Clinical trial results:
A Randomized, Controlled, Open-Label, Phase 2 Trial of SGI-110 and Carboplatin in Subjects with Platinum-Resistant Recurrent Ovarian Cancer

Summary

EudraCT number	2012-001576-12
Trial protocol	GB
Global end of trial date	15 April 2016

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	SGI-110-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01696032
WHO universal trial number (UTN)	-
Other trial identifiers	Health Canada: CN 161678

Notes:

Sponsors

Sponsor organisation name	Astex Pharmaceuticals, Inc.
Sponsor organisation address	4420 Rosewood Drive, Suite 200, Pleasanton, CA, United States, 94588
Public contact	Dr Harold Keer, Astex Pharmaceuticals Inc., 001 9257190741, Harold.Keer@astx.com
Scientific contact	Dr Harold Keer, Astex Pharmaceuticals Inc., 001 9257190741, Harold.Keer@astx.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	15 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objectives:
Stage 1: To assess the safety & tolerability of guadecitabine+carboplatin (G+C) and determine the maximum tolerated dose (MTD) for Stage 2.
Stage 2: To assess & compare progression free survival (PFS) between G+C and treatment choice (TC) arms.

Secondary Objectives:
Stage 1: To determine the objective response rate (ORR) based on both measurable & detectable disease; to assess PFS at 6 months; to determine the clinical benefit rate (CBR), the duration of response (DOR), CA-125 reduction by ≥50%, overall survival (OS), & pharmacokinetics (PK) of G&C in subjects with ovarian cancer, and determine if there is a PK interaction between G&C.

Stage 2: To determine & compare the ORR for G+C & TC arms based on both measurable & detectable disease; to assess & compare PFS at 6 months for G+C and TC arms; to determine & compare the CBR, DOR, CA-125 reduction by ≥50% & OS for G+C & TC arms; to determine the ORR for subjects in the TC arm who cross over to the G+C arm

Protection of trial subjects:

Institutional Review Board (IRB)/Independent Ethics Committee (IEC):
The protocol, amendments, informed consent forms (ICFs), and administrative letters for this study were reviewed and approved by an IRB/IEC at each study center prior to implementation. No subject was treated until the IRB/IEC had provided written approval of the study and the ICF to the investigator and the sponsor. Protocol amendments and all revisions to the ICF after initial IRB/IEC approval were submitted by the investigator to the IRB/IEC for review and approval before implementation in accordance with regulatory requirements. The IRB/IEC regulations for each region were followed at respective centers.

Ethical Conduct of the Study:
The study was conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, applicable local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

Subject Information and Consent:
The ICF(s) used for each study center complied with ICH, the principles enunciated in the Declaration of Helsinki, local regulatory requirements, and ICH GCP guidelines and was approved by the sponsor and the investigator's IRB/IEC. The investigator, or a person delegated by the investigator, explained the medical aspects of the study, including the nature and purpose of the study and the treatment, the procedures involved, and the potential benefits and risks. Other tasks in the informed consent process may have been delegated by the investigator. After having been informed that participation was voluntary and that subjects may withdraw from the study at any time, without prejudice, each subject signed the IRB/IEC-approved ICF prior to undergoing any study specific procedures and enrolment in the study.

Background therapy:

Concomitant medications and therapies deemed necessary for supportive care and safety of the subject were allowed. Specifically, antibiotics were permitted to prevent or manage febrile neutropenia, granulocyte-colony stimulating factor and other white blood cell stimulating factors were permitted during Cycle 1 and onwards, and red blood cell transfusions were permitted at the discretion of the treating physician.

Administration of any other anticancer agents including chemotherapy and biologic agents was not permitted. Similarly, concurrent use of other investigational drugs was not allowed.

Evidence for comparator:

TC Control Group in Stage 2 was given from commercial supply of the following selections based on FDA-approved regimens or National Comprehensive Cancer Network (NCCN) Guidelines in second line and standard of care:

•Topotecan (Hycamtin® or equivalent): recommended dose range of 3.5-4.0 mg/m2/week administered on Days 1, 8, and 15 of a 28-day cycle administered via IV infusion.

•PLD (Doxil® or equivalent): recommended dose range of 40-50 mg/m2 IV on Day 1 of a 28-day cycle.

•Paclitaxel (Taxol® or equivalent): recommended dose range of 60-80 mg/m2/week × 4 on Days 1, 8, 15, and 22 of a 28-day cycle administered via IV infusion.

•Gemcitabine (Gemzar® or equivalent): recommended dose range of 800-1000 mg/m2 IV over 30 minutes on Days 1, 8, and 15 of a 28-day cycle.

Actual start date of recruitment	10 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 81
Worldwide total number of subjects	124
EEA total number of subjects	19

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)	76
From 65 to 84 years	47
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 20 principal investigators at 20 study centers (12 in the US, 5 in the UK, and 3 in Canada) enrolled subjects in this study. The first subject was dosed on 10 December 2012 and the last subject completed observation on 15 April 2016.

Pre-assignment

Screening details:

A total of 145 subjects were assessed for inclusion in the study. Of these, 124 subject were enrolled and 21 subjects failed screening assessments.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Stage 1

Arm description:

Stage 1 was a safety lead-in stage with a dose escalation design. Subjects were evaluated with the combination of G+C, given as 28-day treatment cycles: guadecitabine administered SC daily on Days 1-5, at a starting dose of 45 mg/m2/d, followed by carboplatin IV based on a targeted dose of AUC 5 on Day 8. In a dose escalation design, cohorts of 6 subjects were used to identify the optimum dose of G+C.

Arm type	Experimental
Investigational medicinal product name	Guadecitabine
Investigational medicinal product code	SGI-110
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cohort 1: Guadecitabine 45 mg/m2 SC once daily on Days 1-5 and carboplatin IV AUC 5 on Day 8 of a 28-day cycle (dose was de-escalated after Cycle 1 to 30 mg/m2 guadecitabine for 4 subjects and carboplatin was reduced for 2 subjects).

Cohort 2: Guadecitabine 30 mg/m2 SC once daily on Days 1-5 and carboplatin IV AUC 4 on Day 8 of a 28-day cycle.

Arm title	Stage 2

Arm description:

This stage was conducted as an open-label, randomized, controlled trial. Eligible subjects were randomly assigned in a 1:1 ratio to receive either (1) G+C combination treatment in 28-day cycles, or (2) TC of topotecan, pegylated liposomal doxorubicin (PLD), paclitaxel, or gemcitabine in 28-day cycles.

Arm type	Experimental and comparator
Investigational medicinal product name	Guadecitabine
Investigational medicinal product code	SGI-110
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Guadecitabine 30 mg/m2 SC once daily on Days 1-5 and carboplatin IV AUC 4 on Day 8 of a 28-day cycle.

Reference Therapy, Dose and Mode of Administration:
TC of one of the following approved products using commercially available supply: topotecan, PLD, paclitaxel, or gemcitabine, in 28-day cycles selected at the investigator's discretion, based on recommended dosing, as follows:
•Topotecan: 3.5-4.0 mg/m2/wk administered on Days 1, 8, and 15 via IV infusion.
•PLD: 40-50 mg/m2 administered on Day 1 via IV infusion.
•Paclitaxel: 60-80 mg/m2/wk administered on Days 1, 8, 15, and 22 via IV infusion.
•Gemcitabine: 800-1000 mg/m2 administered on Days 1, 8, and 15 via IV infusion.

Number of subjects in period 1	Stage 1	Stage 2
Started	21	103
Completed	20	100
Not completed	1	3
Physician decision	1	2
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial baseline period

Reporting group description: -

Reporting group values	Overall trial baseline period	Total	
Number of subjects	124	124	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	76	76	
From 65-84 years	47	47	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	124	124	
Male	0	0	

End points

End points reporting groups

Reporting group title	Stage 1

Reporting group description:

Stage 1 was a safety lead-in stage with a dose escalation design. Subjects were evaluated with the combination of G+C, given as 28-day treatment cycles: guadecitabine administered SC daily on Days 1-5, at a starting dose of 45 mg/m2/d, followed by carboplatin IV based on a targeted dose of AUC 5 on Day 8. In a dose escalation design, cohorts of 6 subjects were used to identify the optimum dose of G+C.

Reporting group title	Stage 2

Reporting group description:

This stage was conducted as an open-label, randomized, controlled trial. Eligible subjects were randomly assigned in a 1:1 ratio to receive either (1) G+C combination treatment in 28-day cycles, or (2) TC of topotecan, pegylated liposomal doxorubicin (PLD), paclitaxel, or gemcitabine in 28-day cycles.

Subject analysis set title	Stage 1: G+C, 30 mg/m2
Subject analysis set type	Full analysis

Subject analysis set description:

Guadecitabine 30 mg/m2 SC once daily on Days 1-5 and carboplatin IV AUC 4 on Day 8 of a 28-day cycle.

Subject analysis set title	Stage 1: G+C, 45 mg/m2
Subject analysis set type	Full analysis

Subject analysis set description:

Guadecitabine 45 mg/m2 SC once daily on Days 1-5 and carboplatin IV AUC 5 on Day 8 of a 28-day cycle (dose was de-escalated after Cycle 1 to 30 mg/m2 guadecitabine for 4 subjects and carboplatin was reduced for 2 subjects).

Subject analysis set title	Stage 2: G+C, 30 mg/m2
Subject analysis set type	Full analysis

Subject analysis set description:

Guadecitabine 30 mg/m2 SC once daily on Days 1-5 and carboplatin IV AUC 4 on Day 8 of a 28-day cycle.

Subject analysis set title	Stage 2: TC
Subject analysis set type	Full analysis

Subject analysis set description:

TC of one of the following approved products using commercially available supply: topotecan, PLD, paclitaxel, or gemcitabine, in 28-day cycles selected at the investigator’s discretion, based on recommended dosing, as follows:
• Topotecan: 3.5-4.0 mg/m2/wk administered on Days 1, 8, and 15 via IV infusion.
• PLD: 40-50 mg/m2 administered on Day 1 via IV infusion.
• Paclitaxel: 60-80 mg/m2/wk administered on Days 1, 8, 15, and 22 via IV infusion.
• Gemcitabine: 800-1000 mg/m2 administered on Days 1, 8, and 15 via IV infusion.

Subject analysis set title	Stage 2: Crossover TC to G+C
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects initially randomized to TC who crossed over to receive 30 mg/m2 G+C after having disease progression.

Primary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression free survival time was defined as the time interval from the date of the first dose of study medication until the earlier of disease progression or death.

End point type	Primary

End point timeframe:

Subjects were treated with their assigned treatment (G+C or TC) until disease progression or unacceptable treatment-related toxicity occurred.

End point values	Stage 2: G+C, 30 mg/m2	Stage 2: TC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: days				
median (confidence interval 95%)				
PFS in days	114 (63 to 169)	64 (52 to 105)		

Statistical analyses

Statistical analysis title	Comparison of PFS
Comparison groups	Stage 2: G+C, 30 mg/m2 v Stage 2: TC
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0654
Method	Logrank

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

The ORR was defined as the proportion of subjects who experienced an objective response (best overall response of complete response/full response or partial response, which was confirmed by a subsequent assessment at least 28 days later). Response categories were determined based on RECIST v1.1 criiteria, or on modified Rustin (CA-125) criteria if response assessment could not be made using RECIST criteria.

End point type	Secondary

End point timeframe:

Subjects were treated with their assigned treatment (G+C or TC) until disease progression or unacceptable treatment-related toxicity occurred.

End point values	Stage 2: G+C, 30 mg/m2	Stage 2: TC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: Percentage				
number (confidence interval 95%)				
ORR (CR/FR+PR)	16 (7 to 28.6)	8 (2.3 to 19.6)		

Statistical analyses

Statistical analysis title	Comparison of Objective Response Rate
Comparison groups	Stage 2: TC v Stage 2: G+C, 30 mg/m2
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	Fisher exact

Secondary: Duration of response in responders

End point title	Duration of response in responders

End point description:

Duration of response is defined as the time between the date of the first documentation of complete response/full response or partial response, and the date of disease progression or date of death due to any cause, or the last adequate tumor assessment prior to the start of subsequent anti-cancer therapy including crossing over to G+C from TC arm, whichever occurred earlier. Only subjects who responded were included in the duration of response calculation.

End point type	Secondary

End point timeframe:

Subjects were treated with their assigned treatment (G+C or TC) until disease progression or unacceptable treatment-related toxicity occurred.

End point values	Stage 2: G+C, 30 mg/m2	Stage 2: TC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	14		
Units: Days				
number (confidence interval 95%)				
Median duration, days	186 (147 to 241)	173 (121 to 267)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival rate at 6 months

End point title	Progression Free Survival rate at 6 months

End point description:

Progression free survival rate at 6 months is the proportion of subjects who were alive and did not have disease progression at 6 months after start of treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	Stage 2: G+C, 30 mg/m2	Stage 2: TC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: proportion of subjects				
median (confidence interval 95%)				
PFS rate at 6 months	0.37 (0.24 to 0.50)	0.11 (0.04 to 0.22)		

Statistical analyses

Statistical analysis title	Comparison of PFS rate at 6 months
Comparison groups	Stage 2: G+C, 30 mg/m2 v Stage 2: TC
Number of subjects included in analysis	100
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0027
Method	Logrank

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the number of days from the day the subject was administered the first dose of study treatment to the date of death (regardless of cause). Survival time was censored on the last date the subject was known to be alive or lost to follow-up before reaching the event of death.

End point type	Secondary

End point timeframe:

Subjects were treated with their assigned treatment (G+C or TC) until disease progression or unacceptable treatment-related toxicity occurred.

End point values	Stage 2: G+C, 30 mg/m2	Stage 2: TC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: days				
median (confidence interval 95%)				
OS in days	331 (231 to 415)	221 (145 to 372)		

Statistical analyses

Statistical analysis title	Comparison of Overall Survival
Comparison groups	Stage 2: TC v Stage 2: G+C, 30 mg/m2
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5852
Method	Logrank

Secondary: Overall Survival Rate at 6 months

End point title	Overall Survival Rate at 6 months

End point description:

Overall survival rate at 6 months is the proportion of subjects who were alive at 6 months after the start of study treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	Stage 2: G+C, 30 mg/m2	Stage 2: TC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: proportion of subjects				
median (confidence interval 95%)				
OS rate at 6 months	0.72 (0.58 to 0.83)	0.67 (0.47 to 0.80)		

Statistical analyses

Statistical analysis title	Comparison of Overall Survival rate at 6 months
Comparison groups	Stage 2: TC v Stage 2: G+C, 30 mg/m2
Number of subjects included in analysis	100
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.5629
Method	Logrank

Secondary: Clinical Benefit Rate

End point title	Clinical Benefit Rate

End point description:

CBR was defined as the proportion of subjects who experienced a best overall response of complete response/full response or partial response (confirmed by a subsequent assessment at least 28 days

later), or documented stable disease for at least 3 months after the first dose. Response categories were determined based on RECIST v1.1 criteria, then based on modified Rustin (CA-125) criteria if assessment could not be made using RECIST criteria.

End point type	Secondary

End point timeframe:

Subjects were treated with their assigned treatment (G+C or TC) until disease progression or unacceptable treatment-related toxicity occurred.

End point values	Stage 2: G+C, 30 mg/m2	Stage 2: TC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	49		
Units: Percentage				
number (confidence interval 95%)				
CBR (CR/FR+PR+stable disease)	41 (27.6 to 55.8)	29 (16.6 to 43.3)		

Statistical analyses

Statistical analysis title	Comparison of Clinical Benefit Rate
Comparison groups	Stage 2: G+C, 30 mg/m2 v Stage 2: TC
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.213
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded on scheduled study days and at study follow-up.	
Adverse event reporting additional description:	
Note: only one occurrence per preferred term is reported in the tables below.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Stage 1: G+C, 30 mg/m2
Reporting group description: -	
Reporting group title	Stage 1: G+C, 45 mg/m2
Reporting group description: -	
Reporting group title	Stage 2: G+C, 30 mg/m2
Reporting group description: -	
Reporting group title	Stage 2: TC
Reporting group description: -	
Reporting group title	Stage 2: TC to G+C, 30 mg/m2
Reporting group description: -	

Serious adverse events	Stage 1: G+C, 30 mg/m2	Stage 1: G+C, 45 mg/m2	Stage 2: G+C, 30 mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 14 (57.14%)	4 / 6 (66.67%)	26 / 51 (50.98%)
number of deaths (all causes)	14	4	43
number of deaths resulting from adverse events	0	1	2
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adverse drug reaction			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (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
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Influenza like illness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (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
Elective procedure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary embolism			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Pulmonary oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (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
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Transaminases increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (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
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Sinus tachycardia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Tachycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (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
Seizure			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (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 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Radicular pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	2 / 6 (33.33%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Pancytopenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (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 disorders			
Small intestinal obstruction			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	8 / 51 (15.69%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 51 (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
Ascites			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Large intestine perforation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Abdominal abscess			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (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
Portal vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Musculoskeletal and connective tissue disorders			
Gait disturbance			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in jaw			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Infections and infestations			
Sepsis			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (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
Pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (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
Infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (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
Postoperative fever			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (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 / 14 (0.00%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (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
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (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

Serious adverse events	Stage 2: TC	Stage 2: TC to G+C, 30 mg/m2	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 49 (48.98%)	12 / 27 (44.44%)	
number of deaths (all causes)	18	22	
number of deaths resulting from adverse events	2	2	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse drug reaction			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			

subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elective procedure			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tachycardia			

subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 49 (0.00%)	3 / 27 (11.11%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	4 / 49 (8.16%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 49 (6.12%)	5 / 27 (18.52%)	
occurrences causally related to treatment / all	2 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 49 (10.20%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	4 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	4 / 49 (8.16%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			

subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Gait disturbance			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 49 (4.08%)	3 / 27 (11.11%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	1 / 1	2 / 2	
Pneumonia			

subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative fever			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Stage 1: G+C, 30 mg/m2	Stage 1: G+C, 45 mg/m2	Stage 2: G+C, 30 mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	6 / 6 (100.00%)	50 / 51 (98.04%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	7 / 51 (13.73%)
occurrences (all)	1	0	7
Embolism			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
Haematoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Hypotension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Lymphoedema			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	1	1	0
Deep vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences (all)	0	1	1

Any event			
subjects affected / exposed	2 / 14 (14.29%)	3 / 6 (50.00%)	12 / 51 (23.53%)
occurrences (all)	2	3	12
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 14 (64.29%)	4 / 6 (66.67%)	33 / 51 (64.71%)
occurrences (all)	9	4	33
Injection site reaction			
subjects affected / exposed	8 / 14 (57.14%)	2 / 6 (33.33%)	23 / 51 (45.10%)
occurrences (all)	8	2	23
Pyrexia			
subjects affected / exposed	2 / 14 (14.29%)	4 / 6 (66.67%)	8 / 51 (15.69%)
occurrences (all)	2	4	8
Oedema peripheral			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	5 / 51 (9.80%)
occurrences (all)	2	2	5
Adverse drug reaction			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	2 / 51 (3.92%)
occurrences (all)	3	1	2
Pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	5 / 51 (9.80%)
occurrences (all)	0	0	5
Chills			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	0	0	4
Hernia pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Peripheral swelling			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Early satiety			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	0	0	4
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Injection site pain			
subjects affected / exposed	4 / 14 (28.57%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	4	0	1
Mass			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Any event			
subjects affected / exposed	13 / 14 (92.86%)	6 / 6 (100.00%)	41 / 51 (80.39%)
occurrences (all)	13	6	41
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	10 / 51 (19.61%)
occurrences (all)	2	0	10
Hypersensitivity			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	3 / 51 (5.88%)
occurrences (all)	0	1	3
Any event			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	12 / 51 (23.53%)
occurrences (all)	2	1	12
Reproductive system and breast disorders			
Perineal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Vaginal discharge			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Vaginal ulceration			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal swelling			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pelvic pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	5 / 51 (9.80%)
occurrences (all)	0	0	5
Vaginal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	2
Any event			
subjects affected / exposed	4 / 14 (28.57%)	0 / 6 (0.00%)	9 / 51 (17.65%)
occurrences (all)	4	0	9
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	14 / 51 (27.45%)
occurrences (all)	2	1	14
Cough			
subjects affected / exposed	4 / 14 (28.57%)	2 / 6 (33.33%)	7 / 51 (13.73%)
occurrences (all)	4	2	7
Atelectasis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Dyspnoea exertional			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
Haemoptysis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	3 / 51 (5.88%)
occurrences (all)	1	1	3
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Productive cough			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	5 / 51 (9.80%)
occurrences (all)	0	0	5
Oropharyngeal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	2 / 51 (3.92%)
occurrences (all)	0	1	2
Pulmonary oedema			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Wheezing			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Any event			
subjects affected / exposed	6 / 14 (42.86%)	5 / 6 (83.33%)	26 / 51 (50.98%)
occurrences (all)	6	5	26
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 14 (21.43%)	2 / 6 (33.33%)	6 / 51 (11.76%)
occurrences (all)	3	2	6
Insomnia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	2	0	4
Depression			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	1	0	4
Libido decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0

Any event			
subjects affected / exposed	5 / 14 (35.71%)	2 / 6 (33.33%)	11 / 51 (21.57%)
occurrences (all)	5	2	11
Investigations			
Weight decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	1	0	2
Anion gap increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	2	0	4
Bilirubin urine present			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Blood albumin decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Blood chloride decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Carbon dioxide decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Protein urine present			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Weight increased			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	3 / 51 (5.88%)
occurrences (all)	2	1	3
Specific gravity urine increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Urine ketone body present			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Urine leukocyte esterase positive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Protein total decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Any event			
subjects affected / exposed	5 / 14 (35.71%)	4 / 6 (66.67%)	15 / 51 (29.41%)
occurrences (all)	5	4	15
Blood creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	7 / 51 (13.73%)
occurrences (all)	0	1	7
International normalised ratio increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	1	0	2
Infusion related reaction			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	3 / 51 (5.88%)
occurrences (all)	2	2	3
Procedural pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	1	0	3
Skin abrasion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Stoma site pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Any event			
subjects affected / exposed	3 / 14 (21.43%)	2 / 6 (33.33%)	15 / 51 (29.41%)
occurrences (all)	3	2	15
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	0	0	4
Sinus tachycardia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Any event			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	7 / 51 (13.73%)
occurrences (all)	1	0	7
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	9 / 51 (17.65%)
occurrences (all)	3	0	9
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	5 / 51 (9.80%)
occurrences (all)	1	0	5
Dysgeusia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	0	0	4
Neuropathy peripheral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Paraesthesia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Any event			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	15 / 51 (29.41%)
occurrences (all)	3	0	15
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	7 / 14 (50.00%)	5 / 6 (83.33%)	36 / 51 (70.59%)
occurrences (all)	7	5	36
Leukopenia			
subjects affected / exposed	5 / 14 (35.71%)	2 / 6 (33.33%)	16 / 51 (31.37%)
occurrences (all)	5	2	16
Anaemia			
subjects affected / exposed	7 / 14 (50.00%)	4 / 6 (66.67%)	16 / 51 (31.37%)
occurrences (all)	7	4	16
Thrombocytopenia			
subjects affected / exposed	3 / 14 (21.43%)	6 / 6 (100.00%)	12 / 51 (23.53%)
occurrences (all)	3	6	12
Pancytopenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Any event			
subjects affected / exposed	12 / 14 (85.71%)	6 / 6 (100.00%)	44 / 51 (86.27%)
occurrences (all)	12	6	44
Ear and labyrinth disorders			
Ear discomfort			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Any event			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 14 (71.43%)	2 / 6 (33.33%)	38 / 51 (74.51%)
occurrences (all)	10	2	38
Vomiting			
subjects affected / exposed	6 / 14 (42.86%)	2 / 6 (33.33%)	32 / 51 (62.75%)
occurrences (all)	6	2	32
Constipation			
subjects affected / exposed	5 / 14 (35.71%)	4 / 6 (66.67%)	22 / 51 (43.14%)
occurrences (all)	5	4	22
Abdominal pain			
subjects affected / exposed	4 / 14 (28.57%)	2 / 6 (33.33%)	21 / 51 (41.18%)
occurrences (all)	4	2	21
Diarrohoea			
subjects affected / exposed	4 / 14 (28.57%)	1 / 6 (16.67%)	21 / 51 (41.18%)
occurrences (all)	4	1	21
Stomatitis			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	11 / 51 (21.57%)
occurrences (all)	3	1	11
Abdominal distension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	10 / 51 (19.61%)
occurrences (all)	1	0	10
Dyspepsia			
subjects affected / exposed	3 / 14 (21.43%)	2 / 6 (33.33%)	6 / 51 (11.76%)
occurrences (all)	3	2	6
Ascites			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	4 / 51 (7.84%)
occurrences (all)	2	2	4

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 14 (7.14%)	2 / 6 (33.33%)	8 / 51 (15.69%)
occurrences (all)	1	2	8
Abdominal pain upper			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	3	0	4
Abdominal discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Abdominal pain lower			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Anorectal discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	1 / 14 (7.14%)	2 / 6 (33.33%)	1 / 51 (1.96%)
occurrences (all)	1	2	1
Flatulence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	4 / 51 (7.84%)
occurrences (all)	0	0	4
Haemorrhoids			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Dental caries			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Epigastric discomfort			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Lip dry			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Any event			
subjects affected / exposed	12 / 14 (85.71%)	6 / 6 (100.00%)	48 / 51 (94.12%)
occurrences (all)	12	6	48
Dysphagia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	7 / 51 (13.73%)
occurrences (all)	2	1	7
Alopecia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	6 / 51 (11.76%)
occurrences (all)	1	0	6
Dermatitis contact			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	1	0	2
Erythema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Hyperhidrosis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Night sweats			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Onycholysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 14 (7.14%)	3 / 6 (50.00%)	7 / 51 (13.73%)
occurrences (all)	1	3	7
Rash erythematous			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Any event			
subjects affected / exposed	7 / 14 (50.00%)	4 / 6 (66.67%)	19 / 51 (37.25%)
occurrences (all)	7	4	19
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	5 / 51 (9.80%)
occurrences (all)	2	0	5
Haematuria			

subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	2	0	1
Hydronephrosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Micturition urgency			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Pollakiuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	2
Urinary incontinence			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	1	0	2
Urinary retention			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Any event			
subjects affected / exposed	5 / 14 (35.71%)	1 / 6 (16.67%)	13 / 51 (25.49%)
occurrences (all)	5	1	13
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	9 / 51 (17.65%)
occurrences (all)	3	1	9
Arthralgia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	11 / 51 (21.57%)
occurrences (all)	2	0	11
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	10 / 51 (19.61%)
occurrences (all)	0	1	10
Flank pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Groin pain			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 51 (3.92%)
occurrences (all)	1	0	2
Joint stiffness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	5 / 51 (9.80%)
occurrences (all)	1	0	5
Muscular weakness			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	3 / 51 (5.88%)
occurrences (all)	2	1	3
Musculoskeletal chest pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	5 / 51 (9.80%)
occurrences (all)	1	0	5
Musculoskeletal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	6 / 51 (11.76%)
occurrences (all)	1	0	6
Myalgia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	2	0	3
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Bone pain			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	3	0	1
Any event			
subjects affected / exposed	8 / 14 (57.14%)	2 / 6 (33.33%)	27 / 51 (52.94%)
occurrences (all)	8	2	27
Infections and infestations			
Bacteriuria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Breast cellulitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0

Localised infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Rocky mountain spotted fever			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	8 / 51 (15.69%)
occurrences (all)	2	1	8
Vaginitis bacterial			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Enterococcal infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Any event			
subjects affected / exposed	7 / 14 (50.00%)	3 / 6 (50.00%)	21 / 51 (41.18%)
occurrences (all)	7	3	21
Metabolism and nutrition disorders			
Hypomagnesaemia			

subjects affected / exposed	3 / 14 (21.43%)	4 / 6 (66.67%)	15 / 51 (29.41%)
occurrences (all)	3	4	15
Decreased appetite			
subjects affected / exposed	6 / 14 (42.86%)	2 / 6 (33.33%)	14 / 51 (27.45%)
occurrences (all)	6	2	14
Hypokalaemia			
subjects affected / exposed	3 / 14 (21.43%)	2 / 6 (33.33%)	6 / 51 (11.76%)
occurrences (all)	3	2	6
Hyponatraemia			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	3 / 51 (5.88%)
occurrences (all)	3	1	3
Dehydration			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	4 / 51 (7.84%)
occurrences (all)	1	1	4
Hyperglycaemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Hypoglycaemia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 51 (0.00%)
occurrences (all)	2	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Any event			
subjects affected / exposed	9 / 14 (64.29%)	6 / 6 (100.00%)	27 / 51 (52.94%)
occurrences (all)	9	6	27

Non-serious adverse events	Stage 2: TC	Stage 2: TC to G+C, 30 mg/m2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)	27 / 27 (100.00%)	

Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 49 (12.24%)	2 / 27 (7.41%)	
occurrences (all)	6	2	
Embolism			
subjects affected / exposed	0 / 49 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Flushing			
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Haematoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Hypotension			
subjects affected / exposed	3 / 49 (6.12%)	3 / 27 (11.11%)	
occurrences (all)	3	3	
Lymphoedema			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Deep vein thrombosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Any event			
subjects affected / exposed	14 / 49 (28.57%)	7 / 27 (25.93%)	
occurrences (all)	14	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	26 / 49 (53.06%)	14 / 27 (51.85%)	
occurrences (all)	26	14	
Injection site reaction			
subjects affected / exposed	1 / 49 (2.04%)	9 / 27 (33.33%)	
occurrences (all)	1	9	
Pyrexia			
subjects affected / exposed	3 / 49 (6.12%)	3 / 27 (11.11%)	
occurrences (all)	3	3	
Oedema peripheral			

subjects affected / exposed	14 / 49 (28.57%)	3 / 27 (11.11%)	
occurrences (all)	14	3	
Adverse drug reaction			
subjects affected / exposed	0 / 49 (0.00%)	4 / 27 (14.81%)	
occurrences (all)	0	4	
Pain			
subjects affected / exposed	4 / 49 (8.16%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
Chills			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Hernia pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Peripheral swelling			
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Early satiety			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Asthenia			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Injection site pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Mass			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	39 / 49 (79.59%)	22 / 27 (81.48%)	
occurrences (all)	39	22	
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	3 / 49 (6.12%)	4 / 27 (14.81%)	
occurrences (all)	3	4	
Hypersensitivity			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	3 / 49 (6.12%)	4 / 27 (14.81%)	
occurrences (all)	3	4	
Reproductive system and breast disorders			
Perineal pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Vaginal discharge			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Vaginal ulceration			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Vulvovaginal swelling			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Pelvic pain			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Vaginal haemorrhage			
subjects affected / exposed	2 / 49 (4.08%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Any event			
subjects affected / exposed	5 / 49 (10.20%)	4 / 27 (14.81%)	
occurrences (all)	5	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	15 / 49 (30.61%)	5 / 27 (18.52%)	
occurrences (all)	15	5	
Cough			

subjects affected / exposed	8 / 49 (16.33%)	4 / 27 (14.81%)	
occurrences (all)	8	4	
Atelectasis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Dyspnoea exertional			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Haemoptysis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Pleural effusion			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Productive cough			
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Epistaxis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Pulmonary oedema			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Wheezing			

subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Any event			
subjects affected / exposed	27 / 49 (55.10%)	9 / 27 (33.33%)	
occurrences (all)	27	9	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 49 (12.24%)	1 / 27 (3.70%)	
occurrences (all)	6	1	
Insomnia			
subjects affected / exposed	13 / 49 (26.53%)	3 / 27 (11.11%)	
occurrences (all)	13	3	
Depression			
subjects affected / exposed	5 / 49 (10.20%)	0 / 27 (0.00%)	
occurrences (all)	5	0	
Libido decreased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	18 / 49 (36.73%)	5 / 27 (18.52%)	
occurrences (all)	18	5	
Investigations			
Weight decreased			
subjects affected / exposed	5 / 49 (10.20%)	0 / 27 (0.00%)	
occurrences (all)	5	0	
Anion gap increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 49 (4.08%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Bilirubin urine present			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Blood albumin decreased			

subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 49 (8.16%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
Blood chloride decreased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Carbon dioxide decreased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Protein urine present			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Weight increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 49 (4.08%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Specific gravity urine increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Urine ketone body present			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

Blood phosphorus decreased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Protein total decreased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	15 / 49 (30.61%)	10 / 27 (37.04%)	
occurrences (all)	15	10	
Blood creatinine increased			
subjects affected / exposed	3 / 49 (6.12%)	2 / 27 (7.41%)	
occurrences (all)	3	2	
International normalised ratio increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Infusion related reaction			
subjects affected / exposed	0 / 49 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Procedural pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Stoma site pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	5 / 49 (10.20%)	3 / 27 (11.11%)	
occurrences (all)	5	3	
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Any event			
subjects affected / exposed	4 / 49 (8.16%)	2 / 27 (7.41%)	
occurrences (all)	4	2	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 49 (10.20%)	1 / 27 (3.70%)	
occurrences (all)	5	1	
Dizziness			
subjects affected / exposed	6 / 49 (12.24%)	1 / 27 (3.70%)	
occurrences (all)	6	1	
Dysgeusia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Neuropathy peripheral			
subjects affected / exposed	4 / 49 (8.16%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
Paraesthesia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Any event			
subjects affected / exposed	16 / 49 (32.65%)	7 / 27 (25.93%)	
occurrences (all)	16	7	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	16 / 49 (32.65%)	18 / 27 (66.67%)	
occurrences (all)	16	18	
Leukopenia			

subjects affected / exposed	11 / 49 (22.45%)	12 / 27 (44.44%)	
occurrences (all)	11	12	
Anaemia			
subjects affected / exposed	25 / 49 (51.02%)	8 / 27 (29.63%)	
occurrences (all)	25	8	
Thrombocytopenia			
subjects affected / exposed	12 / 49 (24.49%)	10 / 27 (37.04%)	
occurrences (all)	12	10	
Pancytopenia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Any event			
subjects affected / exposed	35 / 49 (71.43%)	22 / 27 (81.48%)	
occurrences (all)	35	22	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	1 / 49 (2.04%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	28 / 49 (57.14%)	12 / 27 (44.44%)	
occurrences (all)	28	12	
Vomiting			
subjects affected / exposed	15 / 49 (30.61%)	10 / 27 (37.04%)	
occurrences (all)	15	10	
Constipation			
subjects affected / exposed	17 / 49 (34.69%)	10 / 27 (37.04%)	
occurrences (all)	17	10	
Abdominal pain			

subjects affected / exposed	17 / 49 (34.69%)	8 / 27 (29.63%)	
occurrences (all)	17	8	
Diarrohoea			
subjects affected / exposed	11 / 49 (22.45%)	9 / 27 (33.33%)	
occurrences (all)	11	9	
Stomatitis			
subjects affected / exposed	12 / 49 (24.49%)	2 / 27 (7.41%)	
occurrences (all)	12	2	
Abdominal distension			
subjects affected / exposed	12 / 49 (24.49%)	4 / 27 (14.81%)	
occurrences (all)	12	4	
Dyspepsia			
subjects affected / exposed	10 / 49 (20.41%)	3 / 27 (11.11%)	
occurrences (all)	10	3	
Ascites			
subjects affected / exposed	4 / 49 (8.16%)	2 / 27 (7.41%)	
occurrences (all)	4	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 49 (8.16%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
Abdominal pain upper			
subjects affected / exposed	5 / 49 (10.20%)	3 / 27 (11.11%)	
occurrences (all)	5	3	
Abdominal discomfort			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Abdominal pain lower			
subjects affected / exposed	1 / 49 (2.04%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Anorectal discomfort			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Dry mouth			
subjects affected / exposed	4 / 49 (8.16%)	2 / 27 (7.41%)	
occurrences (all)	4	2	
Flatulence			

subjects affected / exposed	2 / 49 (4.08%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Haemorrhoids			
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Proctalgia			
subjects affected / exposed	1 / 49 (2.04%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Toothache			
subjects affected / exposed	1 / 49 (2.04%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Dental caries			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Lip dry			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Oral pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Rectal haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Any event			
subjects affected / exposed	41 / 49 (83.67%)	25 / 27 (92.59%)	
occurrences (all)	41	25	
Dysphagia			
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			

Rash				
subjects affected / exposed	6 / 49 (12.24%)	0 / 27 (0.00%)		
occurrences (all)	6	0		
Alopecia				
subjects affected / exposed	7 / 49 (14.29%)	2 / 27 (7.41%)		
occurrences (all)	7	2		
Dermatitis contact				
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)		
occurrences (all)	1	0		
Dry skin				
subjects affected / exposed	6 / 49 (12.24%)	2 / 27 (7.41%)		
occurrences (all)	6	2		
Erythema				
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)		
occurrences (all)	2	1		
Hyperhidrosis				
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)		
occurrences (all)	1	0		
Night sweats				
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)		
occurrences (all)	1	0		
Onycholysis				
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)		
occurrences (all)	3	0		
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)		
occurrences (all)	3	0		
Pruritus				
subjects affected / exposed	0 / 49 (0.00%)	3 / 27 (11.11%)		
occurrences (all)	0	3		
Rash erythematous				
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)		
occurrences (all)	0	0		
Rash maculo-papular				

subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Skin lesion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Swelling face			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	24 / 49 (48.98%)	8 / 27 (29.63%)	
occurrences (all)	24	8	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 49 (6.12%)	2 / 27 (7.41%)	
occurrences (all)	3	2	
Haematuria			
subjects affected / exposed	3 / 49 (6.12%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Hydronephrosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Micturition urgency			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	2 / 49 (4.08%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Urinary incontinence			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	11 / 49 (22.45%)	5 / 27 (18.52%)	
occurrences (all)	11	5	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 49 (16.33%)	5 / 27 (18.52%)	
occurrences (all)	8	5	
Arthralgia			
subjects affected / exposed	6 / 49 (12.24%)	2 / 27 (7.41%)	
occurrences (all)	6	2	
Pain in extremity			
subjects affected / exposed	8 / 49 (16.33%)	3 / 27 (11.11%)	
occurrences (all)	8	3	
Flank pain			
subjects affected / exposed	0 / 49 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Groin pain			
subjects affected / exposed	1 / 49 (2.04%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Joint stiffness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	4 / 49 (8.16%)	3 / 27 (11.11%)	
occurrences (all)	4	3	
Muscular weakness			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	3 / 49 (6.12%)	2 / 27 (7.41%)	
occurrences (all)	3	2	
Neck pain			

subjects affected / exposed	1 / 49 (2.04%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Bone pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Any event			
subjects affected / exposed	20 / 49 (40.82%)	13 / 27 (48.15%)	
occurrences (all)	20	13	
Infections and infestations			
Bacteriuria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Breast cellulitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Localised infection			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	2 / 49 (4.08%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Rhinitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Rocky mountain spotted fever			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	4 / 49 (8.16%)	3 / 27 (11.11%)	
occurrences (all)	4	3	
Vaginitis bacterial			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	

Enterococcal infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Impetigo			
subjects affected / exposed	0 / 49 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Any event			
subjects affected / exposed	18 / 49 (36.73%)	10 / 27 (37.04%)	
occurrences (all)	18	10	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	8 / 49 (16.33%)	9 / 27 (33.33%)	
occurrences (all)	8	9	
Decreased appetite			
subjects affected / exposed	13 / 49 (26.53%)	6 / 27 (22.22%)	
occurrences (all)	13	6	
Hypokalaemia			
subjects affected / exposed	8 / 49 (16.33%)	3 / 27 (11.11%)	
occurrences (all)	8	3	
Hyponatraemia			
subjects affected / exposed	7 / 49 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	7	1	
Dehydration			
subjects affected / exposed	6 / 49 (12.24%)	5 / 27 (18.52%)	
occurrences (all)	6	5	
Hyperglycaemia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	3 / 49 (6.12%)	3 / 27 (11.11%)	
occurrences (all)	3	3	
Hypocalcaemia			

subjects affected / exposed	2 / 49 (4.08%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Hypoglycaemia			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Hypophosphataemia			
subjects affected / exposed	2 / 49 (4.08%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Any event			
subjects affected / exposed	26 / 49 (53.06%)	18 / 27 (66.67%)	
occurrences (all)	26	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2013	• Eliminated the limit of 3 prior cytotoxic treatment regimens in Stage 2 eligibility criteria. • Clarified definition of subjects who were refractory to platinum treatment as those who had never responded to prior platinum treatment. • Clarified that all subjects treated in Stage 1 would be used to determine if one objective response occurred for the study to proceed into Stage 2 and the objective response no longer needed to be confirmed since RECIST v 1.1 criteria did not require such confirmation. • Clarified that subjects could come off carboplatin treatment and continue SGI-110 alone at the investigator's discretion after at least 4 ycles instead of 6 cycles. Clarified that, in the absence of unacceptable toxicity, subjects should continue treatment with SGI-110 until at least radiographic and clinical disease progression or until the subject needed to be treated with another anti-cancer treatment. • In Inclusion Criterion #7, added a new inclusion requirement for subjects to have platelet counts ≥ 100,000 cells/mm3 to be eligible for treatment.
18 November 2013	• Allowed subjects with other histotypes (endometrioid, mixed cell, or clear cell) to be enrolled. • Allowed pleural fluid to be collected for tumor cell analyses, if such collection was more feasible than tumor biopsy or ascites collection. • Allowed subjects with previous platinum hypersensitivity to be enrolled if they successfully undergo an institutional desensitization protocol. • Allowed more choices in TC arm of Stage 2, with the addition of gemcitabine as a TC option. • Allowed dose reduction for guadecitabine from 30 mg/m2 to 24 mg/m2 in the event of guadecitabine specific toxicity. • Allowed dose reduction for carboplatin by one AUC dose level.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Nil.

Notes: