Clinical trial results:
A phase Ib/II multi-center, open-label, dose escalation study of LGX818 and cetuximab or LGX818, BYL719, and cetuximab in patients with BRAF mutant metastatic colorectal cancer

Summary

EudraCT number	2012-002138-35
Trial protocol	ES DE NL IT NO BE
Global end of trial date	12 February 2019

Results information

Result version number	v1 (current)
This version publication date	21 February 2020
First version publication date	21 February 2020

Trial information

Trial identification

Sponsor protocol code	CLGX818X2103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01719380
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Array BioPharma Inc.
Sponsor organisation address	3200 Walnut Street, Boulder, United States, 80301
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., Array BioPharma Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., Array BioPharma Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	12 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase Ib: To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of encorafenib in combination with cetuximab ± alpelisib
Phase II: To compare the efficacy of the dual (encorafenib, cetuximab) and triple (encorafenib, alpelisib, cetuximab) combinations
Secondary objective (Phase 1b and Phase 2): To characterize the safety and tolerability of encorafenib in combination with cetuximab ± alpelisib

Protection of trial subjects:

Before each subject was admitted to the clinical study, informed consent was to be obtained from the subject (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. The informed consent form (ICF) was to be dated and retained by the investigator as part of the clinical study records. The investigator was not to undertake any investigation specifically required for the clinical study until valid consent was obtained. The date consent was obtained was to be documented in the electronic case report form (eCRF). Each subject was to receive a fully signed copy of each consent form that he/she signed for the clinical study.

Background therapy:

Pre-medications for routine cetuximab infusions must have been used in accordance with the label and with the national and/or institutional standards. Following cetuximab label instructions, medications such as corticosteroids and anti-histamines was administered at the discretion of the Investigator to treat an existing infusion reaction, or as pre-medication for a patient who had previously experienced an infusion reaction.
Concomitant therapy used from the time the subject signed the ICF through the study treatment period was recorded in the eCRF, including medications required for treatment of any AEs or SAEs. The medication name, dosage, date, and indication for use was recorded.

Evidence for comparator: -

Actual start date of recruitment	19 November 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	Netherlands: 41
Country: Number of subjects enrolled	Norway: 12
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 5

Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	156
EEA total number of subjects	80

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)	107
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible subjects for this study were those who had BRAF-mutant mCRC and whose disease had progressed despite previous antineoplastic therapy or for whom no further effective standard therapy was available. For Phase 1b, subjects who were chemo-naïve were eligible if other standard therapy was not considered effective.

Pre-assignment

Screening details:

All screening assessments were completed within 14 days before the first dose for phase Ib and before randomization for phase II, with the exception of the baseline imaging assessments (≤ 21 days), dermatologic evaluations (≤ 21 days), and the determination of the BRAF and KRAS mutational status.

Period 1

Period 1 title	Phase 1b
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label phase I dose escalation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dual (Encorafenib+Cetuximab)

Arm description:

Treatment assignment of subjects in each cohort in the dose escalation part was coordinated by the sponsor with allocation forms.
The starting dose for the dual combination study drugs was 100 mg QD for Encorafenib and 400 mg/m² initial dose (cycle 1 day 1) and 250 mg/m² subsequent weekly doses as an intravenous infusion for Cetuximab. The following dual combinations were used Encorafenib 100 mg QD + Cetuximab; Encorafenib 200 mg (QD) + Cetuximab; Encorafenib 400 mg (QD) + Cetuximab; Encorafenib 450 mg (QD) + Cetuximab 400 mg/m² QW as intravenous infusion.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 25 mg, 50 mg, and 100 mg capsules for oral administration once daily (QD).

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

Dosage and administration details:

Cetuximab initial administered dose (Cycle 1 Day 1) was 400 mg/m2 as a 120-minute intravenous infusion followed by 250 mg/m2 weekly dose infused over 60 minutes. The infusion rate was not exceed 10 mg/min.

Arm title	Triple (Encorafenib+Alpelisib+Cetuximab)

Arm description:

Treatment assignment of subjects in each cohort in the dose escalation part was coordinated by the sponsor with allocation forms.
The following triple combinations were used: Encorafenib 200 mg + Alpelisib 100 mg (QD) + Cetuximab; Encorafenib 200 mg + Alpelisib 200 mg (QD) + Cetuximab; Encorafenib 200 mg + Alpelisib 300 mg (QD) + Cetuximab; Encorafenib 300 mg + Alpelisib 200 mg (QD) + Cetuximab (MTD/RP2D of dual) as intravenous infusion.

Arm type	Experimental
Investigational medicinal product name	Alpelisib
Investigational medicinal product code	BYL719
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alpelisib 50 mg and 200 mg tablets for oral administration QD.

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 25 mg, 50 mg, and 100 mg capsules for oral administration once daily (QD).

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

Dosage and administration details:

Cetuximab initial administered dose (Cycle 1 Day 1) was 400 mg/m2 as a 120-minute intravenous infusion followed by 250 mg/m2 weekly dose infused over 60 minutes. The infusion rate was not exceed 10 mg/min.

Number of subjects in period 1	Dual (Encorafenib+Cetuximab)	Triple (Encorafenib+Alpelisib+Cetuximab)
Started	26	28
Completed	50	52
Not completed	26	28
All subjects from Period 1 have discontinued	26	28
Joined	50	52
New patients enrolled in phase 2 analysis	50	52

Period 2

Period 2 title	Phase 2
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study. Randomization was used in Phase 2 to ensure that treatment assignment was unbiased. Patients were assigned to one of the 2 treatment arms in a ratio of 1:1.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dual (Encorafenib+Cetuximab)

Arm description:

Encorafenib 200 mg QD + Cetuximab 400 mg/m2 on Cycle 1 Day 1 and 250 mg/m2 QW.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 25 mg, 50 mg, and 100 mg capsules for oral administration once daily (QD).

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

Dosage and administration details:

Cetuximab initial administered dose (Cycle 1 Day 1) was 400 mg/m2 as a 120-minute intravenous infusion followed by 250 mg/m2 weekly dose infused over 60 minutes. The infusion rate was not exceed 10 mg/min.

Arm title	Triple (Encorafenib+Alpelisib+Cetuximab)

Arm description:

Encorafenib 200 mg QD + Alpelisib 300 mg QD + Cetuximab 400 mg/m2 on Cycle 1 Day 1 and 250 mg/m2 QW

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib 25 mg, 50 mg, and 100 mg capsules for oral administration once daily (QD).

Investigational medicinal product name	Alpelisib
Investigational medicinal product code	BYL719
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alpelisib 50 mg and 200 mg tablets for oral administration QD.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab initial administered dose (Cycle 1 Day 1) was 400 mg/m2 as a 120-minute intravenous infusion followed by 250 mg/m2 weekly dose infused over 60 minutes. The infusion rate was not exceed 10 mg/min.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The main results are based on Period 2, that is why Period 2 is taken as Baseline period. The design of Phase 1b dose-escalation part (Period 1) of the study was to determine the MTD and/or RP2D of Encorafenib in combination with Cetuximab (dual combination) and the MTD and/or RP2D of Encorafenib in combination with Alpelisib and Cetuximab (triple combination). Randomized Phase (Period 2) was designed to assess clinical efficacy and to characterize the safety of the drug combinations.

Number of subjects in period 2[2]	Dual (Encorafenib+Cetuximab)	Triple (Encorafenib+Alpelisib+Cetuximab)
Started	50	52
Completed	0	1
Not completed	50	51
Adverse event, serious fatal	3	3
Physician decision	1	1
Consent withdrawn by subject	2	2
Adverse event, non-fatal	4	3
Lack of efficacy	40	42

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 156 subjects were enrolled in the study (54 subjects in Phase 1b and 102 subjects in Phase 2). Efficacy and safety data for Full Analysis Set and Safety Set included 102 randomized subjects. Data for Incidence of dose-limiting toxicities for phase 1b (54 subjects) was provided as primary endpoint.

Baseline characteristics

Reporting groups	
Reporting group title	Dual (Encorafenib+Cetuximab)
Reporting group description:	
Encorafenib 200 mg QD + Cetuximab 400 mg/m2 on Cycle 1 Day 1 and 250 mg/m2 QW.	
Reporting group title	Triple (Encorafenib+Alpelisib+Cetuximab)
Reporting group description:	
Encorafenib 200 mg QD + Alpelisib 300 mg QD + Cetuximab 400 mg/m2 on Cycle 1 Day 1 and 250 mg/m2 QW	

Reporting group values	Dual (Encorafenib+Cetuximab)	Triple (Encorafenib+Alpelisib+Cetuximab)	Total
Number of subjects	50	52	102
Age categorical Units: Subjects			
Adults (18-64 years)	32	38	70
From 65-84 years	18	14	32
Age continuous Units: years			
arithmetic mean	49.5	52.5	
full range (min-max)	20 to 79	29 to 76	-
Gender categorical Units: Subjects			
Female	36	27	63
Male	14	25	39

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis set (FAS) - comprised all randomized patients in Phase 2.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set included all subjects from the FAS who received at least one dose of Encorafenib, Alpelisib or Cetuximab and had at least one valid post-baseline safety assessment.	

Reporting group values	Full Analysis Set	Safety Set	
Number of subjects	102	102	
Age categorical Units: Subjects			
Adults (18-64 years)	70	70	
From 65-84 years	32	32	
Age continuous Units: years			
arithmetic mean	49.5	52.5	
full range (min-max)	20 to 79	29 to 76	

Gender categorical Units: Subjects			
Female	63	63	
Male	39	39	

End points

End points reporting groups

Reporting group title	Dual (Encorafenib+Cetuximab)

Reporting group description:

Treatment assignment of subjects in each cohort in the dose escalation part was coordinated by the sponsor with allocation forms.
The starting dose for the dual combination study drugs was 100 mg QD for Encorafenib and 400 mg/m² initial dose (cycle 1 day 1) and 250 mg/m² subsequent weekly doses as an intravenous infusion for Cetuximab. The following dual combinations were used Encorafenib 100 mg QD + Cetuximab; Encorafenib 200 mg (QD) + Cetuximab; Encorafenib 400 mg (QD) + Cetuximab; Encorafenib 450 mg (QD) + Cetuximab 400 mg/m² QW as intravenous infusion.

Reporting group title	Triple (Encorafenib+Alpelisib+Cetuximab)

Reporting group description:

Treatment assignment of subjects in each cohort in the dose escalation part was coordinated by the sponsor with allocation forms.
The following triple combinations were used: Encorafenib 200 mg + Alpelisib 100 mg (QD) + Cetuximab; Encorafenib 200 mg + Alpelisib 200 mg (QD) + Cetuximab; Encorafenib 200 mg + Alpelisib 300 mg (QD) + Cetuximab; Encorafenib 300 mg + Alpelisib 200 mg (QD) + Cetuximab (MTD/RP2D of dual) as intravenous infusion.

Reporting group title	Dual (Encorafenib+Cetuximab)

Reporting group description:

Encorafenib 200 mg QD + Cetuximab 400 mg/m2 on Cycle 1 Day 1 and 250 mg/m2 QW.

Reporting group title	Triple (Encorafenib+Alpelisib+Cetuximab)

Reporting group description:

Encorafenib 200 mg QD + Alpelisib 300 mg QD + Cetuximab 400 mg/m2 on Cycle 1 Day 1 and 250 mg/m2 QW

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis set (FAS) - comprised all randomized patients in Phase 2.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set included all subjects from the FAS who received at least one dose of Encorafenib, Alpelisib or Cetuximab and had at least one valid post-baseline safety assessment.

Primary: Incidence of dose-limiting toxicities

End point title	Incidence of dose-limiting toxicities[1]

End point description:

In Phase 1b, estimation of the MTD of both the dual and triple combination treatments was based on the incidence of dose-limiting toxicity (DLT) in Cycle 1 for patients in the Dose-determining Set. Incidence of serious adverse events were provided for all product strengths in dual (LGX818 + Cetuximab) and triple (LGX818 + BYL719 + Cetuximab) combinations for subjects who participated in Phase 1b.

End point type	Primary

End point timeframe:

Incidence of dose-limiting toxicities (DLTs) were defined from date of taking of first dose of study drug until receipt of at least 21 out of 28 planned daily oral doses in Cycle 1 of treatment.

Notes:

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

End point values	Dual (Encorafenib+Cetuximab)	Triple (Encorafenib+Alpelisib+Cetuximab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: Incidence of serious adverse events				
Incidence of SAEs in LGX818 100 mg+Cetuximab	2	0		
Incidence of SAEs in LGX818 200 mg+Cetuximab	13	0		
Incidence of SAEs in LGX818 400 mg+Cetuximab	14	0		
Incidence of SAEs in LGX818 450 mg+Cetuximab	20	0		
Incidence of SAEs in LGX818 200 mg+BYL719 100 mg+C	0	2		
Incidence of SAEs in LGX818 200 mg+BYL719 200 mg+C	0	16		
Incidence of SAEs in LGX818 200 mg+BYL719 300 mg+C	0	9		
Incidence of SAEs in LGX818 300 mg+BYL719 200 mg+C	0	8		

Statistical analyses

No statistical analyses for this end point

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

The primary efficacy endpoint in Phase 2 was the comparison of the PFS between the dual combination MTD/RP2D and triple combination MTD/RP2D. PFS values were based on Kaplan-Meier estimates. This corresponded to an estimated 19.0% risk reduction in disease progression or death for subjects treated with the triple combination compared to those treated with the dual combination.

End point type	Primary

End point timeframe:

Progression-free survival (PFS) was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause.

End point values	Dual (Encorafenib+Cetuximab)	Triple (Encorafenib+Alpelisib+Cetuximab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: months				
median (confidence interval 95%)				
2 months	87.5 (74.3 to 94.2)	82.6 (69.2 to 90.5)		
4 months	53.1 (37.9 to 66.1)	64.1 (49.1 to 75.7)		

6 months	28.5 (15.9 to 42.4)	38.9 (25.3 to 52.2)		
8 months	18.1 (8.2 to 31.2)	32.4 (19.8 to 45.7)		
10 months	12.9 (4.8 to 25.2)	27.9 (16.1 to 41.1)		
12 months	12.9 (4.8 to 25.2)	25.6 (14.2 to 38.6)		
14 months	7.8 (2.0 to 18.7)	11.6 (4.3 to 22.9)		
16 months	7.8 (2.0 to 18.7)	9.3 (3.0 to 20.0)		
18 months	7.8 (2.0 to 18.7)	7.0 (1.8 to 17.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis Plan

Statistical analysis description:

Statistical Analysis provided Kaplan-Meier plot for progression-free survival. Hazard ratio of dual combination was 4.2 (3.0, 5.1) and for triple combination was 4.9 (4.0, 7.0). P-value: statistical significance (one-sided) at the alpha 0.05 level. This corresponded to an estimated 19.0% risk reduction in disease progression or death for subjects treated with the triple combination compared to those treated with the dual combination

Comparison groups	Dual (Encorafenib+Cetuximab) v Triple (Encorafenib+Alpelisib+Cetuximab)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1645 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.532
upper limit	1.234

Notes:

[2] - one-sided log rank test p = 0.1645

Secondary: Duration of Exposure

End point title	Duration of Exposure

End point description:

Duration of exposure was defined as: date of last exposure to study treatment - date of first administration of study treatment +1. There were no on-treatment patient deaths or AEs leading to discontinuation of study treatment reported between the primary CSR data cutoff date and the last patient assessment.

End point type	Secondary

End point timeframe:

Inclusion of explosure of data from date of randomization until date of last patient assessment.

End point values	Dual (Encorafenib+Cetuximab)	Triple (Encorafenib+Alpelisib+Cetuximab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: weeks				
median (full range (min-max))	17.79 (1.1 to 228.1)	22.14 (0.3 to 161.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for adverse event reporting is from start of treatment within 30 days of the last study medication.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Dual combination
Reporting group description:	
Encorafenib 200 mg QD + Cetuximab 400 mg/m2 on Cycle 1 Day 1 and 250 mg/m2 QW	
Reporting group title	Triple combination
Reporting group description:	
Encorafenib 200 mg QD + Alpelisib 300 mg QD + Cetuximab 400 mg/m2 on Cycle 1 Day 1 and 250 mg/m2 QW	

Serious adverse events	Dual combination	Triple combination	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 50 (52.00%)	33 / 52 (63.46%)	
number of deaths (all causes)	7	9	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Eye naevus			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pelvic venous thrombosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 50 (6.00%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 50 (4.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			

subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 50 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Thrombosis in device			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 50 (10.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractoriness to platelet transfusion			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 50 (10.00%)	5 / 52 (9.62%)	
occurrences causally related to treatment / all	1 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	2 / 50 (4.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 50 (4.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			

subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 50 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
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 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 50 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 50 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			

subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site abscess			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 50 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dual combination	Triple combination	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)	52 / 52 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	5 / 50 (10.00%)	0 / 52 (0.00%)	
occurrences (all)	5	0	
Melanocytic naevus			
subjects affected / exposed	1 / 50 (2.00%)	6 / 52 (11.54%)	
occurrences (all)	1	6	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 50 (8.00%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	25 / 50 (50.00%)	27 / 52 (51.92%)	
occurrences (all)	25	27	
Pyrexia			
subjects affected / exposed	12 / 50 (24.00%)	11 / 52 (21.15%)	
occurrences (all)	12	11	
Oedema peripheral			
subjects affected / exposed	5 / 50 (10.00%)	5 / 52 (9.62%)	
occurrences (all)	5	5	
Pain			
subjects affected / exposed	4 / 50 (8.00%)	0 / 52 (0.00%)	
occurrences (all)	4	0	
Malaise			
subjects affected / exposed	3 / 50 (6.00%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Influenza like illness			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Asthenia			

subjects affected / exposed	0 / 50 (0.00%)	8 / 52 (15.38%)	
occurrences (all)	0	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 50 (16.00%)	7 / 52 (13.46%)	
occurrences (all)	8	7	
Dyspnoea			
subjects affected / exposed	8 / 50 (16.00%)	3 / 52 (5.77%)	
occurrences (all)	8	3	
Oropharyngeal pain			
subjects affected / exposed	4 / 50 (8.00%)	0 / 52 (0.00%)	
occurrences (all)	4	0	
Epistaxis			
subjects affected / exposed	3 / 50 (6.00%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Dysphonia			
subjects affected / exposed	2 / 50 (4.00%)	7 / 52 (13.46%)	
occurrences (all)	2	7	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 50 (16.00%)	8 / 52 (15.38%)	
occurrences (all)	8	8	
Anxiety			
subjects affected / exposed	5 / 50 (10.00%)	2 / 52 (3.85%)	
occurrences (all)	5	2	
Investigations			
Lipase increased			
subjects affected / exposed	17 / 50 (34.00%)	7 / 52 (13.46%)	
occurrences (all)	17	7	
Weight decreased			
subjects affected / exposed	10 / 50 (20.00%)	19 / 52 (36.54%)	
occurrences (all)	10	19	
Amylase increased			
subjects affected / exposed	7 / 50 (14.00%)	3 / 52 (5.77%)	
occurrences (all)	7	3	
Alanine aminotransferase increased			

subjects affected / exposed	5 / 50 (10.00%)	5 / 52 (9.62%)	
occurrences (all)	5	5	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 50 (10.00%)	4 / 52 (7.69%)	
occurrences (all)	5	4	
Neutrophil count decreased			
subjects affected / exposed	4 / 50 (8.00%)	0 / 52 (0.00%)	
occurrences (all)	4	0	
Blood creatinine increased			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Blood bilirubin increased			
subjects affected / exposed	1 / 50 (2.00%)	5 / 52 (9.62%)	
occurrences (all)	1	5	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 50 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 50 (10.00%)	2 / 52 (3.85%)	
occurrences (all)	5	2	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 50 (34.00%)	13 / 52 (25.00%)	
occurrences (all)	17	13	
Dizziness			
subjects affected / exposed	6 / 50 (12.00%)	4 / 52 (7.69%)	
occurrences (all)	6	4	
Dysgeusia			
subjects affected / exposed	4 / 50 (8.00%)	7 / 52 (13.46%)	
occurrences (all)	4	7	
Paraesthesia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	8 / 50 (16.00%)	12 / 52 (23.08%)	
occurrences (all)	8	12	
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 50 (6.00%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Cataract			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Vision blurred			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	23 / 50 (46.00%)	30 / 52 (57.69%)	
occurrences (all)	23	30	
Vomiting			
subjects affected / exposed	18 / 50 (36.00%)	25 / 52 (48.08%)	
occurrences (all)	18	25	
Abdomina pain			
subjects affected / exposed	17 / 50 (34.00%)	21 / 52 (40.38%)	
occurrences (all)	17	21	
Constipation			
subjects affected / exposed	14 / 50 (28.00%)	6 / 52 (11.54%)	
occurrences (all)	14	6	
Diarrhoea			
subjects affected / exposed	14 / 50 (28.00%)	29 / 52 (55.77%)	
occurrences (all)	14	29	
Abdominal pain upper			
subjects affected / exposed	5 / 50 (10.00%)	4 / 52 (7.69%)	
occurrences (all)	5	4	
Stomatitis			
subjects affected / exposed	5 / 50 (10.00%)	18 / 52 (34.62%)	
occurrences (all)	5	18	
Dyspepsia			

subjects affected / exposed	4 / 50 (8.00%)	8 / 52 (15.38%)	
occurrences (all)	4	8	
Ascites			
subjects affected / exposed	3 / 50 (6.00%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Dry mouth			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Flatulence			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	9 / 50 (18.00%)	12 / 52 (23.08%)	
occurrences (all)	9	12	
Dry skin			
subjects affected / exposed	9 / 50 (18.00%)	15 / 52 (28.85%)	
occurrences (all)	9	15	
Rash			
subjects affected / exposed	9 / 50 (18.00%)	18 / 52 (34.62%)	
occurrences (all)	9	18	
Pruritus			
subjects affected / exposed	7 / 50 (14.00%)	9 / 52 (17.31%)	
occurrences (all)	7	9	
Acne			
subjects affected / exposed	6 / 50 (12.00%)	4 / 52 (7.69%)	
occurrences (all)	6	4	
Skin fissures			
subjects affected / exposed	5 / 50 (10.00%)	5 / 52 (9.62%)	
occurrences (all)	5	5	
Alopecia			
subjects affected / exposed	3 / 50 (6.00%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Erythema			
subjects affected / exposed	3 / 50 (6.00%)	1 / 52 (1.92%)	
occurrences (all)	3	1	

Skin hyperpigmentation			
subjects affected / exposed	3 / 50 (6.00%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Hyperkeratosis			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Pruritus generalised			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Rash maculo-papular			
subjects affected / exposed	2 / 50 (4.00%)	11 / 52 (21.15%)	
occurrences (all)	2	11	
Actinic keratosis			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Erythema multiforme			
subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 50 (38.00%)	15 / 52 (28.85%)	
occurrences (all)	19	15	
Back pain			
subjects affected / exposed	12 / 50 (24.00%)	10 / 52 (19.23%)	
occurrences (all)	12	10	
Myalgia			
subjects affected / exposed	8 / 50 (16.00%)	12 / 52 (23.08%)	
occurrences (all)	8	12	
Pain in extremity			
subjects affected / exposed	8 / 50 (16.00%)	9 / 52 (17.31%)	
occurrences (all)	8	9	
Musculoskeletal pain			

subjects affected / exposed	4 / 50 (8.00%)	9 / 52 (17.31%)	
occurrences (all)	4	9	
Muscle spasms			
subjects affected / exposed	2 / 50 (4.00%)	5 / 52 (9.62%)	
occurrences (all)	2	5	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Bone pain			
subjects affected / exposed	0 / 50 (0.00%)	6 / 52 (11.54%)	
occurrences (all)	0	6	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 50 (6.00%)	6 / 52 (11.54%)	
occurrences (all)	3	6	
Gastroenteritis			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Paronychia			
subjects affected / exposed	1 / 50 (2.00%)	7 / 52 (13.46%)	
occurrences (all)	1	7	
Rash pustular			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Cystitis			
subjects affected / exposed	0 / 50 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	
Nail infection			
subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Tooth infection			
subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	16 / 50 (32.00%)	19 / 52 (36.54%)	
occurrences (all)	16	19	
Hypokalaemia			
subjects affected / exposed	6 / 50 (12.00%)	10 / 52 (19.23%)	
occurrences (all)	6	10	
Hyperglycaemia			
subjects affected / exposed	5 / 50 (10.00%)	18 / 52 (34.62%)	
occurrences (all)	5	18	
Hypomagnesaemia			
subjects affected / exposed	4 / 50 (8.00%)	11 / 52 (21.15%)	
occurrences (all)	4	11	
Hyponatraemia			
subjects affected / exposed	3 / 50 (6.00%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Hypophosphataemia			
subjects affected / exposed	3 / 50 (6.00%)	7 / 52 (13.46%)	
occurrences (all)	3	7	
Dehydration			
subjects affected / exposed	2 / 50 (4.00%)	4 / 52 (7.69%)	
occurrences (all)	2	4	
Hypocalcaemia			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2013	Amendment 1 (date 03 July 2013) - The main purpose of this amendment was to introduce enhanced safety monitoring and risk assessment to mitigate any potential development of TLS in patients. This safety monitoring was implemented for all patients enrolled in this study. In addition, collection of overall survival data was added to the phase 1b dose escalation portion of the study as a secondary endpoint to have some initial understanding of long term benefit of patients treated at dual (LGX818 plus cetuximab) and triple (LGX818 plus cetuximab plus BYL719) combination. Lastly, the protocol was amended to allow that doses higher than LGX818 single agent MTD could be explored in combination with cetuximab and/or BYL719.
24 October 2013	Amendment 2 (date 24 October 2013) - The main purpose of this amendment was to further clarify the patient population for this study as preliminary study data suggested that patients with Braf mutations other than V600 E had benefit from the study treatment. In addition, DLT criteria was updated to clarify that any Tumor Lysis Syndrome CTCAE Grade ≥4 (Life-threatening TLS) was considered a DLT regardless whether protocol mandated monitoring was implemented. Inclusion/exclusion criteria was changed to include patients with Braf mutations other than V600, to evaluate early efficacy signals in this population. Patients with elevated blood glucose values, or with a diagnosis of diabetes mellitus, were excluded from protocol participation as BYL719 causes hyperglycemia. However, both LGX818 and cetuximab did not cause blood glucose elevation and given that patients with V600 Braf mutations in metastatic colorectal carcinoma were rare, patients with glucose elevation considered for LGX818 and cetuximab dual combination treatment was not be excluded in the phase 1 dose escalation portion of the study. This amendment introduced the monitoring of tumor markers CEA and CA19-9 during treatment. Intra-patient dose escalation to the recommended phase 2 dose was permitted with this amendment. All radiological assessments obtained for patients was centrally collected and centrally reviewed for confirmation of efficacy.
16 December 2013	Amendment 3 (date 16 December 2013) - The main objective of this amendment was to introduce new safety monitoring for visual toxicities. This amendment implemented routine ophthalmic examinations (baseline, C4D1(day 85), every 3 cycles on day 1 (every 12 weeks) thereafter, end of treatment and as clinically indicated) in order to monitor for the potential risk of retinal/ocular changes and included recommendations for LGX818 dose modifications for visual toxicity. In addition, definitions of ophthalmologic DLTs were provided. In addition, prohibited medications were updated.
17 June 2014	Amendment 4 (date 17 June 2014) - The main purpose of this amendment was to provide guidelines for the management of pneumonitis that was experienced due to BYL719 and Cetuximab combination treatment. In addition, procedures relating to monitoring of patients at risk for tumor lysis syndrome (TLS) were adjusted. This amendment also clarified that patients participating in this trial could also be participated in another optional companion sample collection protocol with a dedicated informed consent. The companion sample collection protocol was intended to collect the samples needed to investigate the mechanisms that underlied the development of acquired resistance to treatment. The biomarker section was updated to indicate that tumor biopsies was banked for the purpose of assay development. Lastly, changes clarified on treatment imaging window for response assessment, addition of the definition of best overall response to the statistical section.

20 July 2015	Amendment 5 (date 20 July 2015) - The purpose of this amendment was to document a change in study sponsorship from Novartis to Array BioPharma. Study design and procedures were not affected. This amendment also removed reference to an optional companion sample collection protocol, as that companion protocol had enrolled no patients from the current study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported