Clinical trial results:
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

Summary

EudraCT number	2017-000758-20
Trial protocol	ES HU BG LT FR PL SK GB IT
Global end of trial date	26 March 2020

Results information

Result version number	v1 (current)
This version publication date	14 February 2021
First version publication date	14 February 2021

Trial information

Trial identification

Sponsor protocol code	DIV-SCLC-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03098030
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	United Therapeutics Corporation
Sponsor organisation address	55 TW Alexander Dr, P.O. Box 14186, Research Triangle Park, United States, NC 27709
Public contact	United Therapeutics Global Medical Information, United Therapeutics Corporation, 001 877-522-2950, MedicalInformation@unither.com
Scientific contact	United Therapeutics Global Medical Information, United Therapeutics Corporation, 001 877-522-2950, MedicalInformation@unither.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 January 2020
Global end of trial reached?	Yes
Global end of trial date	26 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was 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). Secondary objectives of the study included comparison of 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; comparison of the safety of subjects treated with dinutuximab and irinotecan versus subjects treated with irinotecan alone; evaluation of the pharmacokinetics of subjects treated with dinutuximab; and comparison of OS, PFS, ORR and clinical benefit rate (CBR) in subjects treated with dinutuximab and irinotecan versus subjects treated with topotecan alone.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice (GCP), International Council for Harmonisation (ICH) guidelines, all applicable regulatory requirements, and the ethical principles that have their origins in the Declaration of Helsinki. An independent Data Monitoring Committee (DMC) was established to oversee safe and ethical conduct of Part 2 of the study.

Prior to each dinutuximab dose, subjects received IV hydration in addition to premedication with antihistamines and antipyretics. From Cycle 2 onwards, premedication with opioid analgesics (morphine or morphine equivalent) could 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 was to be indicated as the reason for concomitant medication use on the electronic case report form (eCRF). If an opioid was also given as a premedication for possible dinutuximab-related pain, an additional use was to be included on the concomitant medication page and premedication selected as the category (i.e., two entries with distinct indications).

Subjects were 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 were available.

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

Background therapy:

Subjects were permitted to receive antiemetics, antidiarrheal agents, and antibiotics as necessary. Subjects receiving corticosteroids for emesis prophylaxis were to receive the lowest dose and for the shortest period of time according to clinical judgment. The use of growth factors and erythropoietin stimulating agents was permitted as per American Society of Clinical Oncology/ESMO/NCCN Guidelines. Subjects were permitted to receive red blood cell (RBC) transfusions or platelet transfusions if clinically indicated in accordance with institutional guidelines. Palliative radiation for pain management was permitted with the prior approval of the Medical Monitor.

Evidence for comparator:

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.). Additionally, NCCN guidelines recommend irinotecan plus either cisplatin or carboplatin as a possible first-line regimen. European

Society of Medical Oncology (ESMO) guidelines list irinotecan plus cisplatin as an alternative first-line regimen for those patients for whom etoposide is contraindicated.

Topotecan, at the time of the study was the only drug approved in the United States for second-line treatment of SCLC. Evaluation of the effect of the combination group against the topotecan alone group was a secondary objective. Owing to the poor prognosis of patients with relapsed and refractory SCLC, OS was the primary outcome measure of interest. The study findings were intended to support registration of dinutuximab (in combination with irinotecan) if warranted.

Actual start date of recruitment	15 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 83
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	United States: 68
Country: Number of subjects enrolled	Korea, Republic of: 42
Country: Number of subjects enrolled	Russian Federation: 92
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Ukraine: 18
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Georgia: 24
Country: Number of subjects enrolled	India: 7
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Philippines: 3
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Hong Kong: 2
Worldwide total number of subjects	483
EEA total number of subjects	184

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	296
From 65 to 84 years	186
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 483 subjects were enrolled during the study across 153 institutions in US, Spain, Korea, Russia, France, Hungary, Bulgaria, Canada, United Kingdom, Ukraine, Thailand, Italy, Australia, Georgia, India, Taiwan, Poland, Phillippines, Lithuania, Malaysia, Hong Kong and Slovakia

Pre-assignment

Screening details:

Screening assessments included collection of demographic data, medical history, and ongoing medications, laboratory tests for eligibility, physical examination including ophthalmology examination, ECOG status, neurologic assessment, assessment of any pre-existing pain, 12 lead ECG, vital signs, and monitoring of AEs including SAEs.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 - Dinutuximab + Irinotecan

Arm description:

The lead-in phase of the study (referred to as Part 1) had an enrollment target of approximately 10 subjects. In Part 1, dinutuximab was to be administered at increasing doses, as tolerated, together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1 of each 21-day cycle. Subjects were to receive dinutuximab at a starting dose of 10 mg/m2 IV, with increases administered in 2 mg/m2 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 was adequately managed and the drug was otherwise tolerated. The maximum permitted dose of dinutuximab was 17.5 mg/m2 (If this dose was reached, the last dose increment would be 1.5 mg/m2). The dinutuximab dose was to be decreased in 2 mg/m2 decrements per cycle depending on the toxicity observed to as low as 8 mg/m2. If a dose decrease from 17.5 mg/m2 was required, the initial dose reduction was to be 1.5 mg/m2 (and 2 mg/m2 for any subsequent decrements)

Arm type	Experimental
Investigational medicinal product name	Unituxin
Investigational medicinal product code	
Other name	Dinutuximab
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dinutuximab was administered at a doses of 10 mg/m2 (n=2), 14 mg/m2 (n=2), 16 mg/m2 (n=1) and 17.5 mg/m2 (n=7) together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1 of each 21-day cycle.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dinutuximab was administered at a doses of 10 mg/m2 (n=2), 14 mg/m2 (n=2), 16 mg/m2 (n=1) and 17.5 mg/m2 (n=7) together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1 of each 21-day cycle.

Arm title	Part 2 - Irinotecan (Group A)

Arm description:

In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). Subjects randomized to Group A were to receive irinotecan at a dose of 350 mg/m2 on Day 1 of each cycle.

Arm type	Active comparator
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan was administered at a dose of 350 mg/m2 intravenously (IV) on Day 1 of each 21-day cycle.

Arm title	Part 2 - Dinutuximab + Irinotecan (Group B)

Arm description:

In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). Subjects randomized to Group B were to receive dinutuximab on Day 1 of each cycle beginning with a starting dose of 10 mg/m2 IV or a dose recommended by the SRC, and irinotecan at a dose of 350 mg/m2 on Day 1 of each cycle. Dose escalation and de-escalation for dinutuximab was to occur as in Part 1. The maximum dose of dinutuximab that may have been administered was 17.5 mg/m2 (If this dose was reached, the last dose increment would be 1.5 mg/m2. If the dose was reduced from 17.5 mg/m2, the initial dose decrement would be 1.5 mg/m2 to 16 mg/m2.)

Arm type	Experimental
Investigational medicinal product name	Unituxin
Investigational medicinal product code	
Other name	Dinutuximab
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For the first cycle dinutuximab was administered at a dose of 16 mg/m2 together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1. For each subsequent 21-day cycle, dinutuximab was administered at a dose of 17.5 mg/m2 together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For the first cycle dinutuximab was administered at a dose of 16 mg/m2 together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1. For each subsequent 21-day cycle, dinutuximab was administered at a dose of 17.5 mg/m2 together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1.Irinotecan was administered at a dose of 350 mg/m2 together with dinutuximab at a dose of 17.5 mg/m2 intravenously (IV) on Day 1 of each 21-day cycle.

Arm title	Part 2 - Topotecan (Group C)

Arm description:

In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). No crossover between groups was allowed because OS was the primary endpoint. Subjects randomized to Group C were to receive topotecan 1.5 mg/m2 IV for 5 consecutive days of each cycle.

Arm type	Active comparator

Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Topotecan was administered as a dose of 1.5 mg/m2 intravenously (IV) for 5 consecutive days of each cycle.

Number of subjects in period 1	Part 1 - Dinutuximab + Irinotecan	Part 2 - Irinotecan (Group A)	Part 2 - Dinutuximab + Irinotecan (Group B)
Started	12	190	187
Completed	2	24	24
Not completed	10	166	163
Adverse event, serious fatal	10	156	156
Consent withdrawn by subject	-	8	7
Lost to follow-up	-	2	-

Number of subjects in period 1	Part 2 - Topotecan (Group C)
Started	94
Completed	9
Not completed	85
Adverse event, serious fatal	82
Consent withdrawn by subject	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study (overall period)

Reporting group description: -

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	483	483	
Age categorical Units: Subjects			
<65 years	296	296	
≥65 years	187	187	
Age continuous Units: years			
arithmetic mean	61.6		
standard deviation	± 8.7	-	
Gender categorical Units: Subjects			
Female	118	118	
Male	365	365	
Race Units: Subjects			
White	277	277	
Black or African American	6	6	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Asian	80	80	
Multiple	1	1	
Other	3	3	
Unknown	116	116	
Ethnicity Units: Subjects			
Hispanic or Latino	11	11	
Not Hispanic or Latino	355	355	
Unknown	117	117	
ECOG Performance Status			
Baseline was defined as the last measurement obtained prior to first dose for Part 1 subjects or randomization for Part 2 subjects. ECOG Performance Status was used as a measure of how the disease impacted the patient's daily living abilities with eligible grading levels defined as follows: 0 = Fully active, able to carry on all pre-disease performance without restriction 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.			
Units: Subjects			
Grade 0	95	95	
Grade 1	375	375	
Missing	13	13	
Region			
North America includes United States, Canada. Western Europe includes Spain, France, United Kingdom, Italy.			

Central/Eastern Europe includes Bulgaria, Georgia, Hungary, Lithuania, Poland, Slovakia. Asia-Pacific includes Australia, Taiwan, Thailand, South Korea, Hong Kong, India, Philippines, Malaysia			
Units: Subjects			
North America	83	83	
Western Europe	128	128	
Central/Eastern Europe	80	80	
Russia & Ukraine	110	110	
Asia-Pacific	82	82	
Tobacco Use Units: Subjects			
No	46	46	
Yes	437	437	
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
arithmetic mean	43.66		
standard deviation	± 28.67	-	
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
median	40.00		
full range (min-max)	0.5 to 176.0	-	
Height Units: cm			
arithmetic mean	169.19		
standard deviation	± 8.83	-	
Height Units: cm			
median	170.00		
full range (min-max)	143.0 to 191.0	-	
Weight Units: kg			
arithmetic mean	74.20		
standard deviation	± 16.47	-	
Weight Units: kg			
median	72.00		
full range (min-max)	35.8 to 139.1	-	
Body Surface Area Units: m2			
arithmetic mean	1.849		
standard deviation	± 0.229	-	
Body Surface Area Units: m2			
median	1.840		
full range (min-max)	1.23 to 2.54	-	
Body Mass Index Units: kg/m2			
arithmetic mean	25.82		
standard deviation	± 4.94	-	
Body Mass Index			

Units: kg/m2			
median	25.45		
full range (min-max)	14.8 to 43.9	-	

Subject analysis sets

Subject analysis set title	ITT Analysis Set - Part 2 - Group A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Analysis Set was defined as all subjects randomized in Part 2 of the study, as assigned to treatment. The ITT population was the primary population for the analysis of OS and was also used to evaluate all secondary efficacy endpoints and subject characteristics.

Subject analysis set title	ITT Analysis Set - Part 2 - Group B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Analysis Set was defined as all subjects randomized in Part 2 of the study, as assigned to treatment. The ITT population was the primary population for the analysis of OS and was also used to evaluate all secondary efficacy endpoints and subject characteristics.

Subject analysis set title	ITT Analysis Set - Part 2 - Group C
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Analysis Set was defined as all subjects randomized in Part 2 of the study, as assigned to treatment. The ITT population was the primary population for the analysis of OS and was also used to evaluate all secondary efficacy endpoints and subject characteristics.

Subject analysis set title	Safety Analysis Set - Part 1
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

Subject analysis set title	Safety Analysis Set - Part 2 - Group A
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

Subject analysis set title	Safety Analysis Set - Part 2 - Group B
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

Subject analysis set title	Safety Analysis Set - Part 2 - Group C
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were

summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

Subject analysis set title	Efficacy Evaluable Analysis Set - Group A
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Efficacy Evaluable Analysis Set was defined as all subjects randomized in Part 2 of the study who had measurable disease at Baseline, received any amount of the assigned study treatment, and had at least one evaluable post-baseline tumor assessment. Subjects with measurable disease must have had at least one measurable lesion. Measurable lesions were defined (according to RECIST criteria [version 1.1]) as those that could 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 mITT population, the Efficacy Evaluable group was used to evaluate ORR and other tumor response endpoints.

Subject analysis set title	Efficacy Evaluable Analysis Set - Group B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Efficacy Evaluable Analysis Set was defined as all subjects randomized in Part 2 of the study who had measurable disease at Baseline, received any amount of the assigned study treatment, and had at least one evaluable post-baseline tumor assessment. Subjects with measurable disease must have had at least one measurable lesion. Measurable lesions were defined (according to RECIST criteria [version 1.1]) as those that could 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 mITT population, the Efficacy Evaluable group was used to evaluate ORR and other tumor response endpoints.

Subject analysis set title	Efficacy Evaluable Analysis Set - Group C
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Efficacy Evaluable Analysis Set was defined as all subjects randomized in Part 2 of the study who had measurable disease at Baseline, received any amount of the assigned study treatment, and had at least one evaluable post-baseline tumor assessment. Subjects with measurable disease must have had at least one measurable lesion. Measurable lesions were defined (according to RECIST criteria [version 1.1]) as those that could 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 mITT population, the Efficacy Evaluable group was used to evaluate ORR and other tumor response endpoints.

Subject analysis set title	mITT Analysis Set - Part 2 - Group A
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-Treat (mITT) Analysis Set was defined as 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 was the primary population for the sensitivity analysis of OS and all secondary efficacy endpoints.

Subject analysis set title	mITT Analysis Set - Part 2 - Group B
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-Treat (mITT) Analysis Set was defined as 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 was the primary population for the sensitivity analysis of OS and all secondary efficacy endpoints.

Subject analysis set title	mITT Analysis Set - Part 2 - Group C
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-Treat (mITT) Analysis Set was defined as 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 was the primary population for the sensitivity analysis of OS and all secondary efficacy endpoints.

Subject analysis set title	Per Protocol Population Analysis Set - Group A
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Population was defined as all subjects randomized in Part 2 of the study who satisfied 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, 4, 5 and did not meet exclusion criterion 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 was used for sensitivity analysis of the primary efficacy endpoint.

Subject analysis set title	Per Protocol Population Analysis Set - Group B
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Population was defined as all subjects randomized in Part 2 of the study who satisfied 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, 4, 5 and did not meet exclusion criterion 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 was used for sensitivity analysis of the primary efficacy endpoint.

Subject analysis set title	Per Protocol Population Analysis Set - Group C
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Population was defined as all subjects randomized in Part 2 of the study who satisfied 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, 4, 5 and did not meet exclusion criterion 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 was used for sensitivity analysis of the primary efficacy endpoint.

Reporting group values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C
Number of subjects	190	187	94
Age categorical Units: Subjects			
<65 years	123	117	54
≥65 years	67	70	40
Age continuous Units: years			
arithmetic mean	61.5	61.3	62.5
standard deviation	± 9.0	± 8.7	± 8.4
Gender categorical Units: Subjects			
Female	43	45	26
Male	147	142	68
Race Units: Subjects			
White	106	113	54
Black or African American	2	1	3
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	34	28	18
Multiple	1	0	0
Other	2	1	0
Unknown	45	44	19
Ethnicity Units: Subjects			
Hispanic or Latino	2	5	4

Not Hispanic or Latino	142	137	72
Unknown	46	45	18
ECOG Performance Status			
Baseline was defined as the last measurement obtained prior to first dose for Part 1 subjects or randomization for Part 2 subjects. ECOG Performance Status was used as a measure of how the disease impacted the patient's daily living abilities with eligible grading levels defined as follows: 0 = Fully active, able to carry on all pre-disease performance without restriction 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.			
Units: Subjects			
Grade 0	39	36	17
Grade 1	148	147	71
Missing	4	3	6
Region			
North America includes United States, Canada. Western Europe includes Spain, France, United Kingdom, Italy. Central/Eastern Europe includes Bulgaria, Georgia, Hungary, Lithuania, Poland, Slovakia. Asia-Pacific includes Australia, Taiwan, Thailand, South Korea, Hong Kong, India, Philippines, Malaysia			
Units: Subjects			
North America	32	31	16
Western Europe	52	46	22
Central/Eastern Europe	24	34	22
Russia & Ukraine	43	49	18
Asia-Pacific	39	27	16
Tobacco Use Units: Subjects			
No	12	22	12
Yes	178	165	82
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
arithmetic mean	44.80	43.35	41.86
standard deviation	± 31.96	± 26.81	± 24.77
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
median	38.50	40.00	38.50
full range (min-max)	3.6 to 176.0	0.5 to 150.0	5.0 to 141.0
Height Units: cm			
arithmetic mean	170.21	168.55	168.37
standard deviation	± 8.56	± 8.96	± 8.97
Height Units: cm			
median	171.00	169.00	170.0
full range (min-max)	150.8 to 191.0	143.0 to 190.0	145.0 to 187.0
Weight Units: kg			
arithmetic mean	75.42	73.72	72.70
standard deviation	± 16.27	± 16.58	± 16.63
Weight Units: kg			

median	72.50	73.70	70.25
full range (min-max)	38.0 to 127.0	35.8 to 132.9	43.0 to 139.1
Body Surface Area Units: m2			
arithmetic mean	1.870	1.840	1.826
standard deviation	± 0.223	± 0.233	± 0.231
Body Surface Area Units: m2			
median	25.66	25.43	25.16
full range (min-max)	14.8 to 43.4	16.3 to 42.0	16.7 to 43.9
Body Mass Index Units: kg/m2			
arithmetic mean	25.95	25.84	25.54
standard deviation	± 4.91	± 5.01	± 4.89
Body Mass Index Units: kg/m2			
median	25.66	25.43	25.16
full range (min-max)	14.8 to 43.4	16.3 to 42.0	16.7 to 43.9

Reporting group values	Safety Analysis Set - Part 1	Safety Analysis Set - Part 2 - Group A	Safety Analysis Set - Part 2 - Group B
Number of subjects	12	187	183
Age categorical Units: Subjects			
<65 years	2	120	115
≥65 years	10	67	68
Age continuous Units: years			
arithmetic mean	67.9	61.6	61.2
standard deviation	± 8.8	± 8.9	± 8.6
Gender categorical Units: Subjects			
Female	4	42	44
Male	8	145	139
Race Units: Subjects			
White	4	103	110
Black or African American	0	2	1
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	0	34	28
Multiple	0	1	0
Other	0	2	1
Unknown	8	45	43
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	5
Not Hispanic or Latino	4	139	134
Unknown	8	46	44
ECOG Performance Status			
Baseline was defined as the last measurement obtained prior to first dose for Part 1 subjects or randomization for Part 2 subjects.			

ECOG Performance Status was used as a measure of how the disease impacted the patient's daily living abilities with eligible grading levels defined as follows: 0 = Fully active, able to carry on all pre-disease performance without restriction 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.			
Units: Subjects			
Grade 0	3	39	36
Grade 1	9	148	147
Missing	0	0	0
Region			
North America includes United States, Canada. Western Europe includes Spain, France, United Kingdom, Italy. Central/Eastern Europe includes Bulgaria, Georgia, Hungary, Lithuania, Poland, Slovakia. Asia-Pacific includes Australia, Taiwan, Thailand, South Korea, Hong Kong, India, Philippines, Malaysia			
Units: Subjects			
North America	4	29	31
Western Europe	8	52	44
Central/Eastern Europe		24	32
Russia & Ukraine		43	49
Asia-Pacific		39	27
Tobacco Use Units: Subjects			
No	0	12	22
Yes	12	175	161
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
arithmetic mean	52.75	45.07	43.25
standard deviation	± 30.15	± 32.11	± 26.90
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
median	49.50	39.00	40.00
full range (min-max)	10.0 to 122.0	3.6 to 176.0	0.5 to 150.0
Height Units: cm			
arithmetic mean	170.59	170.16	168.39
standard deviation	± 10.20	± 8.53	± 8.95
Height Units: cm			
median	171.30	171.00	169.00
full range (min-max)	153.0 to 187.0	150.8 to 191.0	143.0 to 190.0
Weight Units: kg			
arithmetic mean	77.72	75.18	73.82
standard deviation	± 18.34	± 16.09	± 16.62
Weight Units: kg			
median	82.50	72.00	73.70
full range (min-max)	50.5 to 101.0	38.0 to 127.0	35.8 to 132.9
Body Surface Area Units: m2			

arithmetic mean	1.895	1.867	1.840
standard deviation	± 0.269	± 0.222	± 0.233
Body Surface Area			
Units: m2			
median	1.990	1.850	1.845
full range (min-max)	1.50 to 2.21	1.30 to 2.54	1.23 to 2.48
Body Mass Index			
Units: kg/m2			
arithmetic mean	26.40	25.89	25.92
standard deviation	± 4.42	± 4.89	± 5.0
Body Mass Index			
Units: kg/m2			
median	26.55	25.56	25.50
full range (min-max)	19.1 to 32.6	14.8 to 43.4	16.3 to 42.0

Reporting group values	Safety Analysis Set - Part 2 - Group C	Efficacy Evaluable Analysis Set - Group A	Efficacy Evaluable Analysis Set - Group B
Number of subjects	88	157	164
Age categorical			
Units: Subjects			
<65 years	51		
≥65 years	37		
Age continuous			
Units: years			
arithmetic mean	62.2		
standard deviation	± 8.3	±	±
Gender categorical			
Units: Subjects			
Female	24		
Male	64		
Race			
Units: Subjects			
White	52		
Black or African American	2		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Asian	16		
Multiple	0		
Other	0		
Unknown	18		
Ethnicity			
Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	67		
Unknown	17		
ECOG Performance Status			

Baseline was defined as the last measurement obtained prior to first dose for Part 1 subjects or randomization for Part 2 subjects.
ECOG Performance Status was used as a measure of how the disease impacted the patient's daily living abilities with eligible grading levels defined as follows:
0 = Fully active, able to carry on all pre-disease performance without restriction
1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or

sedentary nature e.g. light house work, office work.			
Units: Subjects			
Grade 0	17		
Grade 1	71		
Missing	0		
Region			
North America includes United States, Canada. Western Europe includes Spain, France, United Kingdom, Italy. Central/Eastern Europe includes Bulgaria, Georgia, Hungary, Lithuania, Poland, Slovakia. Asia-Pacific includes Australia, Taiwan, Thailand, South Korea, Hong Kong, India, Philippines, Malaysia			
Units: Subjects			
North America	15		
Western Europe	20		
Central/Eastern Europe	21		
Russia & Ukraine	18		
Asia-Pacific	14		
Tobacco Use Units: Subjects			
No	10		
Yes	78		
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
arithmetic mean	41.31		
standard deviation	± 25.04	±	±
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
median	35.50		
full range (min-max)	5.0 to 141.0		
Height Units: cm			
arithmetic mean	168.59		
standard deviation	± 8.72	±	±
Height Units: cm			
median	170.00		
full range (min-max)	149.0 to 187.0		
Weight Units: kg			
arithmetic mean	73.10		
standard deviation	± 16.77	±	±
Weight Units: kg			
median	69.65		
full range (min-max)	43.0 to 139.1		
Body Surface Area Units: m2			
arithmetic mean	1.833		
standard deviation	± 0.230	±	±
Body Surface Area			

Units: m2			
median	1.805		
full range (min-max)	1.35 to 2.51		
Body Mass Index			
Units: kg/m2			
arithmetic mean	25.85		
standard deviation	± 4.93	±	±
Body Mass Index			
Units: kg/m2			
median	25.16		
full range (min-max)	16.7 to 43.9		

Reporting group values	Efficacy Evaluable Analysis Set - Group C	mITT Analysis Set - Part 2 - Group A	mITT Analysis Set - Part 2 - Group B
Number of subjects	80	187	183
Age categorical			
Units: Subjects			
<65 years			
≥65 years			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			
Race			
Units: Subjects			
White			
Black or African American			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Asian			
Multiple			
Other			
Unknown			
Ethnicity			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown			
ECOG Performance Status			
Baseline was defined as the last measurement obtained prior to first dose for Part 1 subjects or randomization for Part 2 subjects. ECOG Performance Status was used as a measure of how the disease impacted the patient's daily living abilities with eligible grading levels defined as follows: 0 = Fully active, able to carry on all pre-disease performance without restriction 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.			
Units: Subjects			
Grade 0			

Grade 1 Missing			
Region			
North America includes United States, Canada. Western Europe includes Spain, France, United Kingdom, Italy. Central/Eastern Europe includes Bulgaria, Georgia, Hungary, Lithuania, Poland, Slovakia. Asia-Pacific includes Australia, Taiwan, Thailand, South Korea, Hong Kong, India, Philippines, Malaysia			
Units: Subjects			
North America Western Europe Central/Eastern Europe Russia & Ukraine Asia-Pacific			
Tobacco Use Units: Subjects			
No Yes			
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years arithmetic mean standard deviation	±	±	±
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years median full range (min-max)			
Height Units: cm arithmetic mean standard deviation	±	±	±
Height Units: cm median full range (min-max)			
Weight Units: kg arithmetic mean standard deviation	±	±	±
Weight Units: kg median full range (min-max)			
Body Surface Area Units: m2 arithmetic mean standard deviation	±	±	±
Body Surface Area Units: m2 median full range (min-max)			

Body Mass Index Units: kg/m2 arithmetic mean standard deviation	±	±	±
Body Mass Index Units: kg/m2 median full range (min-max)			

Reporting group values	mITT Analysis Set - Part 2 - Group C	Per Protocol Population Analysis Set - Group A	Per Protocol Population Analysis Set - Group B
Number of subjects	88	153	155
Age categorical Units: Subjects			
<65 years ≥65 years			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
Race Units: Subjects			
White Black or African American American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Asian Multiple Other Unknown			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown			
ECOG Performance Status			
Baseline was defined as the last measurement obtained prior to first dose for Part 1 subjects or randomization for Part 2 subjects. ECOG Performance Status was used as a measure of how the disease impacted the patient's daily living abilities with eligible grading levels defined as follows: 0 = Fully active, able to carry on all pre-disease performance without restriction 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.			
Units: Subjects			
Grade 0 Grade 1 Missing			
Region			

North America includes United States, Canada. Western Europe includes Spain, France, United Kingdom, Italy. Central/Eastern Europe includes Bulgaria, Georgia, Hungary, Lithuania, Poland, Slovakia. Asia-Pacific includes Australia, Taiwan, Thailand, South Korea, Hong Kong, India, Philippines, Malaysia			
Units: Subjects			
North America			
Western Europe			
Central/Eastern Europe			
Russia & Ukraine			
Asia-Pacific			
Tobacco Use			
Units: Subjects			
No			
Yes			
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
arithmetic mean			
standard deviation	±	±	±
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years			
median			
full range (min-max)			
Height			
Units: cm			
arithmetic mean			
standard deviation	±	±	±
Height			
Units: cm			
median			
full range (min-max)			
Weight			
Units: kg			
arithmetic mean			
standard deviation	±	±	±
Weight			
Units: kg			
median			
full range (min-max)			
Body Surface Area			
Units: m2			
arithmetic mean			
standard deviation	±	±	±
Body Surface Area			
Units: m2			
median			
full range (min-max)			
Body Mass Index			
Units: kg/m2			
arithmetic mean			

standard deviation	±	±	±
Body Mass Index Units: kg/m2 median full range (min-max)			

Reporting group values	Per Protocol Population Analysis Set - Group C		
Number of subjects	80		
Age categorical Units: Subjects			
<65 years ≥65 years			
Age continuous Units: years arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Female Male			
Race Units: Subjects			
White Black or African American American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Asian Multiple Other Unknown			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown			
ECOG Performance Status			
Baseline was defined as the last measurement obtained prior to first dose for Part 1 subjects or randomization for Part 2 subjects. ECOG Performance Status was used as a measure of how the disease impacted the patient's daily living abilities with eligible grading levels defined as follows: 0 = Fully active, able to carry on all pre-disease performance without restriction 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.			
Units: Subjects			
Grade 0 Grade 1 Missing			
Region			
North America includes United States, Canada. Western Europe includes Spain, France, United Kingdom, Italy. Central/Eastern Europe includes Bulgaria, Georgia, Hungary, Lithuania, Poland, Slovakia. Asia-Pacific includes Australia, Taiwan, Thailand, South Korea, Hong Kong, India, Philippines, Malaysia			

Units: Subjects			
North America Western Europe Central/Eastern Europe Russia & Ukraine Asia-Pacific			
Tobacco Use Units: Subjects			
No Yes			
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years arithmetic mean standard deviation	±		
Tobacco Use			
Number of Pack Years was defined as number of packs per day x number of years using cigarettes/chewing tobacco			
Units: Years median full range (min-max)			
Height Units: cm arithmetic mean standard deviation	±		
Height Units: cm median full range (min-max)			
Weight Units: kg arithmetic mean standard deviation	±		
Weight Units: kg median full range (min-max)			
Body Surface Area Units: m2 arithmetic mean standard deviation	±		
Body Surface Area Units: m2 median full range (min-max)			
Body Mass Index Units: kg/m2 arithmetic mean standard deviation	±		
Body Mass Index Units: kg/m2			

median full range (min-max)			

End points

End points reporting groups

Reporting group title	Part 1 - Dinutuximab + Irinotecan

Reporting group description:

The lead-in phase of the study (referred to as Part 1) had an enrollment target of approximately 10 subjects. In Part 1, dinutuximab was to be administered at increasing doses, as tolerated, together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1 of each 21-day cycle. Subjects were to receive dinutuximab at a starting dose of 10 mg/m2 IV, with increases administered in 2 mg/m2 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 was adequately managed and the drug was otherwise tolerated. The maximum permitted dose of dinutuximab was 17.5 mg/m2 (If this dose was reached, the last dose increment would be 1.5 mg/m2). The dinutuximab dose was to be decreased in 2 mg/m2 decrements per cycle depending on the toxicity observed to as low as 8 mg/m2. If a dose decrease from 17.5 mg/m2 was required, the initial dose reduction was to be 1.5 mg/m2 (and 2 mg/m2 for any subsequent decrements)

Reporting group title	Part 2 - Irinotecan (Group A)

Reporting group description:

In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). Subjects randomized to Group A were to receive irinotecan at a dose of 350 mg/m2 on Day 1 of each cycle.

Reporting group title	Part 2 - Dinutuximab + Irinotecan (Group B)

Reporting group description:

In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). Subjects randomized to Group B were to receive dinutuximab on Day 1 of each cycle beginning with a starting dose of 10 mg/m2 IV or a dose recommended by the SRC, and irinotecan at a dose of 350 mg/m2 on Day 1 of each cycle. Dose escalation and de-escalation for dinutuximab was to occur as in Part 1. The maximum dose of dinutuximab that may have been administered was 17.5 mg/m2 (If this dose was reached, the last dose increment would be 1.5 mg/m2. If the dose was reduced from 17.5 mg/m2, the initial dose decrement would be 1.5 mg/m2 to 16 mg/m2.)

Reporting group title	Part 2 - Topotecan (Group C)

Reporting group description:

In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). No crossover between groups was allowed because OS was the primary endpoint. Subjects randomized to Group C were to receive topotecan 1.5 mg/m2 IV for 5 consecutive days of each cycle.

Subject analysis set title	ITT Analysis Set - Part 2 - Group A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Analysis Set was defined as all subjects randomized in Part 2 of the study, as assigned to treatment. The ITT population was the primary population for the analysis of OS and was also used to evaluate all secondary efficacy endpoints and subject characteristics.

Subject analysis set title	ITT Analysis Set - Part 2 - Group B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Analysis Set was defined as all subjects randomized in Part 2 of the study, as assigned to treatment. The ITT population was the primary population for the analysis of OS and was also used to evaluate all secondary efficacy endpoints and subject characteristics.

Subject analysis set title	ITT Analysis Set - Part 2 - Group C
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Analysis Set was defined as all subjects randomized in Part 2 of the study, as assigned to treatment. The ITT population was the primary population for the analysis of OS and was also used to evaluate all secondary efficacy endpoints and subject characteristics.

Subject analysis set title	Safety Analysis Set - Part 1
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

Subject analysis set title	Safety Analysis Set - Part 2 - Group A
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

Subject analysis set title	Safety Analysis Set - Part 2 - Group B
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

Subject analysis set title	Safety Analysis Set - Part 2 - Group C
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

Subject analysis set title	Efficacy Evaluable Analysis Set - Group A
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Efficacy Evaluable Analysis Set was defined as all subjects randomized in Part 2 of the study who had measurable disease at Baseline, received any amount of the assigned study treatment, and had at least one evaluable post-baseline tumor assessment. Subjects with measurable disease must have had at least one measurable lesion. Measurable lesions were defined (according to RECIST criteria [version 1.1]) as those that could 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 mITT population, the Efficacy Evaluable group was used to evaluate ORR and other tumor response endpoints.

Subject analysis set title	Efficacy Evaluable Analysis Set - Group B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Efficacy Evaluable Analysis Set was defined as all subjects randomized in Part 2 of the study who had measurable disease at Baseline, received any amount of the assigned study treatment, and had at least one evaluable post-baseline tumor assessment. Subjects with measurable disease must have had at least one measurable lesion. Measurable lesions were defined (according to RECIST criteria [version 1.1]) as those that could 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 mITT population, the Efficacy Evaluable group was used to evaluate ORR and other tumor response endpoints.

Subject analysis set title	Efficacy Evaluable Analysis Set - Group C
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Efficacy Evaluable Analysis Set was defined as all subjects randomized in Part 2 of the study who had measurable disease at Baseline, received any amount of the assigned study treatment, and had at least one evaluable post-baseline tumor assessment. Subjects with measurable disease must have had

at least one measurable lesion. Measurable lesions were defined (according to RECIST criteria [version 1.1]) as those that could 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 mITT population, the Efficacy Evaluable group was used to evaluate ORR and other tumor response endpoints.

Subject analysis set title	mITT Analysis Set - Part 2 - Group A
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-Treat (mITT) Analysis Set was defined as 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 was the primary population for the sensitivity analysis of OS and all secondary efficacy endpoints.

Subject analysis set title	mITT Analysis Set - Part 2 - Group B
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-Treat (mITT) Analysis Set was defined as 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 was the primary population for the sensitivity analysis of OS and all secondary efficacy endpoints.

Subject analysis set title	mITT Analysis Set - Part 2 - Group C
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-Treat (mITT) Analysis Set was defined as 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 was the primary population for the sensitivity analysis of OS and all secondary efficacy endpoints.

Subject analysis set title	Per Protocol Population Analysis Set - Group A
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Population was defined as all subjects randomized in Part 2 of the study who satisfied 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, 4, 5 and did not meet exclusion criterion 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 was used for sensitivity analysis of the primary efficacy endpoint.

Subject analysis set title	Per Protocol Population Analysis Set - Group B
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Population was defined as all subjects randomized in Part 2 of the study who satisfied 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, 4, 5 and did not meet exclusion criterion 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 was used for sensitivity analysis of the primary efficacy endpoint.

Subject analysis set title	Per Protocol Population Analysis Set - Group C
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Population was defined as all subjects randomized in Part 2 of the study who satisfied 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, 4, 5 and did not meet exclusion criterion 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 was used for sensitivity analysis of the primary efficacy endpoint.

Primary: Overall Survival (OS) - ITT Analysis Set

End point title	Overall Survival (OS) - ITT Analysis Set

End point description:

The primary efficacy endpoint was OS, defined as the duration of time from the date of randomization to the date of the subject's death from any cause. The primary objective of the study was 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.

End point type	Primary

End point timeframe:

Overall survival was calculated as (date of death – date of randomization) + 1. Subjects who were alive or permanently lost to follow-up at the cut-off date for the analysis were to be censored at the last date the subject was known to be alive.

End point values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	190	187	94	
Units: months				
median (confidence interval 95%)				
Kaplan-Meier Estimate of OS - 25th Quartile	3.6 (2.8 to 4.3)	3.5 (2.9 to 4.1)	3.8 (2.4 to 5.4)	
Kaplan-Meier Estimate of OS - Median	7.0 (5.6 to 8.9)	6.9 (6.0 to 7.6)	7.4 (6.1 to 9.3)	
Kaplan-Meier Estimate of OS - 75th Quartile	13.1 (10.8 to 16.2)	10.9 (9.7 to 13.9)	12.8 (10.0 to 14.4)	
Rate (%) Surviving for at least 6 months	54.5 (47.1 to 61.3)	57.8 (50.4 to 64.6)	61.7 (51.1 to 70.7)	
Rate (%) Surviving for at least 12 months	29.1 (22.8 to 35.8)	22.6 (16.8 to 28.9)	27.7 (19.1 to 36.9)	
Rate (%) Surviving for at least 18 months	15.8 (10.8 to 21.7)	12.1 (7.7 to 17.6)	10.4 (5.1 to 18.1)	
Rate (%) Surviving for at least 24 months	9.0 (4.4 to 15.4)	12.1 (7.7 to 17.6)	4.5 (0.8 to 13.5)	

Statistical analyses

Statistical analysis title	Hazard Ratio vs Irinotecan

Statistical analysis description:

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

Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group A
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.3132 [2]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.4

Notes:

[1] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)
[2] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Statistical analysis title	Hazard Ratio vs Topotecan

Statistical analysis description:

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

Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group C
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.7233 [4]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.37

Notes:

[3] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)
[4] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Primary: Overall Survival (OS) - mITT Analysis Set

End point title	Overall Survival (OS) - mITT Analysis Set

End point description:

The primary efficacy endpoint was OS, defined as the duration of time from the date of randomization to the date of the subject's death from any cause. The primary objective of the study was 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.

End point type	Primary

End point timeframe:

Overall survival was calculated as (date of death – date of randomization) + 1. Subjects who were alive or permanently lost to follow-up at the cut-off date for the analysis were to be censored at the last date the subject was known to be alive.

End point values	mITT Analysis Set - Part 2 - Group A	mITT Analysis Set - Part 2 - Group B	mITT Analysis Set - Part 2 - Group C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	187	183	88	
Units: months				
number (confidence interval 95%)				
Kaplan-Meier Estimate of OS - 25th Quartile	3.7 (2.8 to 4.4)	3.6 (3.1 to 4.4)	4.1 (2.4 to 5.5)	
Kaplan-Meier Estimate of OS - Median	7.0 (5.6 to 8.9)	7.0 (6.1 to 7.7)	7.4 (6.1 to 9.3)	
Kaplan-Meier Estimate of OS - 75th Quartile	13.1 (10.8 to 16.2)	10.9 (9.9 to 14.0)	13.2 (10.0 to 15.6)	
Rate Surviving for at least 6 months	54.8 (47.4 to 61.7)	59.1 (51.6 to 65.9)	62.5 (51.5 to 71.7)	
Rate Surviving for at least 12 months	29.1 (22.7 to 35.7)	23.1 (17.2 to 29.5)	29.5 (20.4 to 39.2)	
Rate Surviving for at least 18 months	15.5 (10.5 to 21.4)	12.4 (7.9 to 18.0)	11.2 (5.4 to 19.2)	
Rate Surviving for at least 24 months	8.5 (4.0 to 14.9)	12.4 (7.9 to 18.0)	4.8 (0.9 to 14.3)	

Statistical analyses

Statistical analysis title	Hazard Ratio vs Irinotecan

Statistical analysis description:

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

Comparison groups	mITT Analysis Set - Part 2 - Group A v mITT Analysis Set - Part 2 - Group B
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.4507 [6]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.36

Notes:

[5] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)
[6] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Statistical analysis title	Hazard Ratio vs Topotecan

Statistical analysis description:

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

Comparison groups	mITT Analysis Set - Part 2 - Group B v mITT Analysis Set - Part 2 - Group C
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.681 [8]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.39

Notes:

[7] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)
[8] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Primary: Overall Survival (OS) - Sensitivity Analysis of Per-Protocol Population

End point title	Overall Survival (OS) - Sensitivity Analysis of Per-Protocol Population

End point description:

Protocol-compliant Subjects who received ≥80% Assigned Dose. The primary efficacy endpoint was OS, defined as the duration of time from the date of randomization to the date of the subject's death from any cause. The primary objective of the study was 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.

End point type	Primary

End point timeframe:

Overall survival was calculated as (date of death – date of randomization) + 1. Subjects who were alive or permanently lost to follow-up at the cut-off date for the analysis were to be censored at the last date the subject was known to be alive.

End point values	Per Protocol Population Analysis Set - Group A	Per Protocol Population Analysis Set - Group B	Per Protocol Population Analysis Set - Group C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	153	155	80	
Units: months				
number (confidence interval 95%)				
Kaplan-Meier Estimate of OS - 25th Quartile	4.4 (3.6 to 5.3)	4.1 (3.4 to 5.3)	4.7 (2.7 to 6.1)	
Kaplan-Meier Estimate of OS - Median	8.3 (6.4 to 9.5)	7.6 (6.6 to 8.4)	8.4 (6.4 to 9.7)	
Kaplan-Meier Estimate of OS - 75th Quartile	13.7 (11.9 to 16.6)	12.1 (10.3 to 15.5)	13.6 (11.3 to 16.0)	
Rate Surviving for at least 6 months	59.5 (51.3 to 66.8)	63.5 (55.4 to 70.6)	66.3 (54.8 to 75.5)	
Rate Surviving for at least 12 months	31.7 (24.5 to 39.2)	25.8 (19.1 to 33.0)	32.5 (22.6 to 42.8)	
Rate Surviving for at least 18 months	16.4 (10.8 to 23.1)	14.7 (9.4 to 21.1)	12.3 (6.0 to 21.0)	

Rate Surviving for at least 24 months	8.6 (3.9 to 15.7)	14.7 (9.4 to 21.1)	5.3 (0.9 to 15.6)	

Statistical analyses

Statistical analysis title	Hazard Ratio vs Irinotecan

Statistical analysis description:

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

Comparison groups	Per Protocol Population Analysis Set - Group A v Per Protocol Population Analysis Set - Group B
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.5514 [10]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.38

Notes:

[9] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

[10] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Statistical analysis title	Hazard Ratio vs Topotecan

Statistical analysis description:

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

Comparison groups	Per Protocol Population Analysis Set - Group B v Per Protocol Population Analysis Set - Group C
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.8294 [12]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.38

Notes:

[11] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)
[12] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Primary: Overall Survival (OS) - Sensitivity Analysis Consider Subjects Lost to Follow-Up as Deaths at Last Follow-up Date

End point title	Overall Survival (OS) - Sensitivity Analysis Consider Subjects Lost to Follow-Up as Deaths at Last Follow-up Date

End point description:

Sensitivity analysis considering subjects lost to follow-up as deaths at last follow-up date inthe ITT Analysis Set. The primary efficacy endpoint was OS, defined as the duration of time from the date of randomization to the date of the subject's death from any cause. The primary objective of the study was 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.

End point type	Primary

End point timeframe:

Overall survival was calculated as (date of death – date of randomization) + 1. Subjects who were alive or permanently lost to follow-up at the cut-off date for the analysis were to be censored at the last date the subject was known to be alive.

End point values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	190	187	94	
Units: months				
number (confidence interval 95%)				
Kaplan-Meier Estimate of OS - 25th Quartile	3.6 (2.8 to 4.3)	3.5 (2.9 to 4.1)	3.8 (2.4 to 5.4)	
Kaplan-Meier Estimate of OS - Median	7.0 (5.6 to 8.9)	6.9 (6.0 to 7.6)	7.4 (6.1 to 9.3)	
Kaplan-Meier Estimate of OS - 75th Quartile	12.9 (10.8 to 15.7)	10.9 (9.7 to 13.9)	12.8 (10.0 to 14.4)	
Rate for Survival for at least 6 months	54.5 (47.1 to 61.3)	57.8 (50.4 to 64.6)	61.7 (51.1 to 70.7)	
Rate for Survival for at least 12 months	29.1 (22.8 to 35.8)	22.6 (16.8 to 28.9)	27.7 (19.1 to 36.9)	
Rate for Survival for at least 18 months	14.9 (10.0 to 20.6)	12.1 (7.7 to 17.6)	9.6 (4.6 to 16.9)	
Rate for Survival for at least 24 months	8.4 (4.2 to 14.6)	12.1 (7.7 to 17.6)	4.1 (0.7 to 12.6)	

Statistical analyses

Statistical analysis title	Hazard Ratio vs Irinotecan

Statistical analysis description:

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

Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group A

Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.3569 [14]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.38

Notes:

[13] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)
[14] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Statistical analysis title	Hazard Ratio vs Topotecan

Statistical analysis description:

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

Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group C
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.7848 [16]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.35

Notes:

[15] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)
[16] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Secondary: Progression Free Survival (PFS) - ITT Analysis Set

End point title	Progression Free Survival (PFS) - ITT Analysis Set

End point description:

PFS was evaluated using the stratified log-rank test, as described for OS, with specific conventions for censoring. PFS data were censored on the date of the last tumor assessment documenting absence of PD for subjects who 1) were given anti-tumor treatment other than the study treatment prior to observing objective tumor progression; 2) were removed from the study prior to documentation of objective tumor progression; 3) were ongoing and did not have objective tumor progression at the time of the analysis. Death or disease progression that occurred after more than one missed visit (i.e., 12 weeks) was censored on the date of the last tumor assessment prior to the first missed visit. Subjects with no post-baseline tumor assessments were censored on the date of randomization.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of first documentation of tumor progression or death from any cause, whichever occurred first.

End point values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	190	187	94	
Units: months				
number (confidence interval 95%)				
Kaplan-Meier Estimate of PFS - 25th Quartile	1.4 (1.4 to 1.7)	1.5 (1.4 to 1.8)	1.6 (1.4 to 2.5)	
Kaplan-Meier Estimate of PFS - Median	3.0 (2.7 to 4.2)	3.5 (2.8 to 4.2)	3.4 (2.8 to 4.2)	
Kaplan-Meier Estimate of PFS - 75th Quartile	5.7 (5.5 to 6.9)	6.2 (5.6 to 7.7)	6.1 (4.5 to 7.3)	
Percentage Alive and Progression Free at 6 months	25.8 (19.7 to 32.4)	29.5 (23.0 to 36.4)	29.5 (20.4 to 39.2)	
Percentage Alive and Progression Free at 12 months	5.2 (2.3 to 9.9)	9.4 (5.3 to 14.7)	5.3 (1.6 to 12.4)	
Percentage Alive and Progression Free at 18 months	3.9 (1.3 to 8.7)	5.1 (2.2 to 9.8)	5.3 (1.6 to 12.4)	
Percentage Alive and Progression Free at 24 months	3.9 (1.3 to 8.7)	3.1 (0.7 to 8.8)	5.3 (1.6 to 12.4)	

Statistical analyses

Statistical analysis title	Hazard Ratio vs Irinotecan

Statistical analysis description:

Progression-Free Survival was evaluated using the stratified log-rank test, as described for OS, with specific conventions for censoring.

Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group A
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.3482 [18]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.13

Notes:

[17] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

[18] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Statistical analysis title	Hazard Ratio vs Topotecan

Statistical analysis description:

Progression-Free Survival was evaluated using the stratified log-rank test, as described for OS, with specific conventions for censoring.

Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group C
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.9728 [20]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.31

Notes:

[19] - Based on Cox proportional hazards model, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).
[20] - Log-rank test, stratified by duration of response to prior platinum therapy (<3 months, >=3 months)

Secondary: Best Overall Response

End point title	Best Overall Response

End point description:

The number and percentage of subjects in each BOR category (i.e., CR, PR, SD, PD, and unevaluable) were summarized by treatment group. Subjects with unconfirmed CR or PR assessments were categorized separately. The table included 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 were classified as having SD if assessed as SD (or better) at least 6 weeks after first dose date.

End point type	Secondary

End point timeframe:

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 was sooner), taking into account any requirement for confirmation.

End point values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C	Efficacy Evaluable Analysis Set - Group A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190	187	94	157
Units: Number				
Complete Response (CR)	4	1	2	4
Complete Response Unconfirmed (CRu)	1	0	0	1
Partial Response (PR)	32	31	17	32
Partial Response Unconfirmed (PRu)	10	13	4	10
Stable Disease (SD)	65	81	41	61
Progressive Disease (PD)	46	41	18	45
Not Evaluable (NE)	4	1	0	4

End point values	Efficacy Evaluable Analysis Set - Group B	Efficacy Evaluable Analysis Set - Group C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	164	80		
Units: Number				
Complete Response (CR)	1	2		
Complete Response Unconfirmed (CRu)	0	0		
Partial Response (PR)	31	17		
Partial Response Unconfirmed (PRu)	13	4		
Stable Disease (SD)	79	39		
Progressive Disease (PD)	39	18		
Not Evaluable (NE)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (Confirmed)

End point title	Overall Response Rate (Confirmed)

End point description:

Overall Response Rate was defined as the percentage of subjects with best overall response (BOR) of either CR or PR. Subjects with no post-baseline results were considered non-responders. Overall Response Rate was calculated by treatment group for ITT and Efficacy Evaluable subjects. Both confirmed and unconfirmed CR/PR were tabulated. The rates were presented along with two-sided 95% exact CIs. The 95% CIs were 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 a small N.

End point type	Secondary

End point timeframe:

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 was sooner), taking into account any requirement for confirmation

End point values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C	Efficacy Evaluable Analysis Set - Group A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190	187	94	157
Units: Number				
number (confidence interval 95%)				
Number of Subjects with CR/PR	18.9 (13.6 to 25.3)	17.1 (12.0 to 23.3)	20.2 (12.6 to 29.8)	22.9 (16.6 to 30.3)

End point values	Efficacy Evaluable Analysis Set - Group B	Efficacy Evaluable Analysis Set - Group C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	164	80		
Units: Number				
number (confidence interval 95%)				
Number of Subjects with CR/PR	19.5 (13.7 to 26.4)	23.8 (14.9 to 34.6)		

Statistical analyses

Statistical analysis title	Odds Ratio vs Irinotecan - ITT Analysis Set
Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group A
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.5987 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.47

Notes:

[21] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1indicates an advantage for the dinutuximab combination treatment group.

[22] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months)

Statistical analysis title	Odds Ratio vs Topotecan - ITT Analysis Set
Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group C
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.5892 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.59

Notes:

[23] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1indicates an advantage for the dinutuximab combination treatment group.
[24] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months)

Statistical analysis title	Odds Ratio vs Irinotecan - Efficacy Evaluable Set
Comparison groups	Efficacy Evaluable Analysis Set - Group A v Efficacy Evaluable Analysis Set - Group B
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.4375 [26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.39

Notes:

[25] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1indicates an advantage for the dinutuximab combination treatment group.
[26] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months)

Statistical analysis title	Odds Ratio vs Topotecan - Efficacy Evaluable Set
Comparison groups	Efficacy Evaluable Analysis Set - Group B v Efficacy Evaluable Analysis Set - Group C
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.477 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.52

Notes:

[27] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1indicates an advantage for the dinutuximab combination treatment group.
[28] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months)

Secondary: Overall Response Rate (Unconfirmed + Confirmed)

End point title	Overall Response Rate (Unconfirmed + Confirmed)

End point description:

Overall Response Rate was defined as the percentage of subjects with best overall response (BOR) of either CR or PR. Subjects with no post-baseline results were considered non-responders. Overall Response Rate was calculated by treatment group for ITT and Efficacy Evaluable subjects. Both confirmed and unconfirmed CR/PR were tabulated. The rates were presented along with two-sided 95% exact CIs. The 95% CIs were 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 a small N.

End point type	Secondary

End point timeframe:

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 was sooner), taking into account any requirement for confirmation.

End point values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C	Efficacy Evaluable Analysis Set - Group A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190	187	94	157
Units: Number				
number (confidence interval 95%)				
Number of Subjects with CR/Cru/PR/PRu	24.7 (18.8 to 31.5)	24.1 (18.1 to 30.8)	24.5 (16.2 to 34.4)	29.9 (22.9 to 37.8)

End point values	Efficacy Evaluable Analysis Set - Group B	Efficacy Evaluable Analysis Set - Group C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	164	80		
Units: Number				
number (confidence interval 95%)				
Number of Subjects with CR/Cru/PR/PRu	27.4 (20.8 to 34.9)	28.8 (19.2 to 40.0)		

Statistical analyses

Statistical analysis title	Odds Ratio vs Irinotecan - ITT Analysis Set
Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group A

Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.8043 [30]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.52

Notes:

[29] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1 indicates an advantage for the dinutuximab combination treatment group.

[30] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

Statistical analysis title	Odds Ratio vs Topotecan - ITT Analysis Set
Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group C
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.9231 [32]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.87

Notes:

[31] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1 indicates an advantage for the dinutuximab combination treatment group.

[32] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

Statistical analysis title	Odds Ratio vs Irinotecan - Efficacy Evaluable Set
Comparison groups	Efficacy Evaluable Analysis Set - Group A v Efficacy Evaluable Analysis Set - Group B
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.5883 [34]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.43

Notes:

[33] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1 indicates an advantage for the dinutuximab combination treatment group.

[34] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

Statistical analysis title	Odds Ratio vs Topotecan - Efficacy Evaluable Set
Comparison groups	Efficacy Evaluable Analysis Set - Group B v Efficacy Evaluable Analysis Set - Group C
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.9074 [36]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.79

Notes:

[35] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1 indicates an advantage for the dinutuximab combination treatment group.

[36] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

Secondary: Clinical Benefit Rate

End point title	Clinical Benefit Rate

End point description:

The CBR was defined as the percentage of subjects with either a CR or PR, or SD (confirmed and unconfirmed). Subjects with no post-baseline tumor assessments were considered to have achieved no clinical benefit. Subjects were classified as having SD if assessed as SD (or better) at least 6 weeks after first dose date.

End point type	Secondary

End point timeframe:

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 was sooner), taking into account any requirement for confirmation.

End point values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C	Efficacy Evaluable Analysis Set - Group A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190	187	94	157
Units: Number				
number (confidence interval 95%)				
Number of Subjects with CR/CRu/PR/PRu/SD	58.9 (51.6 to 66.0)	67.4 (60.2 to 74.0)	68.1 (57.7 to 77.3)	68.8 (60.9 to 75.9)

End point values	Efficacy Evaluable Analysis Set - Group B	Efficacy Evaluable Analysis Set - Group C		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	164	80		
Units: Number				
number (confidence interval 95%)				
Number of Subjects with CR/CRu/PR/PRu/SD	75.6 (68.3 to 82.0)	77.5 (66.8 to 86.1)		

Statistical analyses

Statistical analysis title	Odds Ratio vs Irinotecan - ITT Analysis Set
Comparison groups	ITT Analysis Set - Part 2 - Group A v ITT Analysis Set - Part 2 - Group B
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.0989 [38]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	2.19

Notes:

[37] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1 indicates an advantage for the Dinutuximab combination treatment group.

[38] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

Statistical analysis title	Odds Ratio vs Topotecan - ITT Analysis Set
Comparison groups	ITT Analysis Set - Part 2 - Group B v ITT Analysis Set - Part 2 - Group C

Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.9605 [40]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.68

Notes:

[39] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1 indicates an advantage for the Dinutuximab combination treatment group.

[40] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

Statistical analysis title	Odds Ratio vs Irinotecan - Efficacy Evaluable Set
Comparison groups	Efficacy Evaluable Analysis Set - Group A v Efficacy Evaluable Analysis Set - Group B
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.1768 [42]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2.3

Notes:

[41] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1 indicates an advantage for the Dinutuximab combination treatment group.

[42] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

Statistical analysis title	Odds Ratio vs Topotecan - Efficacy Evaluable Set
Comparison groups	Efficacy Evaluable Analysis Set - Group B v Efficacy Evaluable Analysis Set - Group C
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.7719 [44]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.72

Notes:

[43] - Mantel-Haenszel estimate of the odds ratio, with stratification by duration of response to prior platinum therapy (<3 months, ≥3 months). An odds ratio >1 indicates an advantage for the Dinutuximab combination treatment group.

[44] - p-value based on Cochran Mantel-Haenszel chi-square test, stratified by duration of response to prior platinum therapy (<3 months, ≥3 months).

Other pre-specified: Time to Response

End point title	Time to Response

End point description:

The TTR was defined as the time interval between the date of randomization and the date of first documented CR or PR. Complete Response or PR required confirmation at least 4 weeks apart. Once confirmed, the first documented CR or PR was considered as the start of the response. Time to Response was descriptively summarized for subjects who responded.

End point type	Other pre-specified

End point timeframe:

From the date of randomization and the date of first documented CR or PR.

End point values	ITT Analysis Set - Part 2 - Group A	ITT Analysis Set - Part 2 - Group B	ITT Analysis Set - Part 2 - Group C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	190	187	94	
Units: weeks				
arithmetic mean (standard deviation)				
Mean	8.08 (± 4.63)	11.58 (± 10.28)	10.92 (± 8.78)	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for all enrolled subjects beginning with first dose of study medication.

Adverse event reporting additional description:

For AE reporting, the Investigator was to report the highest NCI-CTCAE version 4.03 grade if there was a difference in the reported value between contemporaneous local laboratory and central laboratory results. Serious adverse events (and AEs based on local regulations) were to be collected starting on the day of written informed consent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Safety Analysis Set - Part 1

Reporting group description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

The lead-in phase of the study (referred to as Part 1) had an enrollment target of approximately 10 subjects. In Part 1, dinutuximab was to be administered at increasing doses, as tolerated, together with irinotecan at a dose of 350 mg/m2 intravenously (IV) on Day 1 of each 21-day cycle.

Reporting group title	Safety Analysis Set - Part 2 - Group A

Reporting group description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).

In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). Subjects randomized to Group A were to receive irinotecan at a dose of 350 mg/m2 on Day 1 of each cycle.

Reporting group title	Safety Analysis Set - Part 2 - Group B

Reporting group description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or listing).
In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). Subjects randomized to Group B were to receive dinutuximab on Day 1 of each cycle beginning with a starting dose of 10 mg/m2 IV or a dose recommended by the SRC, and irinotecan at a dose of 350 mg/m2 on Day 1 of each cycle.

Reporting group title	Safety Analysis Set - Part 2 - Group C

Reporting group description:

The Safety Analysis Set was defined as all subjects who received at least one dose of any study medication (even a partial dose), grouped by actual treatment received. This set served 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 were summarized or listed separately for Part 1 and Part 2 (even when included within the same table or

listing).
In Part 2, approximately 460 additional subjects with relapsed or refractory SCLC were to be randomized in a 2:2:1 allocation (184/irinotecan group, 184/dinutuximab + irinotecan group, and 92/topotecan group). No crossover between groups was allowed because OS was the primary endpoint. Subjects randomized to Group C were to receive topotecan 1.5 mg/m2 IV for 5 consecutive days of each cycle.

Serious adverse events	Safety Analysis Set - Part 1	Safety Analysis Set - Part 2 - Group A	Safety Analysis Set - Part 2 - Group B
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)	76 / 187 (40.64%)	74 / 183 (40.44%)
number of deaths (all causes)	1	15	20
number of deaths resulting from adverse events	1	15	20
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Shock haemorrhagic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 187 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
General physical health deterioration			

subjects affected / exposed	0 / 12 (0.00%)	2 / 187 (1.07%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Sudden death			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 12 (8.33%)	2 / 187 (1.07%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 187 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 187 (0.53%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 2
Myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Acute coronary syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation	Additional description: Acute fibrillation		
subjects affected / exposed	1 / 12 (8.33%)	0 / 187 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	17 / 187 (9.09%)	8 / 183 (4.37%)
occurrences causally related to treatment / all	0 / 0	17 / 17	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 2
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	7 / 187 (3.74%)	7 / 183 (3.83%)
occurrences causally related to treatment / all	1 / 1	7 / 7	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 187 (1.07%)	4 / 183 (2.19%)
occurrences causally related to treatment / all	0 / 0	2 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	17 / 187 (9.09%)	8 / 183 (4.37%)
occurrences causally related to treatment / all	2 / 2	17 / 17	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 12 (8.33%)	3 / 187 (1.60%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 12 (8.33%)	9 / 187 (4.81%)	6 / 183 (3.28%)
occurrences causally related to treatment / all	1 / 1	9 / 9	6 / 6
deaths causally related to treatment / all	0 / 0	2 / 2	3 / 3
Sepsis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	2 / 2
Neutropenic sepsis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Septic shock			
subjects affected / exposed	1 / 12 (8.33%)	3 / 187 (1.60%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Bronchitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 187 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 12 (8.33%)	4 / 187 (2.14%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 187 (0.53%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 187 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Safety Analysis Set -		

	Part 2 - Group C		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 88 (44.32%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	2 / 2		
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General physical health deterioration			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden death			

subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	2 / 2		
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Atrial fibrillation	Additional description: Acute fibrillation		
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhagic stroke			

subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Tumour lysis syndrome				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety Analysis Set - Part 1	Safety Analysis Set - Part 2 - Group A	Safety Analysis Set - Part 2 - Group B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	183 / 187 (97.86%)	183 / 183 (100.00%)
Investigations			
Weight decreased			
subjects affected / exposed	1 / 12 (8.33%)	25 / 187 (13.37%)	24 / 183 (13.11%)
occurrences (all)	1	25	24
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)	6 / 187 (3.21%)	19 / 183 (10.38%)
occurrences (all)	0	6	19
Neutrophil count decreased			
subjects affected / exposed	1 / 12 (8.33%)	28 / 187 (14.97%)	18 / 183 (9.84%)
occurrences (all)	1	28	18
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	13 / 187 (6.95%)	12 / 183 (6.56%)
occurrences (all)	0	13	12
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	11 / 187 (5.88%)	10 / 183 (5.46%)
occurrences (all)	0	11	10
Platelet count decreased			
subjects affected / exposed	1 / 12 (8.33%)	6 / 187 (3.21%)	10 / 183 (5.46%)
occurrences (all)	1	6	10
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 12 (0.00%)	6 / 187 (3.21%)	7 / 183 (3.83%)
occurrences (all)	0	6	7
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	12 / 187 (6.42%)	6 / 183 (3.28%)
occurrences (all)	0	12	6
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	4 / 187 (2.14%)	5 / 183 (2.73%)
occurrences (all)	0	4	5
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 12 (8.33%)	9 / 187 (4.81%)	15 / 183 (8.20%)
occurrences (all)	1	9	15
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	4 / 187 (2.14%)	14 / 183 (7.65%)
occurrences (all)	1	4	14
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 12 (16.67%)	12 / 187 (6.42%)	21 / 183 (11.48%)
occurrences (all)	2	12	21
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	15 / 187 (8.02%)	12 / 183 (6.56%)
occurrences (all)	0	15	12
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 12 (25.00%)	55 / 187 (29.41%)	67 / 183 (36.61%)
occurrences (all)	3	55	67
Neutropenia			
subjects affected / exposed	4 / 12 (33.33%)	47 / 187 (25.13%)	59 / 183 (32.24%)
occurrences (all)	4	47	59
Leukopenia			
subjects affected / exposed	0 / 12 (0.00%)	22 / 187 (11.76%)	30 / 183 (16.39%)
occurrences (all)	0	22	30
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)	13 / 187 (6.95%)	18 / 183 (9.84%)
occurrences (all)	0	13	18
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	18 / 187 (9.63%)	11 / 183 (6.01%)
occurrences (all)	0	18	11
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 12 (33.33%)	39 / 187 (20.86%)	44 / 183 (24.04%)
occurrences (all)	4	39	44
Fatigue			
subjects affected / exposed	3 / 12 (25.00%)	48 / 187 (25.67%)	36 / 183 (19.67%)
occurrences (all)	3	48	36

Non-cardiac chest pain			
subjects affected / exposed	1 / 12 (8.33%)	8 / 187 (4.28%)	24 / 183 (13.11%)
occurrences (all)	1	8	24
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)	10 / 187 (5.35%)	19 / 183 (10.38%)
occurrences (all)	2	10	19
Pain			
subjects affected / exposed	0 / 12 (0.00%)	5 / 187 (2.67%)	13 / 183 (7.10%)
occurrences (all)	0	5	13
Chest pain			
subjects affected / exposed	1 / 12 (8.33%)	5 / 187 (2.67%)	11 / 183 (6.01%)
occurrences (all)	1	5	11
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 12 (83.33%)	116 / 187 (62.03%)	118 / 183 (64.48%)
occurrences (all)	10	116	118
Abdominal pain			
subjects affected / exposed	5 / 12 (41.67%)	24 / 187 (12.83%)	82 / 183 (44.81%)
occurrences (all)	5	24	82
Nausea			
subjects affected / exposed	7 / 12 (58.33%)	88 / 187 (47.06%)	81 / 183 (44.26%)
occurrences (all)	7	88	81
Vomiting			
subjects affected / exposed	5 / 12 (41.67%)	57 / 187 (30.48%)	65 / 183 (35.52%)
occurrences (all)	5	57	65
Abdominal pain upper			
subjects affected / exposed	2 / 12 (16.67%)	11 / 187 (5.88%)	30 / 183 (16.39%)
occurrences (all)	2	11	30
Constipation			
subjects affected / exposed	4 / 12 (33.33%)	16 / 187 (8.56%)	16 / 183 (8.74%)
occurrences (all)	4	16	16
Dysphagia			
subjects affected / exposed	1 / 12 (8.33%)	3 / 187 (1.60%)	6 / 183 (3.28%)
occurrences (all)	1	3	6
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 12 (8.33%)	4 / 187 (2.14%)	4 / 183 (2.19%)
occurrences (all)	1	4	4
Stomatitis			
subjects affected / exposed	1 / 12 (8.33%)	9 / 187 (4.81%)	4 / 183 (2.19%)
occurrences (all)	1	9	4
Abdominal pain lower			
subjects affected / exposed	1 / 12 (8.33%)	2 / 187 (1.07%)	3 / 183 (1.64%)
occurrences (all)	1	2	3
Dry mouth			
subjects affected / exposed	1 / 12 (8.33%)	4 / 187 (2.14%)	3 / 183 (1.64%)
occurrences (all)	1	4	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 12 (33.33%)	16 / 187 (8.56%)	28 / 183 (15.30%)
occurrences (all)	4	16	28
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	18 / 187 (9.63%)	27 / 183 (14.75%)
occurrences (all)	0	18	27
Productive cough			
subjects affected / exposed	1 / 12 (8.33%)	6 / 187 (3.21%)	11 / 183 (6.01%)
occurrences (all)	1	6	11
Dysphonia			
subjects affected / exposed	1 / 12 (8.33%)	4 / 187 (2.14%)	8 / 183 (4.37%)
occurrences (all)	1	4	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 12 (8.33%)	33 / 187 (17.65%)	49 / 183 (26.78%)
occurrences (all)	1	33	49
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	6 / 187 (3.21%)	9 / 183 (4.92%)
occurrences (all)	0	6	9
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 12 (50.00%)	11 / 187 (5.88%)	47 / 183 (25.68%)
occurrences (all)	6	11	47

Pain in extremity			
subjects affected / exposed	3 / 12 (25.00%)	5 / 187 (2.67%)	31 / 183 (16.94%)
occurrences (all)	3	5	31
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)	8 / 187 (4.28%)	16 / 183 (8.74%)
occurrences (all)	1	8	16
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 187 (1.60%)	13 / 183 (7.10%)
occurrences (all)	0	3	13
Musculoskeletal chest pain			
subjects affected / exposed	2 / 12 (16.67%)	3 / 187 (1.60%)	12 / 183 (6.56%)
occurrences (all)	2	3	12
Arthralgia			
subjects affected / exposed	2 / 12 (16.67%)	2 / 187 (1.07%)	11 / 183 (6.01%)
occurrences (all)	2	2	11
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)	10 / 187 (5.35%)	2 / 183 (1.09%)
occurrences (all)	1	10	2
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	11 / 187 (5.88%)	12 / 183 (6.56%)
occurrences (all)	1	11	12
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	10 / 187 (5.35%)	5 / 183 (2.73%)
occurrences (all)	1	10	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 12 (41.67%)	58 / 187 (31.02%)	60 / 183 (32.79%)
occurrences (all)	5	58	60
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	16 / 187 (8.56%)	18 / 183 (9.84%)
occurrences (all)	1	16	18
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	17 / 187 (9.09%)	14 / 183 (7.65%)
occurrences (all)	0	17	14
Dehydration			

subjects affected / exposed	2 / 12 (16.67%)	14 / 187 (7.49%)	10 / 183 (5.46%)
occurrences (all)	2	14	10
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 187 (2.14%)	8 / 183 (4.37%)
occurrences (all)	0	4	8
Hypomagnesaemia			
subjects affected / exposed	3 / 12 (25.00%)	9 / 187 (4.81%)	7 / 183 (3.83%)
occurrences (all)	3	9	7
Hypoalbuminaemia			
subjects affected / exposed	0 / 12 (0.00%)	11 / 187 (5.88%)	6 / 183 (3.28%)
occurrences (all)	0	11	6

Non-serious adverse events	Safety Analysis Set - Part 2 - Group C		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 88 (97.73%)		
Investigations			
Weight decreased			
subjects affected / exposed	8 / 88 (9.09%)		
occurrences (all)	8		
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	23 / 88 (26.14%)		
occurrences (all)	23		
Alanine aminotransferase increased			
subjects affected / exposed	8 / 88 (9.09%)		
occurrences (all)	8		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 88 (9.09%)		
occurrences (all)	8		
Platelet count decreased			
subjects affected / exposed	18 / 88 (20.45%)		
occurrences (all)	18		
Blood alkaline phosphatase increased			

subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
White blood cell count decreased			
subjects affected / exposed	14 / 88 (15.91%)		
occurrences (all)	14		
Lymphocyte count decreased			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Hypertension			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	4		
Dizziness			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	58 / 88 (65.91%)		
occurrences (all)	58		
Neutropenia			
subjects affected / exposed	45 / 88 (51.14%)		
occurrences (all)	45		
Leukopenia			
subjects affected / exposed	12 / 88 (13.64%)		
occurrences (all)	12		
Thrombocytopenia			
subjects affected / exposed	22 / 88 (25.00%)		
occurrences (all)	22		
Febrile neutropenia			

subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 88 (28.41%)		
occurrences (all)	25		
Fatigue			
subjects affected / exposed	16 / 88 (18.18%)		
occurrences (all)	16		
Non-cardiac chest pain			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	13 / 88 (14.77%)		
occurrences (all)	13		
Pain			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 88 (14.77%)		
occurrences (all)	13		
Abdominal pain			
subjects affected / exposed	9 / 88 (10.23%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	22 / 88 (25.00%)		
occurrences (all)	22		
Vomiting			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	6		
Abdominal pain upper			

subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	13 / 88 (14.77%)		
occurrences (all)	13		
Dysphagia			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	6		
Abdominal pain lower			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 88 (10.23%)		
occurrences (all)	9		
Dyspnoea			
subjects affected / exposed	13 / 88 (14.77%)		
occurrences (all)	13		
Productive cough			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	3		
Dysphonia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	10 / 88 (11.36%) 10		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 88 (4.55%) 4		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all)	6 / 88 (6.82%) 6 3 / 88 (3.41%) 3 2 / 88 (2.27%) 2 2 / 88 (2.27%) 2 3 / 88 (3.41%) 3 4 / 88 (4.55%) 4 3 / 88 (3.41%) 3		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 88 (10.23%) 9 2 / 88 (2.27%) 2		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 88 (26.14%)		
occurrences (all)	23		
Hypokalaemia			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	4		
Hyponatraemia			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	9 / 88 (10.23%)		
occurrences (all)	9		
Hypomagnesaemia			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	4		
Hypoalbuminaemia			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2017	Amendment 1 Additions to protect safety of trial participants, including addition of exclusion criteria for subjects with a history of atypical thrombotic thrombocytopenic purpura or hemolytic uremic syndrome Added prompt for Investigators to consider discontinuing dinutuximab if Grade 3 pain recurred after reducing the dose of dinutuximab once. Added statement to inform Investigators of potential for immunogenic interaction between rasburicase and dinutuximab. Added ophthalmology examination to determine whether any clinically significant deterioration in vision was observed during the study. Updated collection time points for sparse PK sample collection in Part 2, Group B. Added text regarding a detailed pain medication log to allow for a more thorough analysis of pain and pain management associated with dinutuximab. Details regarding safety monitoring and data analyses, including when the DMC will be alerted to the potential for excess risk and grounds for stopping the study due to elevated mortality risk associated with dinutuximab. Added details on when the DMC will meet and the review and consideration of safety data including AEs of particular concern for dinutuximab. Added a reference to support approach for safety data monitoring.
19 December 2017	Amendment 2 Added summary of Part 1 data in adults from the current study in Section 1.15 of the protocol and made edits throughout protocol resulting from availability of Part 1 data, including updates to dinutuximab dosing. Clarified the intended patient population to be enrolled through additional or clearer language and updated contraception requirements to be consistent with international guidelines. Modified prior treatment/trauma exclusion criteria to be consistent with recovery based criteria, removed hypersensitivity exclusion given prior therapy with study drugs is prohibited and based on Part 1 experience, and added exclusion criterion based on prescribing information for irinotecan. Updated Estimated Study Duration section to focus on Part 2 only and define study end. Updated text to allow for locally approved prescribing information and maximize potential for dinutuximab treatment effect. Clarified potential reasons for treatment discontinuation and main reasons subjects may withdraw or be withdrawn from the study. Clarified how treatment delays should be handled for subjects randomized to Group B. Updated pain management guidelines and management guidelines for peripheral neuropathy based on Part 1 study experience. Post-screening assessments specific to pain were removed in order to avoid biasing the results. Pain was still reported as an AE, as appropriate, but the subjects were not specifically asked about pain every 15 minutes throughout the infusion. Clarified source of irinotecan and topotecan prescribing information and included additional information from topotecan US prescribing information. Clarified collection of concomitant medication information for enrolled/randomized subjects, expanded the list of permitted concomitant medications, and addressed the use of steroids.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported