Clinical trial results:
A Phase 1/2 Study to Assess the Safety and Efficacy of Lorvotuzumab Mertansine (IMGN901) in Combination with Carboplatin/Etoposide in Patients with Advanced Solid Tumors Including Extensive Stage Small Cell Lung Cancer

Summary

EudraCT number	2010-022950-17
Trial protocol	GB
Global end of trial date	12 May 2015

Results information

Result version number	v1 (current)
This version publication date	21 May 2016
First version publication date	21 May 2016

Trial information

Trial identification

Sponsor protocol code	Immunogen 0007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01237678
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ImmunoGen Europe Ltd
Sponsor organisation address	24 Chiswell Street, London, United Kingdom, EC1Y 4YX
Public contact	James Stec, Director, Scientific Affairs, ImmunoGen Inc., James.Stec@immunogen.com
Scientific contact	Dr. Richard Bates, Sr. Manager, Publications, ImmunoGen Inc., Richard.Bates@immunogen.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	05 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 November 2014
Global end of trial reached?	Yes
Global end of trial date	12 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of phase I of the study was to determine the maximum tolerated dose (MTD) and characterize the dose-limiting toxicities of lorvotuzumab mertansine (IMGN901) when administered in combination with carboplatin + etoposide chemotherapy followed by IMGN901 alone in patients with solid tumors. The primary objective of phase II was to determine the efficacy of IMGN901 in combination with carboplatin + etoposide chemotherapy followed by IMGN901 alone as first-line treatment for patients with extensive stage small cell lung cancer (SCLC). Secondary objectives were to determine the safety and tolerability of IMGN901 in combination with carboplatin + etoposide chemotherapy followed by IMGN901 alone versus carboplatin + etoposide chemotherapy for patients with extensive stage SCLC.

Protection of trial subjects:

Patients received prophylactic administration of dexamethasone and acetaminophen and/or diphenhydramine (at Investigators discretion) prior to drug infusion in order to minimize/prevent infusion reactions. All patients in cycles 1 and 2 of Phase II received post-infusion prophylaxis with granulocyte-colony stimulating factor (G-CSF), administered per label, starting on Day 4. In cycle 3 and beyond, administration of G-CSF was permitted at the discretion of the Investigator.

A Data Monitoring Committee was instituted for the phase II portion of the study in order to ensure ongoing patient safety, which held regular safety review meetings.

Background therapy: -

Evidence for comparator:

Chemotherapeutic regimens of a platinum agent (carboplatin or cisplatin) in combination with etoposide represents standard-of-care treatment for patients with extensive stage SCLC. Moreover IMGN901 was shown to potentiate the antitumor activity of the carboplatin + etoposide doublet in preclinical models of SCLC.

Actual start date of recruitment	17 November 2010
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	United States: 115
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Canada: 11
Worldwide total number of subjects	181
EEA total number of subjects	55

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)	98
From 65 to 84 years	81
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from, and treated at, 45 study sites in the U.S., Canada, Spain, and the U.K. between November 2010 and May 2015.

Pre-assignment

Screening details:

Patients were screened during a 28-day period. Of the 98 patients randomized to the first Arm of Phase II (IMGN901 + carboplatin + etoposide), 94 subjects were treated; of the 50 patients randomized to the second Arm of Phase II (carboplatin + etoposide), 47 subjects were treated.

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	Phase I - IMGN901 + carboplatin + etoposide

Arm description:

Participants received IMGN901 on Days 1 and 8 of a 21-day cycle. All patients also received carboplatin on Day 1 and etoposide on Days 1, 2, and 3 of each 21-day cycle.The starting dose of IMGN901 was 60 mg/m2; dose escalation proceeded, as tolerated, through 75, 90, and 112 mg/m2. Carboplatin was originally dosed at an AUC 6 however due to poor tolerability this was reduced to an AUC of 5. Study drug combinations were administered for four cycles, with up to 6 cycles allowed. IMGN901 was continued as monotherapy for patients who achieved a response or stable disease.

Arm type	Experimental
Investigational medicinal product name	Lorvotuzumab mertansine
Investigational medicinal product code	
Other name	IMGN901
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

IMGN901 was administered as an IV infusion on Days 1 and 8 of a 21-day cycle

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered by IV infusion over 30-60 minutes or as per institutional guidelines on Day 1 of each treatment cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Etoposide was administered by IV infusion at a dose of 100 mg/m2 over 30-60 minutes or as per institutional guidelines on Days 1, 2, and 3 of each treatment cycle

Arm title	Phase II - IMGN901 + carboplatin + etoposide

Arm description:

IMGN901 was administered at the RP2D determined in Phase I (112 mg/m2; later reduced to 90 mg/m2) on Days 1 and 8 of each 21-day cycle. Patients also received carboplatin (AUC 5) on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. Study drug combinations were administered for four cycles, with up to 6 cycles allowed. IMGN901 was continued as monotherapy for patients who achieved a response or stable disease.

Arm type	Experimental
Investigational medicinal product name	Lorvotuzumab mertansine
Investigational medicinal product code	
Other name	IMGN901
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

IMGN901 was administered as an IV infusion on Days 1 and 8 of a 21-day cycle

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered by IV infusion over 30-60 minutes or as per institutional guidelines on Day 1 of each treatment cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Etoposide was administered by IV infusion at a dose of 100 mg/m2 over 30-60 minutes or as per institutional guidelines on Days 1, 2, and 3 of each treatment cycle

Arm title	Phase II - carboplatin + etoposide

Arm description:

Carboplatin (AUC 5) was administered on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. Drugs were administered for 6 cycles as tolerated.

Arm type	Active comparator
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered by IV infusion over 30-60 minutes or as per institutional guidelines on Day 1 of each treatment cycle.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Etoposide was administered by IV infusion at a dose of 100 mg/m2 over 30-60 minutes or as per institutional guidelines on Days 1, 2, and 3 of each treatment cycle

Number of subjects in period 1[1]	Phase I - IMGN901 + carboplatin + etoposide	Phase II - IMGN901 + carboplatin + etoposide	Phase II - carboplatin + etoposide
Started	33	94	47
Received intervention	33	94	47
Completed	0	0	0
Not completed	33	94	47
Adverse event, serious fatal	-	18	3
Consent withdrawn by subject	3	1	5
Sponsor Decision/Study Closed	-	18	7
Adverse event, non-fatal	5	21	6
Completed Cycles 4-6	-	11	21
Death	-	-	2
Incorrect Original Diagnosis	1	-	-
Lack of efficacy	24	25	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 181 patients were enrolled in the study: 33 in Phase I and 148 in Phase II. Within the Phase II population, 98 subjects were randomized to the experimental arm (IMGN901+ carboplatin + etoposide), however only 94 subjects were treated. Of the 50 patients randomized to the comparator arm (carboplatin + etoposide), 47 subjects were treated.

Baseline characteristics

Reporting groups	
Reporting group title	Phase I - IMGN901 + carboplatin + etoposide
Reporting group description:	
Participants received IMGN901 on Days 1 and 8 of a 21-day cycle. All patients also received carboplatin on Day 1 and etoposide on Days 1, 2, and 3 of each 21-day cycle.The starting dose of IMGN901 was 60 mg/m2; dose escalation proceeded, as tolerated, through 75, 90, and 112 mg/m2. Carboplatin was originally dosed at an AUC 6 however due to poor tolerability this was reduced to an AUC of 5. Study drug combinations were administered for four cycles, with up to 6 cycles allowed. IMGN901 was continued as monotherapy for patients who achieved a response or stable disease.	
Reporting group title	Phase II - IMGN901 + carboplatin + etoposide
Reporting group description:	
IMGN901 was administered at the RP2D determined in Phase I (112 mg/m2; later reduced to 90 mg/m2) on Days 1 and 8 of each 21-day cycle. Patients also received carboplatin (AUC 5) on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. Study drug combinations were administered for four cycles, with up to 6 cycles allowed. IMGN901 was continued as monotherapy for patients who achieved a response or stable disease.	
Reporting group title	Phase II - carboplatin + etoposide
Reporting group description:	
Carboplatin (AUC 5) was administered on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. Drugs were administered for 6 cycles as tolerated.	

Reporting group values	Phase I - IMGN901 + carboplatin + etoposide	Phase II - IMGN901 + carboplatin + etoposide	Phase II - carboplatin + etoposide
Number of subjects	33	94	47
Age Categorical			
A total of 174 patients were included in the analyses (Phase I, 33; Phase II IMGN901 + carboplatin + etoposide, 94; Phase II carboplatin + etoposide, 47) due to a total of 7 patients in Phase II who were randomized but did not receive treatment.			
Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	21	49	26
>=65 years	12	45	21
Age continuous			
Units: years			
arithmetic mean	57.3	64.3	64.4
standard deviation	± 13.5	± 9.2	± 9.4
Gender, Male/Female			
Units: participants			
Female	20	40	22
Male	13	54	25
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	3	2
White	30	90	44
More than one race	0	0	0
Unknown or Not Reported	0	0	1

Eastern Cooperative Oncology Group (ECOG) Performance Status			
0 = Fully active, able to carry out 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. 2 = Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
0x	14	22	12
1x	19	62	32
2x	0	10	3
History of Smoking Units: Subjects			
Yes	21	93	46
No	12	1	1

Reporting group values	Total		
Number of subjects	174		
Age Categorical			
A total of 174 patients were included in the analyses (Phase I, 33; Phase II IMGN901 + carboplatin + etoposide, 94; Phase II carboplatin + etoposide, 47) due to a total of 7 patients in Phase II who were randomized but did not receive treatment.			
Units: participants			
<=18 years	0		
Between 18 and 65 years	96		
>=65 years	78		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender, Male/Female Units: participants			
Female	82		
Male	92		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	7		
White	164		
More than one race	0		
Unknown or Not Reported	1		
Eastern Cooperative Oncology Group (ECOG) Performance Status			
0 = Fully active, able to carry out 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. 2 = Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
0x	48		
1x	113		
2x	13		

History of Smoking Units: Subjects			
Yes	160		
No	14		

End points

End points reporting groups

Reporting group title	Phase I - IMGN901 + carboplatin + etoposide

Reporting group description:

Participants received IMGN901 on Days 1 and 8 of a 21-day cycle. All patients also received carboplatin on Day 1 and etoposide on Days 1, 2, and 3 of each 21-day cycle.The starting dose of IMGN901 was 60 mg/m2; dose escalation proceeded, as tolerated, through 75, 90, and 112 mg/m2. Carboplatin was originally dosed at an AUC 6 however due to poor tolerability this was reduced to an AUC of 5. Study drug combinations were administered for four cycles, with up to 6 cycles allowed. IMGN901 was continued as monotherapy for patients who achieved a response or stable disease.

Reporting group title	Phase II - IMGN901 + carboplatin + etoposide

Reporting group description:

IMGN901 was administered at the RP2D determined in Phase I (112 mg/m2; later reduced to 90 mg/m2) on Days 1 and 8 of each 21-day cycle. Patients also received carboplatin (AUC 5) on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. Study drug combinations were administered for four cycles, with up to 6 cycles allowed. IMGN901 was continued as monotherapy for patients who achieved a response or stable disease.

Reporting group title	Phase II - carboplatin + etoposide

Reporting group description:

Carboplatin (AUC 5) was administered on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. Drugs were administered for 6 cycles as tolerated.

Primary: Occurrence of Dose Limiting Toxicities (DLT)

End point title	Occurrence of Dose Limiting Toxicities (DLT)[1][2]

End point description:

The primary outcome measure for Phase I was to determine the maximum tolerated dose (MTD) and characterize the dose limiting toxicities (DLT) of IMGN901 when administered in combination with carboplatin/etoposide chemotherapy followed by IMGN901 alone in patients with solid tumors. For the purposes of dose escalation and determination of MTD, DLTs were defined as AEs or abnormal laboratory values related to study treatment which occurred in Cycle 1 of the Dose Escalation phase, including any AEs that resulted in failure to meet the criteria for re-treatment. The following events were considered DLTs (using the most current version of CTCAE): febrile neutropenia; Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding; ≥ Grade 3 peripheral neuropathy; ≥ Grade 3 vomiting, nausea, or diarrhea that persisted despite the use of optimal therapy; other ≥ grade 3 non-hematologic toxicity (with the exception of brief fatigue i.e. ≤ 72 hours and alopecia)

End point type	Primary

End point timeframe:

21 days (Cycle 1)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only DLTs that occurred in the first reporting arm (i.e. Phase I- IMGN901 + carboplatin + etoposide) were considered for decisions regarding dose escalation and determination of MTD/RP2D.

End point values	Phase I - IMGN901 + carboplatin + etoposide			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: participants				
number (not applicable)				

Grade 3 febrile neutropenia	1			
Grade 4 febrile neutropenia	3			
Grade 4 thrombocytopenia	4			
Grade 4 granulocytopenia	1			
Grade 3 lobar pneumonia	1			

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (PFS) in Phase II

End point title	Progression Free Survival (PFS) in Phase II[3][4]

End point description:

The primary outcome measure for Phase II was to determine the efficacy of IMGN901 in combination with carboplatin/etoposide chemotherapy as first-line treatment for patients with extensive stage small cell lung cancer. PFS was defined as the time from enrollment until objective tumor progression according to RECIST 1.1 or death on study due to any cause, whichever occurred first.

End point type	Primary

End point timeframe:

From randomization to objective tumor progression or death (up to post-treatment follow-up 28 days after last dose)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: For design purposes, the number of patients who were progression-free at 6 months were used to test hypotheses against historical 6-month PFS rates typically seen in patients treated with carboplatin/etoposide. The trial was not powered to permit a statistically informative comparison of the randomized treatment groups with respect to PFS.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The trial was not powered to permit a statistically informative comparison of the randomized treatment groups with respect to PFS, therefore only the results from the Phase II experimental arm (Phase II - IMGN901 + carboplatin + etoposide) are presented.

End point values	Phase II - IMGN901 + carboplatin + etoposide			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: months				
number (confidence interval 95%)	6.2 (5.4 to 7.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Overview of Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

To assess the type and frequency of Adverse Events (AEs) and Serious Adverse Events (SAEs). An AE was defined as any noxious, pathologic, or unintended change un anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of the study, whether or not deemed study drug-related. An SAE was any AE resulting in death, life-threatening experience, initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, or congenital defect. All AEs were reported from the time of the first dose of study treatment until 28 days after the final dose of study drug. the severity of AEs were graded by the Investigator using National cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) version 4.0.

End point type	Secondary

End point timeframe:

From the first dose of study drug on Cycle 1, Day 1 until 28 days after the last study treatment.

End point values	Phase I - IMGN901 + carboplatin + etoposide	Phase II - IMGN901 + carboplatin + etoposide	Phase II - carboplatin + etoposide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	94	47	
Units: participants				
number (not applicable)				
Any TEAE	33	94	46	
Related TEAE	32	90	39	
Any SAE	16	54	23	
Related SAE	8	30	9	
TEAEs leading to discontinuation	8	50	6	
Any Grade ≥ 3 TEAE	29	92	42	
Related Grade ≥ 3 TEAE	22	83	33	
Deaths within 28 days of last dose	1	14	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) rate at 6 months

End point title	Progression Free Survival (PFS) rate at 6 months[5]

End point description:

End point type	Secondary

End point timeframe:

6 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study was not powered to permit a statistically informative comparison of the randomized treatment groups with respect to PFS. The activity of IMGN901 was assessed by comparing the PFS rate at six months in the IMGN901 experimental arm against the historical 6-month PFS rate 0.44 (equivalently a median PFS = 5 months). The control arm was primarily used to serve as an informal validation of historical data. therefore, only data from the Phase II experimental arm are presented.

End point values	Phase II - IMGN901 + carboplatin + etoposide			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: percentage				
number (confidence interval 95%)	39 (28.4 to 50.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival (OS) in Phase II

End point title	Median Overall Survival (OS) in Phase II[6]

End point description:

A secondary outcome measure for Phase II was to determine the overall survival of patients treated with IMGN901 in combination with carboplatin/etoposide chemotherapy alone versus carbolatin/etoposide chemotherapy as first-line treatment for patients with extensive stage small cell lung cancer.

End point type	Secondary

End point timeframe:

From the time of enrollment until death on study due to any cause (up to post-treatment follow-up 28 days after last dose)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point reports only on the two Phase II arms; patients in the dose escalation baseline arm (Phase I - IMGN901 + carboplatin + etoposide) were not included.

End point values	Phase II - IMGN901 + carboplatin + etoposide	Phase II - carboplatin + etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	39		
Units: months				
number (confidence interval 95%)	10.1 (8.7 to 18.1)	10.97 (7.5 to 11.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) rate at 12 months

End point title	Overall Survival (OS) rate at 12 months[7]

End point description:

OS was analyzed based on a binary definition of the number of patients dead or censored prior to 12 months and the number of patients alive at 12 months.

End point type	Secondary

End point timeframe:

12 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study was not powered to permit a statistically informative comparison of the randomized treatment groups with respect to OS; therefore only the results from the Phase II experimental arm (Phase II - IMGN901 + carboplatin + etoposide) are presented.

End point values	Phase II - IMGN901 + carboplatin + etoposide			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: percentage				
number (confidence interval 95%)	61 (49.6 to 71.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reported SAEs include events from the first dose of study drug on Cycle 1, Day 1 until 28 days after the last study treatment.

Adverse event reporting additional description:

AEs and laboratory results were graded using the NCI CTCAE, version 4.0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Phase I - IMGN901 + carboplatin + etoposide

Reporting group description:

Participants received IMGN901 on Days 1 and 8 of a 21-day cycle. All patients also received carboplatin on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. The starting dose of IMGN901 was 60 mg/m2; dose escalation proceeded, as tolerated, through 75, 90, and 112 mg/m2. Carboplatin was originally dosed at an AUC 6 however due to poor tolerability this was reduced to an AUC of 5. Study drug combinations were administered for four cycles, with up to 6 cycles allowed. IMGN901 was continued as monotherapy for patients who achieved a response or stable disease.

Reporting group title	Phase II - IMGN901 + carboplatin + etoposide

Reporting group description:

IMGN901 was administered at the RP2D determined in Phase I (112 mg/m2; later reduced to 90 mg/m2) on Days 1 and 8 of each 21-day cycle. Patients also received carboplatin (AUC 5) on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. Study drug combinations were administered for four cycles, with up to 6 cycles allowed. IMGN901 was continued as monotherapy for patients who achieved a response or stable disease.

Reporting group title	Phase II - carboplatin + etoposide

Reporting group description:

Carboplatin (AUC 5) was administered on Day 1 and etoposide (100 mg/m2) on Days 1, 2, and 3 of each 21-day cycle. Drugs were administered for 6 cycles as tolerated.

Serious adverse events	Phase I - IMGN901 + carboplatin + etoposide	Phase II - IMGN901 + carboplatin + etoposide	Phase II - carboplatin + etoposide
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 33 (48.48%)	54 / 94 (57.45%)	23 / 47 (48.94%)
number of deaths (all causes)	1	18	3
number of deaths resulting from adverse events	0	9	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal cancer metastatic			

subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)	2 / 94 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial thrombosis limb			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 94 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 94 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 94 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Fatigue			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vulval haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 33 (0.00%)	2 / 94 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 33 (0.00%)	5 / 94 (5.32%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			

subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal inflammation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Confusional state			

subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial defibrillation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorder			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 33 (3.03%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nerve root compression			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 33 (0.00%)	3 / 94 (3.19%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Polyneuropathy			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 94 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	4 / 33 (12.12%)	6 / 94 (6.38%)	5 / 47 (10.64%)
occurrences causally related to treatment / all	4 / 4	6 / 6	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 94 (3.19%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Thrombocytopenia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 94 (1.06%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 33 (3.03%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	2 / 94 (2.13%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Pancreatitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal heamorrhage			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haematemesis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal heamorrhage			

subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Cellulitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 94 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lobar pneumonia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	2 / 94 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 33 (0.00%)	4 / 94 (4.26%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	4 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonia			
subjects affected / exposed	0 / 33 (0.00%)	6 / 94 (6.38%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	5 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	3 / 4	0 / 1
Sepsis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 94 (2.13%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	1 / 2	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 1	2 / 2	1 / 1
Septic shock			
subjects affected / exposed	0 / 33 (0.00%)	3 / 94 (3.19%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	3 / 3	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 33 (0.00%)	3 / 94 (3.19%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Hypomagnesaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 94 (0.00%)	0 / 47 (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
Hyponatraemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 33 (0.00%)	1 / 94 (1.06%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Phase I - IMGN901 + carboplatin + etoposide	Phase II - IMGN901 + carboplatin + etoposide	Phase II - carboplatin + etoposide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	91 / 94 (96.81%)	43 / 47 (91.49%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 33 (6.06%)	7 / 94 (7.45%)	0 / 47 (0.00%)
occurrences (all)	3	10	0
Hypotension			
subjects affected / exposed	2 / 33 (6.06%)	10 / 94 (10.64%)	4 / 47 (8.51%)
occurrences (all)	2	10	6
Hot flush			
subjects affected / exposed	0 / 33 (0.00%)	5 / 94 (5.32%)	0 / 47 (0.00%)
occurrences (all)	0	5	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 33 (9.09%)	29 / 94 (30.85%)	10 / 47 (21.28%)
occurrences (all)	3	61	25
Chills			
subjects affected / exposed	2 / 33 (6.06%)	6 / 94 (6.38%)	2 / 47 (4.26%)
occurrences (all)	2	6	2
Fatigue			
subjects affected / exposed	17 / 33 (51.52%)	46 / 94 (48.94%)	14 / 47 (29.79%)
occurrences (all)	35	77	23
Influenza like illness			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Mucosal inflammation			
subjects affected / exposed	2 / 33 (6.06%)	13 / 94 (13.83%)	6 / 47 (12.77%)
occurrences (all)	5	16	12
Oedema peripheral			
subjects affected / exposed	3 / 33 (9.09%)	19 / 94 (20.21%)	5 / 47 (10.64%)
occurrences (all)	3	20	6
Pain			
subjects affected / exposed	5 / 33 (15.15%)	7 / 94 (7.45%)	2 / 47 (4.26%)
occurrences (all)	5	7	2
Pyrexia			

subjects affected / exposed	8 / 33 (24.24%)	10 / 94 (10.64%)	5 / 47 (10.64%)
occurrences (all)	10	13	5
Malaise			
subjects affected / exposed	0 / 33 (0.00%)	6 / 94 (6.38%)	0 / 47 (0.00%)
occurrences (all)	0	6	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 33 (0.00%)	7 / 94 (7.45%)	6 / 47 (12.77%)
occurrences (all)	0	8	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 33 (18.18%)	11 / 94 (11.70%)	10 / 47 (21.28%)
occurrences (all)	8	12	10
Dysphonia			
subjects affected / exposed	2 / 33 (6.06%)	8 / 94 (8.51%)	2 / 47 (4.26%)
occurrences (all)	2	9	2
Dyspnoea			
subjects affected / exposed	5 / 33 (15.15%)	18 / 94 (19.15%)	7 / 47 (14.89%)
occurrences (all)	5	21	8
Epistaxis			
subjects affected / exposed	2 / 33 (6.06%)	5 / 94 (5.32%)	2 / 47 (4.26%)
occurrences (all)	2	5	2
Oropharyngeal pain			
subjects affected / exposed	5 / 33 (15.15%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	5	0	0
Pulmonary embolism			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Haemoptysis			
subjects affected / exposed	0 / 33 (0.00%)	6 / 94 (6.38%)	1 / 47 (2.13%)
occurrences (all)	0	7	1
Hiccups			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
Hypoxia			

subjects affected / exposed	0 / 33 (0.00%)	5 / 94 (5.32%)	1 / 47 (2.13%)
occurrences (all)	0	5	1
Productive cough			
subjects affected / exposed	0 / 33 (0.00%)	2 / 94 (2.13%)	4 / 47 (8.51%)
occurrences (all)	0	2	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 33 (6.06%)	8 / 94 (8.51%)	1 / 47 (2.13%)
occurrences (all)	2	10	1
Depression			
subjects affected / exposed	2 / 33 (6.06%)	5 / 94 (5.32%)	1 / 47 (2.13%)
occurrences (all)	2	5	2
Insomnia			
subjects affected / exposed	6 / 33 (18.18%)	19 / 94 (20.21%)	4 / 47 (8.51%)
occurrences (all)	9	21	4
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 33 (6.06%)	11 / 94 (11.70%)	0 / 47 (0.00%)
occurrences (all)	4	16	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 33 (6.06%)	8 / 94 (8.51%)	1 / 47 (2.13%)
occurrences (all)	7	8	1
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 33 (6.06%)	8 / 94 (8.51%)	1 / 47 (2.13%)
occurrences (all)	2	14	1
Blood creatine increased			
subjects affected / exposed	3 / 33 (9.09%)	2 / 94 (2.13%)	3 / 47 (6.38%)
occurrences (all)	10	3	5
Blood pressure increased			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 33 (9.09%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	7	0	0
Lipase increased			

subjects affected / exposed	2 / 33 (6.06%)	3 / 94 (3.19%)	3 / 47 (6.38%)
occurrences (all)	2	4	3
Lymphocyte count decreased			
subjects affected / exposed	7 / 33 (21.21%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	29	0	0
Neutrophil count decreased			
subjects affected / exposed	7 / 33 (21.21%)	11 / 94 (11.70%)	7 / 47 (14.89%)
occurrences (all)	14	23	22
Platelet count decreased			
subjects affected / exposed	2 / 33 (6.06%)	16 / 94 (17.02%)	6 / 47 (12.77%)
occurrences (all)	6	31	13
Weight decreased			
subjects affected / exposed	2 / 33 (6.06%)	7 / 94 (7.45%)	3 / 47 (6.38%)
occurrences (all)	2	10	3
White blood cell count decreased			
subjects affected / exposed	7 / 33 (21.21%)	8 / 94 (8.51%)	4 / 47 (8.51%)
occurrences (all)	19	13	9
Blood amylase increased			
subjects affected / exposed	0 / 33 (0.00%)	7 / 94 (7.45%)	2 / 47 (4.26%)
occurrences (all)	0	7	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 33 (9.09%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	4	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 33 (0.00%)	5 / 94 (5.32%)	0 / 47 (0.00%)
occurrences (all)	0	8	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 33 (9.09%)	13 / 94 (13.83%)	5 / 47 (10.64%)
occurrences (all)	3	16	5
Dysgeusia			
subjects affected / exposed	4 / 33 (12.12%)	10 / 94 (10.64%)	6 / 47 (12.77%)
occurrences (all)	4	10	6
Headache			

subjects affected / exposed	7 / 33 (21.21%)	16 / 94 (17.02%)	5 / 47 (10.64%)
occurrences (all)	11	18	7
Paraesthesia			
subjects affected / exposed	2 / 33 (6.06%)	20 / 94 (21.28%)	2 / 47 (4.26%)
occurrences (all)	3	43	3
Peripheral motor neuropathy			
subjects affected / exposed	2 / 33 (6.06%)	7 / 94 (7.45%)	0 / 47 (0.00%)
occurrences (all)	2	14	0
Peripheral sensory neuropathy			
subjects affected / exposed	17 / 33 (51.52%)	56 / 94 (59.57%)	4 / 47 (8.51%)
occurrences (all)	36	126	5
Restless legs syndrome			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Hyporeflexia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 94 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	5
Neurotoxicity			
subjects affected / exposed	0 / 33 (0.00%)	8 / 94 (8.51%)	1 / 47 (2.13%)
occurrences (all)	0	15	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 33 (72.73%)	50 / 94 (53.19%)	21 / 47 (44.68%)
occurrences (all)	54	113	57
Leukocytosis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Leukopenia			
subjects affected / exposed	9 / 33 (27.27%)	10 / 94 (10.64%)	6 / 47 (12.77%)
occurrences (all)	15	12	19
Lymphopenia			
subjects affected / exposed	4 / 33 (12.12%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	11	0	0
Neutropenia			
subjects affected / exposed	10 / 33 (30.30%)	53 / 94 (56.38%)	24 / 47 (51.06%)
occurrences (all)	24	118	74

Pancytopenia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Thrombocytopenia			
subjects affected / exposed	16 / 33 (48.48%)	32 / 94 (34.04%)	19 / 47 (40.43%)
occurrences (all)	49	65	46
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 33 (24.24%)	5 / 94 (5.32%)	3 / 47 (6.38%)
occurrences (all)	10	6	3
Constipation			
subjects affected / exposed	12 / 33 (36.36%)	30 / 94 (31.91%)	9 / 47 (19.15%)
occurrences (all)	14	35	12
Diarrhoea			
subjects affected / exposed	9 / 33 (27.27%)	30 / 94 (31.91%)	8 / 47 (17.02%)
occurrences (all)	17	40	11
Dyspepsia			
subjects affected / exposed	6 / 33 (18.18%)	13 / 94 (13.83%)	0 / 47 (0.00%)
occurrences (all)	7	14	0
Dysphagia			
subjects affected / exposed	3 / 33 (9.09%)	1 / 94 (1.06%)	4 / 47 (8.51%)
occurrences (all)	3	1	5
Flatulence			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	13 / 33 (39.39%)	40 / 94 (42.55%)	17 / 47 (36.17%)
occurrences (all)	17	56	25
Vomiting			
subjects affected / exposed	11 / 33 (33.33%)	23 / 94 (24.47%)	11 / 47 (23.40%)
occurrences (all)	12	26	15
Abdominal distension			
subjects affected / exposed	0 / 33 (0.00%)	5 / 94 (5.32%)	0 / 47 (0.00%)
occurrences (all)	0	8	0
Abdominal pain upper			

subjects affected / exposed	0 / 33 (0.00%)	6 / 94 (6.38%)	2 / 47 (4.26%)
occurrences (all)	0	6	2
Stomatitis			
subjects affected / exposed	0 / 33 (0.00%)	6 / 94 (6.38%)	2 / 47 (4.26%)
occurrences (all)	0	6	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 33 (30.30%)	32 / 94 (34.04%)	16 / 47 (34.04%)
occurrences (all)	12	36	20
Dry skin			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Skin lesion			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Pruritis			
subjects affected / exposed	0 / 33 (0.00%)	6 / 94 (6.38%)	1 / 47 (2.13%)
occurrences (all)	0	6	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 33 (12.12%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	5	0	0
Urinary retention			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 33 (24.24%)	18 / 94 (19.15%)	5 / 47 (10.64%)
occurrences (all)	9	28	5
Back pain			
subjects affected / exposed	4 / 33 (12.12%)	12 / 94 (12.77%)	4 / 47 (8.51%)
occurrences (all)	4	13	4
Bone pain			

subjects affected / exposed	2 / 33 (6.06%)	5 / 94 (5.32%)	3 / 47 (6.38%)
occurrences (all)	2	5	3
Muscle spasms			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Muscular weakness			
subjects affected / exposed	2 / 33 (6.06%)	6 / 94 (6.38%)	2 / 47 (4.26%)
occurrences (all)	2	10	2
Musculoskeletal chest pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	4	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 33 (6.06%)	7 / 94 (7.45%)	2 / 47 (4.26%)
occurrences (all)	3	15	2
Neck pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Pain in extremity			
subjects affected / exposed	6 / 33 (18.18%)	11 / 94 (11.70%)	3 / 47 (6.38%)
occurrences (all)	8	13	3
Myalgia			
subjects affected / exposed	0 / 33 (0.00%)	12 / 94 (12.77%)	3 / 47 (6.38%)
occurrences (all)	0	18	3
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	3 / 33 (9.09%)	5 / 94 (5.32%)	2 / 47 (4.26%)
occurrences (all)	3	5	2
Urinary tract infection			
subjects affected / exposed	5 / 33 (15.15%)	10 / 94 (10.64%)	7 / 47 (14.89%)
occurrences (all)	5	12	10
Upper respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	6 / 94 (6.38%)	2 / 47 (4.26%)
occurrences (all)	0	7	2
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	6 / 33 (18.18%)	32 / 94 (34.04%)	16 / 47 (34.04%)
occurrences (all)	9	45	22
Dehydration			
subjects affected / exposed	3 / 33 (9.09%)	15 / 94 (15.96%)	6 / 47 (12.77%)
occurrences (all)	5	23	7
Hypercalcaemia			
subjects affected / exposed	3 / 33 (9.09%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	4	0	0
Hyperglycaemia			
subjects affected / exposed	2 / 33 (6.06%)	5 / 94 (5.32%)	2 / 47 (4.26%)
occurrences (all)	6	8	2
Hypoalbuminaemia			
subjects affected / exposed	3 / 33 (9.09%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	8	0	0
Hypocalcaemia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 94 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	9 / 33 (27.27%)	13 / 94 (13.83%)	3 / 47 (6.38%)
occurrences (all)	20	32	4
Hypomagnesaemia			
subjects affected / exposed	7 / 33 (21.21%)	16 / 94 (17.02%)	6 / 47 (12.77%)
occurrences (all)	15	36	6
Hyponatraemia			
subjects affected / exposed	8 / 33 (24.24%)	12 / 94 (12.77%)	6 / 47 (12.77%)
occurrences (all)	13	15	7
Hypophospataemia			
subjects affected / exposed	5 / 33 (15.15%)	5 / 94 (5.32%)	1 / 47 (2.13%)
occurrences (all)	5	5	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2011	Substantive changes made to the protocol by Amendment 1 included the following: • The design of phase II was modified to employ a Simon two-stage design - the approximate number of patients enrolled in both phase I and II was updated from 125 to a total of 90-160. • The provision to potentially explore a chemotherapy-naïve cohort of patients in phase I to determine if higher doses of IMGN901 could be tolerated in patients whose bone marrow had not been compromised by prior cytotoxic chemotherapy regimens was added to the protocol. • The inclusion criterion regarding 24-hour creatinine clearance and the exclusion criteria related to neurotoxicity and brain metastases were updated. Specifically, the inclusion of patients with a 24-hour creatinine clearance ≥ 50 mL/min was revised to a 24-hour creatinine clearance ≥ 60 mL/min, and the exclusion of patients with neurotoxicity was changed from ≥ grade 1 neurotoxicity to ≥ grade 2. The criterion relating to CNS metastases was modified to exclude patients with untreated brain metastases in phase II. • The definition of DLT was modified such that isolated, asymptomatic elevations in biochemistry laboratory values lasting ≤ 7 days were not considered dose-limiting. • The dose modification procedures were modified to allow carboplatin to be reduced to AUC = 4 and etoposide to be reduced to 60 mg/m2. • The criteria to continue treatment, begin a new cycle of therapy, and re-initiate therapy after the occurrence of a DLT were modified to state that all non-hematologic toxicities were to be ≤ grade 2 (except alopecia) or returned to baseline. The original protocol had stated that these toxicities had to be ≤ grade 1. • The use of growth factor support for ongoing related toxicities was permitted. • Hematology and clinical chemistries were added on Day 15 of Cycle 1 through 4
30 June 2011	Substantive changes made to the protocol by Amendment 2 included the following: • The number of cycles of carboplatin + etoposide to be administered was changed from a range of four to six to six, as tolerated, in phase II. • The entrance criteria were changed such that patients with an activity malignancy rather than any malignancy within the previous three years were excluded. Furthermore, the exclusion criterion regarding CNS metastases was modified to provide guidance regarding steroid therapy such that patients with CNS metastases who were previously treated with surgery or radiation and who were receiving stable, decreasing, or no steroids were eligible. • Guidelines allowing for IMGN901 dose reductions for the management of hematologic toxicities were provided. • A DMC was added for review of safety information during the phase II portion of the study.

04 May 2012	Substantive changes made to the protocol by Amendment 3 included the following: • The entrance criterion regarding previous radiotherapy was clarified to include cranial irradiation. Furthermore, patients with uncontrolled 3rd space fluid retention were no longer excluded, as patients with SCLC may have pleural effusions that do not necessarily disqualify them from participation in the study. It was further clarified that patients with asymptomatic brain metastases who had been treated were eligible for study participation; those with untreated brain metastases were excluded. • The RP2D for phase II, IMGN901 112 mg/m2 plus carboplatin (AUC5) + etoposide 100 mg/m2, was indicated in the protocol. • It was clarified that the individual study agents may have been discontinued independent of each other. Furthermore, dose level reductions based on the RP2D were clarified. • Wider visit windows were permitted, including 21 rather than seven days for safety follow-up assessments; a delay of up to seven rather than three days due to logistical reasons for starting a new cycle; and seven rather than three days for evaluation of toxicity prior to Day 1 of a new cycle. • The definition of WCBP was updated. • It was clarified that the IMGN901 dose was to be calculated based on the patient's body weight at first treatment. Adjustments were to be made for significant (≥ 10%) changes in body weight not influenced by fluid retention. • The protocol was clarified to indicate that patients in phase II, Arm 2, were to receive pre-medications prior to carboplatin + etoposide in accordance with institutional guidelines. • The dose modification procedures were clarified.
30 August 2012	Substantive changes made to the protocol by Amendment 4 included the following: • The requirement for PK sample collection was removed, as sufficient PK data had already been collected in the study. • It was clarified that laboratory abnormalities were to be reported as AEs. • Additional guidance regarding SAE reporting was provided, including identification of events that did not qualify as inpatient hospitalizations; clarification of when death was reported as an SAE rather than an SAE outcome; clarification of what constituted the primary SAE term; and specification that sites were to provide SAE reports to the local IRB/IEC in accordance with local requirements. • Replacement of patients in phase II was allowed by Amendment 4. • The list of critical documents required from an Investigator before initiating the study was updated in accordance with ImmunoGen SOPs.
11 April 2013	Substantive changes made to the protocol by Amendment 5 included the following: • The IMGN901 dose in phase II was lowered from 112 mg/m2 to 90 mg/m2 based on analysis of data from phase II that showed an increased frequency of peripheral neuropathy in patients treated with IMGN901 112 mg/m2 plus carboplatin + etoposide. • Given the findings noted above, the definition of DLT regarding peripheral neuropathy and procedures for the management of peripheral neuropathy were revised. • An exploratory assessment of CTCs was added. • The sample size was increased in phase II, with an additional 15 patients planned to be enrolled at IMGN 90 mg/m2 dose level in order to permit an analysis to rule out a six-month PFS rate <40%. • The number of sites was increased from up to 40 to up to 50. • The permissible window for delaying the start of a cycle due to logistical reasons was widened. • It was clarified that for patients undergoing PCI, AEs and concomitant medications were to be recorded for 28 days thereafter in order to allow a comparison of safety after PCI between the two treatment arms. • Magnesium was added as a clinical chemistry parameter to be measured. • The definition of the PP population was clarified to indicate that patients included must have been evaluable by RECIST.

16 October 2013	Substantive changes made to the protocol by Amendment 6 included the following: • It was clarified that for patients in phase II, Arm 2, the EOT visit was to occur after the completion of C6, and follow-up response assessments were to be performed for patients in phase II, Arm 2, who completed six cycles of treatment. • Measurement of cytokines was added as a study assessment. • As an aggregate analysis of safety data from this study indicated an increase in the frequency of serious infectious events, with most occurring in Cycles 1 and 2, and an association of such events with neutropenia, the requirement for prophylactic administration of G-CSF during Cycle 1 and 2 was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported