference between incidence rates for Group B (dinutuximab + irinotecan) minus Group A (irinotecan alone). 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 to ensure that actual coverage is close to the nominal level.

In addition to the 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. Futility will be based on interim ORR values and the resulting conditional power (CP). 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).

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.

Selected safety and efficacy tables, listings, and figures will be provided for DMC review meetings. Details of the DMC analysis plan will be provided in the DMC Charter.

6 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
3. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982; 38: 29-41.
4. Kalbfleisch JD, Prentice RL. (1980) The statistical analysis of failure time data. John Wiley & Sons, Inc.
5. Proschan MA, Lan GKK, and Wittes JT. (2006) Statistical Monitoring of Clinical Trials – A Unified Approach. Springer Science, New York, NY.

7 PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® Version 9.4 (or higher). Generated outputs will adhere to the following specifications.

7.1 Table, Listing, and Figure Format

7.1.1 General

1) All TLFs will be produced in landscape format.
2) All TLFs will be produced using the Courier New font, size 9.
3) The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
4) Headers and footers for figures will be in Courier New font, size 9.
5) Legends will be used for all figures with more than 1 variable, group, or item displayed.
6) Tables and listings will be in black and white (no color). Figures may be in color.
7) Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs. On some occasions, superscripts 1, 2, or 3 may be used (see below).
8) Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain superscripts (e.g., cm^2) will be employed on a case-by-case basis.
9) Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats.

7.1.2 Headers

All output will have the following header at the top of the page:

```
Product: DINUTUXIMAB                                    Page n of N

Protocol: DIV-SCLC-301                        United Therapeutics
```

All output will have page numbers. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

7.1.3 Display Titles

Each TLF will be identified by a numeral, and the designation (i.e., Table 1) should be centered above the title. A decimal system (Table 14.x.y.z, Figure 14.x.y.z, and Listing 16.2.x.y) should be used to identify TLFs with related contents. The title will be centered in initial capital characters. The analysis set will be identified on the line immediately following the title. The title and table designation will be single spaced. A solid line spanning the margins will separate the titles from the column headers. There will be 1 blank line between the last title line and the solid line.

```
Table 14.x.y-z

First Line of Title

Second Line of Title if Needed

Safety Analysis Set
```

7.1.4 Column Headers

1) Column headings will be displayed immediately below the solid line described above, in initial upper-case characters.
2) For numeric variables, units will be included in column or row heading when appropriate.
3) Analysis set sizes will be presented for each treatment cohort in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
4) The order of treatments in the tables and listings will be: (listing only), Dinutuximab + Irinotecan, Irinotecan, Topotecan, and Total [if applicable]).

7.1.5 Body of the Data Display

1) Listings will be sorted for presentation in order of schedule, treatment cohort, subject ID, collection day, and collection time.

2) If the categories of a parameter are ordered, then all categories between the maximum and minimum category will be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
Grade 1	20
Grade 2	5
Grade 3	3
Grade 4	5
Grade 5	0

Where percentages are presented in these tables, any counts of 0 will be presented as 0 and not as 0 (0%).

3) If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups will be included.

4) An Unknown or Missing category will be added to the summary of any categorical parameter for which information is not available for 1 or more subjects.

5) Unless otherwise specified, the estimated mean and median for a set of values will be presented to 1 more significant digit than the original values, and standard deviations will be presented to 2 more significant digits than the original values. The minimum and maximum will report the same number of significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean (SD)	XXX.X (X.XX)
Median	XXX.X
Min - Max	XXX, XXX

6) Data in columns of a table will be formatted as follows:

- alphanumeric values left-justified;
- whole numbers (e.g., counts) right-justified; and
- numbers containing fractional portions decimal-aligned.

7) Percentage values will be formatted with 1 digit to the right of the decimal point in parentheses, 1 space after the count (e.g., 7 (12.8%), 13 (5.4%)). Less-than signs (e.g., "<0.1%") will appear when values are >0.0% and <0.1% (but not equal to 0.0%). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment cohort who have an observation (i.e., at risk) will be the denominator.

8) Tabular displays of data for prior/concomitant medications and all tabular displays of adverse event data will be presented by the drug class, or SOC with the highest occurrence in the MTD cohort(s) (Schedule 1 and Schedule 2 separately), in decreasing order. Within the drug class and SOC, drugs (by ATC code), and adverse events (by PT) will be displayed in decreasing order. If the incidences for multiple terms are identical, they will be sorted alphabetically.

9) Missing data will be represented on subject listings as either a hyphen ("-") with a corresponding footnote (" - = unknown or not evaluated"), or as "N/A" (footnote "N/A = not applicable"), whichever is appropriate. Missing descriptive statistics or p-values due to non-estimability will be reported as "-" with a corresponding footnote ("- = not estimable").

10) Dates will be formatted in SAS®ISO date format yyyy-mm-dd (e.g., "2000-07-01"). Missing portions of dates will be represented on subject listings as blank (e.g., "2000-07"). Dates that are missing because they are not applicable for the particular subject will be presented as "N/A", unless otherwise specified.

11) All observed time values will be presented using a 24-hour clock in hh:mm:ss format (e.g., "01:35:45", "21:26"). Time values will be reported only if they were measured as part of the study. Vital signs measured relative to dinutuximab infusion are captured on a single date. If clock times run past 24:00 for a given cycle, then add +1 to date.

7.1.6 Footnotes

1) A solid line spanning the margins will separate the body of the data display from the footnotes.

2) All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

3) Informational footnote will begin with "Note:". Annotation footnotes will begin with an asterisk and other non-numeric symbol. Each new footnote will start on a new line.

4) Footnotes will appear on each page. Subject specific footnotes will be avoided.

5) Footnotes will be used sparingly, and only if they add value to the table, figure, or data listing. If a data display has more than 4 footnotes, then a cover page may be used to display footnotes, and only those footnotes essential to comprehension of the data will be repeated on each page. Footnotes will not repeat definitions already provided in the SAP.

6) The last line of the footnote section will be a standard source line, indicating the data source used by the SAS program that produced the data display, the name of the SAS program, and running date/time.

7.2 Data-Handling Rules

This section describes naming conventions and rules for calculations common to all applicable tables. Some rules specific to a table can be found in the relevant mock-ups.

7.2.1 Unit Conversion to Months

If months are calculated for a duration, the following conversion is used.

1) Duration (months): {Duration (days)} / 30.42

7.2.2 Visits

1) Relative Study Day: The first day of study treatment is Day 1. A minus (-) sign indicates days prior to the start of study treatment (e.g., Day -5 represents 5 days before start of the study treatment. There is no Day 0.). The relative study day for a specific visit is calculated as (Visit Date – Date of First Dose +1).

2) Baseline: For all study variables, baseline is defined as the last measurement obtained prior to the first dose of the study treatment.

7.2.3 Demographics and Baseline Characteristics

1) Age = (Date of informed consent–Date of birth + 1) / 365.25 and truncated to complete years.

2) Conversion factors and calculations for height, weight, BMI and BSA:

   a) Height (in cm) = height (in inches) * 2.54

   b) Weight (in kg) = weight (in lbs) * 0.4536

   c) BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

   d) BSA (m^2) = ([Weight (kg) x Height (cm)] / 3600)$^{1/2}$

3) Geographic regions will be defined as follows:

North America	Canada, US
Western Europe	France, Italy, Spain, UK
Central/Eastern Europe	Bulgaria, Georgia, Hungary, Lithuania, Poland, Slovakia
Russia & Ukraine	Russia, Ukraine
Asia-Pacific	Australia, Hong Kong, India, Korea, Malaysia, Philippines, Taiwan, and Thailand

7.2.4 Prior and Concomitant Medications

1) Prior and concomitant medications will be coded and classified using the World Health Organization (WHO) Drug Dictionary (September 2016 or higher). The specific dictionary version will appear in the footnote of the SAS tables/listings.

2) Counting rules for prior/concomitant medications: Prior medications include medications that were taken prior to the start of study treatment but stopped before the first dose of study treatment. Concomitant medications during treatment period include medications that started at any time and were taken at any time after the start of study treatment until the 30 days after the end of study treatment.

3) Medications missing both start and stop dates, or having a start date prior to 30 days post the last dose of study treatment with the stop date missing, or having a stop date after the start of study treatment with the start date missing, will be counted as concomitant. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the medication either ended prior to the start of study treatment or started after 30 days post the end of study treatment. If the above cannot be conclusively established based on the partial and/or present dates, then the medication will be counted as concomitant.

7.2.5 Safety

1) Adverse events will be coded and classified using MedDRA 20.0 or higher. The specific dictionary version will appear in a footnote of the SAS tables/listings.
2) Counting rules for AEs: AEs with missing start dates, but with stop dates either overlapping the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. Special care will be taken regarding partial dates, applying similar logic to that of the prior/concomitant medications.
3) For purposes of flagging individual subject data, laboratory test result abnormalities are defined as values above or below the normal range.

7.2.6 SAS® Procedures

This section provides sample SAS® code to illustrate statistical analyses specified in the statistical methods section. All computer output from SAS® statistical procedures serving as a basis for extracted results (e.g., LIFETEST) will be retained for quality control procedures and will be included in CSR appendices.

Exact 95% confidence interval on ORR/DCR:

```
proc freq;
   by trt;
   table resp / binomial;
run;
```

Median survival time and survival rates with 95% confidence intervals:

```
proc lifetest method=lt intervals =(0 to 24 by 6) outsurv=surv;
   time tte*censor(0);
   strata trt
run;
```

Note: 95% confidence intervals for time intervals (e.g., 3 months, 6 months) will be extracted from the data set SURV.

Cox proportional hazard ratio:

```
proc phreg data=kmvar;
   model aval*cnsr(1) = trtpn/rl;
   strata st1n;
run;
```

Stratified log-rank test p-value:

```
Ods output HomTests=pval;
proc lifetest data=kmvar;
   time aval*cnsr(1);
   strata st1n / group = trtpn;
run;
```

Additional SAS® code is provided, where necessary, in programming notes for table mock-ups.

8 LIST OF TABLES, LISTINGS, AND FIGURES

8.1 LIST OF TABLES

Table Number	Table Title
14.2.1.3	Summary of Overall Survival (OS) [Sensitivity 1: "Per Protocol Population" (Patients who were protocol compliant and received >= 80% assigned dose)]
14.2.1.4	Summary of Overall Survival (OS) [Sensitivity 2: Consider subjects lost to follow-up as deaths at last follow-up date]
14.2.1.5	Effect of Prognostic Factors on Overall Survival (OS) – ITT Analysis Set
14.2.1.6	Final Prognostic Factor Model for Overall Survival (OS) – ITT Analysis Set
14.2.2.1	Summary of Progression-Free Survival (PFS) – ITT Analysis Set
14.2.2.2	Summary of Progression-Free Survival (PFS) – mITT Analysis Set
14.2.3.1	Summary of Best Overall Response – ITT Analysis Set
14.2.3.2	Summary of Best Overall Response – mITT Analysis Set
14.2.3.3	Summary of Best Overall Response – Efficacy Evaluable
14.2.3.4	Summary of Clinical Benefit Rate – ITT Analysis Set
14.2.3.5	Summary of Clinical Benefit Rate – mITT Analysis Set
14.2.3.6	Summary of Clinical Benefit Rate – Efficacy Evaluable
14.2.4.1	Summary of Time to Response –ITT Analysis Set
14.2.5.1	Summary of Duration of Response – ITT Analysis Set
14.3.1.1.1	Overview of Adverse Events (Part 1) – Safety Analysis Set
14.3.1.1.2	Overview of Adverse Events (Part 2) – Safety Analysis Set
14.3.1.2	Number (%) of Subjects with Treatment-Emergent Adverse Events (TEAEs), By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.3.1	Number (%) of Subjects with Dinutuximab Related TEAEs By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.3.2	Number (%) of Subjects with Irinotecan or Topotecan Related Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.3.3	Number (%) of Subjects with Any Treatment Related Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.4	Number (%) of Subjects with Treatment-Emergent Adverse Events (TEAEs) By System Organ Class, Preferred Term, and Highest CTCAE Grade – Safety Analysis Set

Table Number	Table Title
14.3.1.5.1	Number (%) of Subjects with Dinutuximab Related TEAEs by System Organ Class, Preferred Term, and Highest CTCAE Grade – Safety Analysis Set
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14.3.1.5.3	Number (%) of Subjects with Any Treatment Related Adverse Events by System Organ Class, Preferred Term, and Highest CTCAE Grade – Safety Analysis Set
14.3.1.6	Number (%) of Subjects with Grade >= 3 Treatment-Emergent Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.7.1	Number (%) of Subjects with Dinutuximab Related Grade >= 3 Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.7.2	Number (%) of Subjects with Irinotecan or Topotecan Related Grade >= 3 Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.7.3	Number (%) of Subjects with Any Treatment-Related Grade >= 3 Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
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14.3.1.9.1	Number (%) of Subjects with Dinutuximab Related Serious Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.9.2	Number (%) of Subjects with Irinotecan or Topotecan Related Serious Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.9.3	Number (%) of Subjects with Any Treatment-Related Serious Adverse Events By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.10.1	Number (%) of Subjects with Treatment-Emergent Adverse Events (TEAEs) Leading to Dinutuximab Discontinuation By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.10.2	Number (%) of Subjects with Treatment-Emergent Adverse Events (TEAEs) Leading to Irinotecan or Topotecan Discontinuation By System Organ Class and Preferred Term – Safety Analysis Set

Table Number	Table Title
14.3.1.10.3	Number (%) of Subjects with Treatment-Emergent Adverse Events (TEAEs) Leading to Any Treatment Discontinuation By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.11.1	Number (%) of Subjects with Treatment-Emergent Adverse Events (TEAEs) Leading to Dinutuximab Reduction By System Organ Class and Preferred Term – Safety Analysis Set
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14.3.1.11.3	Number (%) of Subjects with Treatment-Emergent Adverse Events (TEAEs) Leading to Any Treatment Reduction By System Organ Class and Preferred Term – Safety Analysis Set
14.3.1.12	Number (%) of Subjects with Treatment-Emergent Fatal Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
14.3.2.1.1	Summary of Chemistry Laboratory Values and Change from Baseline – Safety Analysis Set
14.3.2.1.2	Summary of Hematology Laboratory Values and Change from Baseline – Safety Analysis Set
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14.3.3.1.1	Summary of Vital Signs and Change from Baseline – Safety Analysis Set
14.3.3.2	Summary of Weight Values and Change from Baseline – Safety Analysis Set
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14.3.5	ECOG Performance Status – Safety Analysis Set
14.3.6.1	Summary of Concomitant Pain Medications – Safety Analysis Set

8.2 LIST OF LISTINGS

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16.2.2.1	Protocol Deviations

Listing Number	Listing Title
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16.2.4.1	Demographics
16.2.4.2.1	Small Cell Lung Cancer Disease History
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16.2.4.2.2.2	Post Study Cancer Therapy
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16.2.7.1	Adverse Events
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Listing Number	Listing Title
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8.3 LIST OF FIGURES

Figure Number	Figure Title
14.2.1.1	Plot of Kaplan-Meier Curve for Overall Survival – ITT Analysis Set
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14.2.1.1.2	Plot of Kaplan-Meier Curve for Overall Survival by Age Group [< 65 years vs. >= 65 years] – ITT Analysis Set
14.2.1.1.3	Plot of Kaplan-Meier Curve for Overall Survival by Geographic Region [North America/Europe/Asia-Pacific] – ITT Analysis Set
14.2.1.1.4	Plot of Kaplan-Meier Curve for Overall Survival by Baseline Tumor Burden [Lowest, Middle, and Highest] –ITT Analysis Set
14.2.1.2	Plot of Kaplan-Meier Curve for Overall Survival – mITT Analysis Set
14.2.1.3	Plot of Kaplan-Meier Curve for Overall Survival [Sensitivity 1: “Per Protocol Population” (Subjects who were protocol compliant and received >= 80% assigned dose)]
14.2.1.4	Plot of Kaplan-Meier Curve for Overall Survival [Sensitivity 2: counting subjects lost to follow-up as deaths at time of last follow-up]
14.2.2.1	Plot of Kaplan-Meier Curve for Progression-free Survival – ITT Analysis Set
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Figure Number	Figure Title
14.2.3	Maximum Percent Change in Tumor Burden by Best Overall Response (RECIST v1.1) – Waterfall plot – ITT Analysis Set