Clinical trial results:
A phase II, multi-center, open-label study of AUY922 administered i.v. on a once weekly schedule in patients with advanced non-small-cell lung cancer (NSCLC) who have received at least two lines of prior chemotherapy.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2010-020116-11
Trial protocol	NL ES FR DE
Global end of trial date	12 August 2014

Results information

Result version number	v1 (current)
This version publication date	27 May 2016
First version publication date	27 May 2016

Trial information

Trial identification

Sponsor protocol code	CAUY922A2206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01124864
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, trialandresults.registries@novartis.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 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate efficacy for each study strata at 18 weeks as assessed by Response Evaluation Criteria in Solid Tumors (RECIST).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 October 2010
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: 3
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Korea, Republic of: 29
Worldwide total number of subjects	153
EEA total number of subjects	86

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)	108
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Two patients who were ongoing at the data cut-off of 30-Jul-2013 are considered as 'completed' in this study.

Pre-assignment

Screening details:

All patients were to receive weekly i.v. administrations of AUY922 at a dose of 70 mg/m2. However, patients were also stratified to one of the following five groups based on the molecular etiology of their baseline tumors: EGFR mutant, KRAS mutant, EML4-ALK translocations, EGFR and KRAS wild type, and modified EGFR mutant.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Kras mutant patients

Arm description:

Patients with KRAS mutant tumors. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Arm type	Experimental
Investigational medicinal product name	AUY922
Investigational medicinal product code	AUY922
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

Arm title	EGFR mutant patients

Arm description:

Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented T790M activating mutation). Patients received AUY922 at 70 mg/m^2 weekly infusions.

Arm type	Experimental
Investigational medicinal product name	AUY922
Investigational medicinal product code	AUY922
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

Arm title	EGFR and Kras wild type patients

Arm description:

Patients exhibiting both mutations were stratified to the KRAS mutation stratum. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Arm type	Experimental

Investigational medicinal product name	AUY922
Investigational medicinal product code	AUY922
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

Arm title	Patients with EML4-ALK translocation

Arm description:

Patients with NSCLC who have tumors with an inversion in the short arm of chromosome 2 that results in the fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene leading to the production of an EML4-ALK fusion tyrosine kinase. ALK is a transmembrane protein, which has a kinase domain and is not usually expressed in the lung. EML4 mediate ligand-independent dimerization, and therefore constitutive activity of the ALK tyrosine kinase domain. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Arm type	Experimental
Investigational medicinal product name	AUY922
Investigational medicinal product code	AUY922
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

Arm title	Modified EGFR mutant patients

Arm description:

The modified EGFR stratum was defined as patients less heavily pretreated who had received one or two lines of prior therapy, with a documented response to a EGFR tyrosine kinase inhibitor (TKI) (complete response (CR), partial response (PR) or stable disease (SD) for ≥ 6 months), unless the patient had de novo resistance to EGFR TKI. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Arm type	Experimental
Investigational medicinal product name	AUY922
Investigational medicinal product code	AUY922
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

Arm title	Unknown

Arm description:

For some patients, it was not possible to determine their genotype, and hence their stratum membership could not be determined. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Arm type	Experimental
Investigational medicinal product name	AUY922
Investigational medicinal product code	AUY922
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Investigational treatment consisted of AUY922. This was supplied by Novartis in individual

Number of subjects in period 1	Kras mutant patients	EGFR mutant patients	EGFR and Kras wild type patients
Started	28	35	34
Completed	0	0	0
Not completed	28	35	34
Adverse event, serious fatal	6	9	6
Consent withdrawn by subject	2	3	4
Follow up phase competed as per protocol	18	22	24
Lost to follow-up	1	1	-
Protocol deviation	1	-	-

Number of subjects in period 1	Patients with EML4-ALK translocation	Modified EGFR mutant patients	Unknown
Started	22	31	3
Completed	1	1	0
Not completed	21	30	3
Adverse event, serious fatal	2	1	-
Consent withdrawn by subject	-	2	1
Follow up phase competed as per protocol	18	26	2
Lost to follow-up	1	-	-
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Kras mutant patients
Reporting group description:	
Patients with KRAS mutant tumors. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	EGFR mutant patients
Reporting group description:	
Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented T790M activating mutation). Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	EGFR and Kras wild type patients
Reporting group description:	
Patients exhibiting both mutations were stratified to the KRAS mutation stratum. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	Patients with EML4-ALK translocation
Reporting group description:	
Patients with NSCLC who have tumors with an inversion in the short arm of chromosome 2 that results in the fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene leading to the production of an EML4-ALK fusion tyrosine kinase. ALK is a transmembrane protein, which has a kinase domain and is not usually expressed in the lung. EML4 mediate ligand-independent dimerization, and therefore constitutive activity of the ALK tyrosine kinase domain. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	Modified EGFR mutant patients
Reporting group description:	
The modified EGFR stratum was defined as patients less heavily pretreated who had received one or two lines of prior therapy, with a documented response to a EGFR tyrosine kinase inhibitor (TKI) (complete response (CR), partial response (PR) or stable disease (SD) for ≥ 6 months), unless the patient had de novo resistance to EGFR TKI. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	Unknown
Reporting group description:	
For some patients, it was not possible to determine their genotype, and hence their stratum membership could not be determined. Patients received AUY922 at 70 mg/m^2 weekly infusions.	

Reporting group values	Kras mutant patients	EGFR mutant patients	EGFR and Kras wild type patients
Number of subjects	28	35	34
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	21	23
From 65-84 years	8	14	11
85 years and over	0	0	0
Gender, Male/Female Units: Participants			
Female	11	25	18
Male	17	10	16

Reporting group values	Patients with EML4-ALK translocation	Modified EGFR mutant patients	Unknown
Number of subjects	22	31	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	25	1
From 65-84 years	4	6	2
85 years and over	0	0	0
Gender, Male/Female Units: Participants			
Female	15	19	0
Male	7	12	3

Reporting group values	Total		
Number of subjects	153		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	108		
From 65-84 years	45		
85 years and over	0		
Gender, Male/Female Units: Participants			
Female	88		
Male	65		

End points

End points reporting groups

Reporting group title	Kras mutant patients
Reporting group description:	
Patients with KRAS mutant tumors. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	EGFR mutant patients
Reporting group description:	
Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented T790M activating mutation). Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	EGFR and Kras wild type patients
Reporting group description:	
Patients exhibiting both mutations were stratified to the KRAS mutation stratum. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	Patients with EML4-ALK translocation
Reporting group description:	
Patients with NSCLC who have tumors with an inversion in the short arm of chromosome 2 that results in the fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene leading to the production of an EML4-ALK fusion tyrosine kinase. ALK is a transmembrane protein, which has a kinase domain and is not usually expressed in the lung. EML4 mediate ligand-independent dimerization, and therefore constitutive activity of the ALK tyrosine kinase domain. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	Modified EGFR mutant patients
Reporting group description:	
The modified EGFR stratum was defined as patients less heavily pretreated who had received one or two lines of prior therapy, with a documented response to a EGFR tyrosine kinase inhibitor (TKI) (complete response (CR), partial response (PR) or stable disease (SD) for ≥ 6 months), unless the patient had de novo resistance to EGFR TKI. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Reporting group title	Unknown
Reporting group description:	
For some patients, it was not possible to determine their genotype, and hence their stratum membership could not be determined. Patients received AUY922 at 70 mg/m^2 weekly infusions.	
Subject analysis set title	AUY922
Subject analysis set type	Full analysis
Subject analysis set description:	
AUY922 Plasma Concentration	
Subject analysis set title	BJP762
Subject analysis set type	Full analysis
Subject analysis set description:	
AUY Metabolite	
Subject analysis set title	AUY922
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
AUY922 Plasma Concentration	
Subject analysis set title	BJP762
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
AUY Metabolite	
Subject analysis set title	AUY922
Subject analysis set type	Safety analysis
Subject analysis set description:	
AUY922 Plasma Concentration	
Subject analysis set title	BJP762

Subject analysis set type	Safety analysis

Subject analysis set description:

AUY Metabolite

Primary: Response assessment by study stratum - per Investigator assessment

End point title	Response assessment by study stratum - per Investigator assessment[1]

End point description:

The primary endpoint of the study was the investigator assessment of efficacy at 18 weeks in terms of response complete response (CR)/partial response (PR), stable disease (SD), or non clinical benefit (NCB) as assessed by response evaluation criteriain solid tumors (RECIST) version 1.0. ORR = patients with confirmed complete or partial response. Stable disease at 18 weeks = patients without response and with no assessment of progressive disease up to 18 weeks, but with an assessment of stable disease or better either within 2 weeks prior to the 18 week time point, or at the next non-missing assessment after the 18 week time point. No clinical benefit = all other patients.

End point type	Primary

End point timeframe:

18 weeks

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 was no statistical analysis done to compare the arms.

End point values	Kras mutant patients	EGFR mutant patients	EGFR and Kras wild type patients	Patients with EML4-ALK translocation
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	35	34	22
Units: Participants				
Overall respose rate (ORR)	0	6	3	7
Stable disease for ≥18 weeks	2	3	3	2
No clinical benefit	26	26	28	13

End point values	Modified EGFR mutant patients	Unknown		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	3		
Units: Participants				
Overall respose rate (ORR)	3	1		
Stable disease for ≥18 weeks	7	0		
No clinical benefit	21	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival rate using Kaplan Meier estimates - per Investigator radiological review

End point title	Overall Survival rate using Kaplan Meier estimates - per

	Investigator radiological review

End point description:

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival was censored at the date of last contact.

End point type	Secondary

End point timeframe:

Week 12, Week 18

End point values	Kras mutant patients	EGFR mutant patients	EGFR and Kras wild type patients	Patients with EML4-ALK translocation
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	35	34	22
Units: Percentage of participants				
number (not applicable)				
12 weeks	68.7	77	78.6	90.7
18 weeks	55.9	74.1	72.3	71.6

End point values	Modified EGFR mutant patients	Unknown		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	3		
Units: Percentage of participants				
number (not applicable)				
12 weeks	96.7	66.7		
18 weeks	93.3	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) rate as per Investigator using Kaplan Meier estimates - per Investigator radiological review

End point title	Progression Free Survival (PFS) rate as per Investigator using Kaplan Meier estimates - per Investigator radiological review

End point description:

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient did not have an event, progression-free survival was censored at the date of last adequate tumor assessment. A Novartis modified response evaluation criteria in solid tumors RECIST 1.1 criteria was applied to CT/MRI imaging data when assessing any responses to AUY922 treatment. All images were evaluated locally by the investigator. All complete or partial responses were confirmed by a second assessment at least 4 weeks later.

End point type	Secondary

End point timeframe:

Week 12, Week 18

End point values	Kras mutant patients	EGFR mutant patients	EGFR and Kras wild type patients	Patients with EML4-ALK translocation
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	35	34	22
Units: Percentage of participants				
number (not applicable)				
12 weeks	31.5	44.4	31.5	45.5
18 weeks	9	27.7	24	36.4

End point values	Modified EGFR mutant patients	Unknown		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	3		
Units: Percentage of participants				
number (not applicable)				
12 weeks	56.4	33.3		
18 weeks	37.8	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: AUCinf

End point title	Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: AUCinf

End point description:

Summary of PK parameters for all patients one hour post 70 mg/m2 AUY922 infusion for area under the curve infinity. There are discrepancies between sample numbers and study population because PK samples were not collected from all study subjects and thus were not analyzed.

End point type	Secondary

End point timeframe:

1 hour after infusion

End point values	AUY922	BJP762		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	119	117		
Units: h*ng/mL				
arithmetic mean (standard deviation)	2101.27 (± 990.32)	13963.07 (± 13006.537)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: AUClast

End point title	Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: AUClast

End point description:

Summary of PK parameters for all patients one hour post 70 mg/m2 AUY922 infusion for area under the curve last. There are discrepancies between sample numbers and study population because PK samples were not collected from all study subjects and thus were not analyzed.

End point type	Secondary

End point timeframe:

1 hour after infusion

End point values	AUY922	BJP762		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139	142		
Units: h*ng/mL				
arithmetic mean (standard deviation)	1997.04 (± 894.903)	12496.75 (± 12035.525)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: Cmax

End point title	Pharmacokinetics (PK) of plasma concentration of AUY922 and its metabolite BJP762: Cmax

End point description:

Summary of PK parameters for all patients one hour post 70 mg/m2 AUY922 infusion for concentration max. There are discrepancies between sample numbers and study population because PK samples were not collected from all study subjects and thus were not analyzed.

End point type	Secondary

End point timeframe:

1 hour after infusion

End point values	AUY922	BJP762		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: ng/mL				
arithmetic mean (standard deviation)	1130.59 (± 705.177)	2332.86 (± 1377.35)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	KRAS mutant

Reporting group description:

Patients with KRAS mutant tumors. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Reporting group title	EGFR mutant

Reporting group description:

Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented T790M activating mutation). Patients received AUY922 at 70 mg/m^2 weekly infusions.

Reporting group title	Unknown

Reporting group description:

For some patients, it was not possible to determine their genotype, and hence their stratum membership could not be determined. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Reporting group title	EML4-ALK translocation

Reporting group description:

Patients with NSCLC who have tumors with an inversion in the short arm of chromosome 2 that results in the fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene leading to the production of an EML4-ALK fusion tyrosine kinase. ALK is a transmembrane protein, which has a kinase domain and is not usually expressed in the lung. EML4 mediate ligand-independent dimerization, and therefore constitutive activity of the ALK tyrosine kinase domain. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Reporting group title	Modified EGFR mutant

Reporting group description:

The modified EGFR stratum was defined as patients less heavily pretreated who had received one or two lines of prior therapy, with a documented response to a EGFR tyrosine kinase inhibitor (TKI) (complete response (CR), partial response (PR) or stable disease (SD) for ≥ 6 months), unless the patient had de novo resistance to EGFR TKI. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Reporting group title	KRAS and EGFR wild type

Reporting group description:

Patients exhibiting both mutations were stratified to the KRAS mutation stratum. Patients received AUY922 at 70 mg/m^2 weekly infusions.

Serious adverse events	KRAS mutant	EGFR mutant	Unknown
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 28 (60.71%)	18 / 35 (51.43%)	2 / 3 (66.67%)
number of deaths (all causes)	5	7	1

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases To Central Nervous System			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Metastatic Pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Hypertension			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	0 / 3 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Fatigue			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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 Physical Health Deterioration			

subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Mucosal Inflammation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Oedema Peripheral			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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			
Acute Respiratory Failure			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Dyspnoea			
subjects affected / exposed	3 / 28 (10.71%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Hypoxia			

subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Pleural Effusion			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Pneumothorax			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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 Embolism			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Depression			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Bundle Branch Block Right			

subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Palpitations			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Pericardial Effusion			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Tachycardia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Supraventricular Tachycardia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain Compression			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Balance Disorder			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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 Disorder			

subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Spinal Cord Compression			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Vocal Cord Paresis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Eye disorders			
Night Blindness			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Fissure			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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

Proctalgia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Vomiting			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Cholelithiasis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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			
Bone Pain			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	0 / 3 (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
Musculoskeletal Pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Neck Pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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			
Atypical Pneumonia			

subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Bronchitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Lung Infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Klebsiella Infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (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
Perirectal Abscess			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Pneumonia			
subjects affected / exposed	3 / 28 (10.71%)	1 / 35 (2.86%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Failure To Thrive			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid Intake Reduced			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Hypercalcaemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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
Hyperglycaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (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
Hyperkalaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (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

Serious adverse events	EML4-ALK translocation	Modified EGFR mutant	KRAS and EGFR wild type

Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)	11 / 31 (35.48%)	22 / 34 (64.71%)
number of deaths (all causes)	2	1	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases To Central Nervous System			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (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
Metastatic Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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			
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Physical Health Deterioration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal Inflammation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Oedema Peripheral			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (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
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	0 / 34 (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
Dyspnoea			
subjects affected / exposed	3 / 22 (13.64%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			

subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 22 (0.00%)	4 / 31 (12.90%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (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
Pulmonary Embolism			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	0 / 34 (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
Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Atrial Fibrillation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle Branch Block Right			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Palpitations			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Pericardial Effusion			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Supraventricular Tachycardia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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			
Brain Compression			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Balance Disorder			

subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous System Disorder			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Spinal Cord Compression			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal Cord Paresis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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			
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Eye disorders			
Night Blindness			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rectal Fissure			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Proctalgia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Cholelithiasis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Neck Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Atypical Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	0 / 34 (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
Bronchitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Lung Infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	0 / 34 (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
Klebsiella Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Perirectal Abscess			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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 Tract Infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	0 / 34 (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
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Decreased Appetite			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure To Thrive			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid Intake Reduced			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (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
Hypercalcaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (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
Hyperglycaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Hyperkalaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (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
Hyponatraemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	KRAS mutant	EGFR mutant	Unknown
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)	35 / 35 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Hot Flush			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Hypertension			
subjects affected / exposed	0 / 28 (0.00%)	4 / 35 (11.43%)	0 / 3 (0.00%)
occurrences (all)	0	14	0
Hypotension			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 28 (46.43%)	14 / 35 (40.00%)	1 / 3 (33.33%)
occurrences (all)	17	18	1
Catheter Site Pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chest Pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	1 / 3 (33.33%)
occurrences (all)	1	3	1
Pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	1 / 3 (33.33%)
occurrences (all)	1	2	1
Fatigue			

subjects affected / exposed	7 / 28 (25.00%)	9 / 35 (25.71%)	0 / 3 (0.00%)
occurrences (all)	7	14	0
Gait Disturbance			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oedema Peripheral			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Pyrexia			
subjects affected / exposed	5 / 28 (17.86%)	3 / 35 (8.57%)	2 / 3 (66.67%)
occurrences (all)	5	3	2
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	5 / 28 (17.86%)	8 / 35 (22.86%)	1 / 3 (33.33%)
occurrences (all)	7	12	1
Dyspnoea			
subjects affected / exposed	5 / 28 (17.86%)	11 / 35 (31.43%)	1 / 3 (33.33%)
occurrences (all)	5	11	1
Dysphonia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dyspnoea Exertional			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Haemoptysis			

subjects affected / exposed	4 / 28 (14.29%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences (all)	5	3	0
Epistaxis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pleural Effusion			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Wheezing			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Productive Cough			
subjects affected / exposed	1 / 28 (3.57%)	4 / 35 (11.43%)	0 / 3 (0.00%)
occurrences (all)	1	5	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Depressed Mood			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hallucination			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 28 (0.00%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Nervousness			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 28 (0.00%)	4 / 35 (11.43%)	0 / 3 (0.00%)
occurrences (all)	0	5	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood Creatinine Increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
C-Reactive Protein Increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Heart Rate Increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hypophonesis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Transaminases Increased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Weight Decreased			
subjects affected / exposed	4 / 28 (14.29%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	4	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0

Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Balance Disorder			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	1 / 3 (33.33%)
occurrences (all)	1	2	1
Dysgeusia			
subjects affected / exposed	2 / 28 (7.14%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Headache			
subjects affected / exposed	8 / 28 (28.57%)	8 / 35 (22.86%)	2 / 3 (66.67%)
occurrences (all)	10	25	3
Hypoaesthesia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 28 (0.00%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Memory Impairment			
subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Neuropathy Peripheral			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			

subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Lymphopenia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Accommodation Disorder			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Blepharitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cataract Subcapsular			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Lacrimation Increased			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Eye Pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dry Eye			

subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Colour Blindness Acquired			
subjects affected / exposed	0 / 28 (0.00%)	3 / 35 (8.57%)	1 / 3 (33.33%)
occurrences (all)	0	3	1
Night Blindness			
subjects affected / exposed	3 / 28 (10.71%)	10 / 35 (28.57%)	1 / 3 (33.33%)
occurrences (all)	3	12	1
Loss Of Visual Contrast Sensitivity			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ocular Toxicity			
subjects affected / exposed	4 / 28 (14.29%)	4 / 35 (11.43%)	1 / 3 (33.33%)
occurrences (all)	4	7	1
Photophobia			
subjects affected / exposed	3 / 28 (10.71%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Retinal Disorder			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences (all)	1	4	0
Photopsia			
subjects affected / exposed	3 / 28 (10.71%)	5 / 35 (14.29%)	0 / 3 (0.00%)
occurrences (all)	3	5	0
Vision Blurred			
subjects affected / exposed	5 / 28 (17.86%)	6 / 35 (17.14%)	0 / 3 (0.00%)
occurrences (all)	5	7	0
Visual Acuity Reduced			
subjects affected / exposed	1 / 28 (3.57%)	6 / 35 (17.14%)	0 / 3 (0.00%)
occurrences (all)	1	8	0
Vitreous Floaters			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	1 / 3 (33.33%)
occurrences (all)	1	3	1
Visual Impairment			
subjects affected / exposed	6 / 28 (21.43%)	8 / 35 (22.86%)	0 / 3 (0.00%)
occurrences (all)	6	11	0
Gastrointestinal disorders			

Abdominal Distension			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Abdominal Pain			
subjects affected / exposed	5 / 28 (17.86%)	5 / 35 (14.29%)	0 / 3 (0.00%)
occurrences (all)	5	6	0
Abdominal Pain Upper			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Dry Mouth			
subjects affected / exposed	5 / 28 (17.86%)	4 / 35 (11.43%)	0 / 3 (0.00%)
occurrences (all)	5	4	0
Diarrhoea			
subjects affected / exposed	25 / 28 (89.29%)	23 / 35 (65.71%)	3 / 3 (100.00%)
occurrences (all)	46	39	4
Constipation			
subjects affected / exposed	6 / 28 (21.43%)	6 / 35 (17.14%)	0 / 3 (0.00%)
occurrences (all)	6	7	0
Dyspepsia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 35 (2.86%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	16 / 28 (57.14%)	19 / 35 (54.29%)	1 / 3 (33.33%)
occurrences (all)	27	38	1
Oral Pain			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Rectal Haemorrhage			
subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Stomatitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Vomiting			
subjects affected / exposed	13 / 28 (46.43%)	13 / 35 (37.14%)	2 / 3 (66.67%)
occurrences (all)	18	21	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 28 (7.14%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Pain Of Skin			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dry Skin			
subjects affected / exposed	1 / 28 (3.57%)	3 / 35 (8.57%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Dermatitis Acneiform			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	8 / 28 (28.57%)	5 / 35 (14.29%)	0 / 3 (0.00%)
occurrences (all)	8	7	0
Arthralgia			
subjects affected / exposed	1 / 28 (3.57%)	4 / 35 (11.43%)	0 / 3 (0.00%)
occurrences (all)	2	6	0
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Muscle Spasms			
subjects affected / exposed	2 / 28 (7.14%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Flank Pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal Pain			

subjects affected / exposed	3 / 28 (10.71%)	2 / 35 (5.71%)	1 / 3 (33.33%)
occurrences (all)	3	2	2
Bone Pain			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	0 / 28 (0.00%)	4 / 35 (11.43%)	1 / 3 (33.33%)
occurrences (all)	0	6	1
Neck Pain			
subjects affected / exposed	2 / 28 (7.14%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Pain In Extremity			
subjects affected / exposed	2 / 28 (7.14%)	4 / 35 (11.43%)	0 / 3 (0.00%)
occurrences (all)	2	4	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory Tract Infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 35 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Urinary Tract Infection			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	17 / 28 (60.71%)	15 / 35 (42.86%)	1 / 3 (33.33%)
occurrences (all)	17	17	1
Dehydration			
subjects affected / exposed	1 / 28 (3.57%)	1 / 35 (2.86%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hyperglycaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 35 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	2 / 28 (7.14%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	3	5	0
Hypomagnesaemia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 35 (5.71%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Hyponatraemia			
subjects affected / exposed	2 / 28 (7.14%)	4 / 35 (11.43%)	0 / 3 (0.00%)
occurrences (all)	2	4	0

Non-serious adverse events	EML4-ALK translocation	Modified EGFR mutant	KRAS and EGFR wild type
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	31 / 31 (100.00%)	33 / 34 (97.06%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Hot Flush			
subjects affected / exposed	2 / 22 (9.09%)	1 / 31 (3.23%)	1 / 34 (2.94%)
occurrences (all)	2	1	1
Hypertension			
subjects affected / exposed	3 / 22 (13.64%)	5 / 31 (16.13%)	3 / 34 (8.82%)
occurrences (all)	4	8	4
Hypotension			

subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 22 (45.45%)	5 / 31 (16.13%)	10 / 34 (29.41%)
occurrences (all)	14	6	16
Catheter Site Pain			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Chest Pain			
subjects affected / exposed	4 / 22 (18.18%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	8	0	0
Pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	6 / 34 (17.65%)
occurrences (all)	0	1	8
Fatigue			
subjects affected / exposed	3 / 22 (13.64%)	15 / 31 (48.39%)	13 / 34 (38.24%)
occurrences (all)	3	17	17
Gait Disturbance			
subjects affected / exposed	2 / 22 (9.09%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 22 (9.09%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	2	1	2
Oedema Peripheral			
subjects affected / exposed	3 / 22 (13.64%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	3	3	1
Pyrexia			
subjects affected / exposed	6 / 22 (27.27%)	4 / 31 (12.90%)	4 / 34 (11.76%)
occurrences (all)	7	5	5
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Atelectasis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Cough			
subjects affected / exposed	7 / 22 (31.82%)	8 / 31 (25.81%)	9 / 34 (26.47%)
occurrences (all)	11	9	16
Dyspnoea			
subjects affected / exposed	2 / 22 (9.09%)	2 / 31 (6.45%)	9 / 34 (26.47%)
occurrences (all)	3	3	9
Dysphonia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Dyspnoea Exertional			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Haemoptysis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	4 / 34 (11.76%)
occurrences (all)	1	0	4
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 22 (0.00%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	0	3	2
Pleural Effusion			
subjects affected / exposed	2 / 22 (9.09%)	2 / 31 (6.45%)	3 / 34 (8.82%)
occurrences (all)	2	2	3
Wheezing			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Productive Cough			
subjects affected / exposed	2 / 22 (9.09%)	1 / 31 (3.23%)	7 / 34 (20.59%)
occurrences (all)	5	2	7

Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 22 (9.09%)	2 / 31 (6.45%)	3 / 34 (8.82%)
occurrences (all)	2	2	3
Depressed Mood			
subjects affected / exposed	2 / 22 (9.09%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	3	0	2
Hallucination			
subjects affected / exposed	2 / 22 (9.09%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	5 / 22 (22.73%)	4 / 31 (12.90%)	6 / 34 (17.65%)
occurrences (all)	6	4	6
Nervousness			
subjects affected / exposed	2 / 22 (9.09%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 22 (4.55%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	1	3	1
Aspartate Aminotransferase Increased			
subjects affected / exposed	2 / 22 (9.09%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	2	3	1
Blood Creatinine Increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
C-Reactive Protein Increased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 22 (0.00%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	0	3	1

Heart Rate Increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Hypophonesis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Transaminases Increased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Weight Decreased			
subjects affected / exposed	1 / 22 (4.55%)	4 / 31 (12.90%)	3 / 34 (8.82%)
occurrences (all)	1	4	3
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Balance Disorder			
subjects affected / exposed	1 / 22 (4.55%)	3 / 31 (9.68%)	0 / 34 (0.00%)
occurrences (all)	1	3	0
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	1	3	1
Dysgeusia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	14 / 22 (63.64%)	13 / 31 (41.94%)	8 / 34 (23.53%)
occurrences (all)	41	15	13
Hypoaesthesia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	4	2	2
Neuralgia			

subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Memory Impairment			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Neuropathy Peripheral			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Somnolence			
subjects affected / exposed	2 / 22 (9.09%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Paraesthesia			
subjects affected / exposed	3 / 22 (13.64%)	3 / 31 (9.68%)	2 / 34 (5.88%)
occurrences (all)	3	5	2
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Anaemia			
subjects affected / exposed	3 / 22 (13.64%)	4 / 31 (12.90%)	5 / 34 (14.71%)
occurrences (all)	3	4	6
Lymphopenia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	3
Vertigo			
subjects affected / exposed	2 / 22 (9.09%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	2	1	2
Eye disorders			

Accommodation Disorder			
subjects affected / exposed	2 / 22 (9.09%)	5 / 31 (16.13%)	2 / 34 (5.88%)
occurrences (all)	2	5	2
Blepharitis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Cataract Subcapsular			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Lacrimation Increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Eye Pain			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Dry Eye			
subjects affected / exposed	2 / 22 (9.09%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	2
Colour Blindness Acquired			
subjects affected / exposed	5 / 22 (22.73%)	4 / 31 (12.90%)	2 / 34 (5.88%)
occurrences (all)	6	4	2
Night Blindness			
subjects affected / exposed	5 / 22 (22.73%)	10 / 31 (32.26%)	6 / 34 (17.65%)
occurrences (all)	9	13	7
Loss Of Visual Contrast Sensitivity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Ocular Toxicity			
subjects affected / exposed	3 / 22 (13.64%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	3	5	1
Photophobia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	5 / 34 (14.71%)
occurrences (all)	0	2	5
Retinal Disorder			
subjects affected / exposed	5 / 22 (22.73%)	7 / 31 (22.58%)	1 / 34 (2.94%)
occurrences (all)	5	7	1

Photopsia			
subjects affected / exposed	10 / 22 (45.45%)	6 / 31 (19.35%)	10 / 34 (29.41%)
occurrences (all)	11	6	11
Vision Blurred			
subjects affected / exposed	6 / 22 (27.27%)	6 / 31 (19.35%)	7 / 34 (20.59%)
occurrences (all)	6	6	9
Visual Acuity Reduced			
subjects affected / exposed	7 / 22 (31.82%)	5 / 31 (16.13%)	7 / 34 (20.59%)
occurrences (all)	7	6	10
Vitreous Floaters			
subjects affected / exposed	1 / 22 (4.55%)	2 / 31 (6.45%)	1 / 34 (2.94%)
occurrences (all)	1	2	1
Visual Impairment			
subjects affected / exposed	6 / 22 (27.27%)	7 / 31 (22.58%)	3 / 34 (8.82%)
occurrences (all)	6	8	4
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	2 / 22 (9.09%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Abdominal Pain			
subjects affected / exposed	6 / 22 (27.27%)	2 / 31 (6.45%)	4 / 34 (11.76%)
occurrences (all)	10	2	4
Abdominal Pain Upper			
subjects affected / exposed	0 / 22 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	3	2
Dry Mouth			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	6 / 34 (17.65%)
occurrences (all)	0	1	6
Diarrhoea			
subjects affected / exposed	17 / 22 (77.27%)	24 / 31 (77.42%)	25 / 34 (73.53%)
occurrences (all)	79	105	72
Constipation			
subjects affected / exposed	5 / 22 (22.73%)	5 / 31 (16.13%)	5 / 34 (14.71%)
occurrences (all)	6	5	6
Dyspepsia			

subjects affected / exposed	4 / 22 (18.18%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	11	5	1
Flatulence			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	11 / 22 (50.00%)	12 / 31 (38.71%)	13 / 34 (38.24%)
occurrences (all)	21	22	18
Oral Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rectal Haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Vomiting			
subjects affected / exposed	9 / 22 (40.91%)	4 / 31 (12.90%)	4 / 34 (11.76%)
occurrences (all)	18	26	11
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 22 (4.55%)	4 / 31 (12.90%)	1 / 34 (2.94%)
occurrences (all)	1	5	1
Pain Of Skin			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	10
Dry Skin			
subjects affected / exposed	0 / 22 (0.00%)	4 / 31 (12.90%)	1 / 34 (2.94%)
occurrences (all)	0	5	1
Dermatitis Acneiform			
subjects affected / exposed	1 / 22 (4.55%)	2 / 31 (6.45%)	0 / 34 (0.00%)
occurrences (all)	1	7	0
Rash			
subjects affected / exposed	1 / 22 (4.55%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	1	1	0

Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 22 (13.64%)	7 / 31 (22.58%)	8 / 34 (23.53%)
occurrences (all)	4	7	8
Arthralgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	1	3	2
Muscle Spasms			
subjects affected / exposed	3 / 22 (13.64%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	4	0	3
Flank Pain			
subjects affected / exposed	0 / 22 (0.00%)	4 / 31 (12.90%)	0 / 34 (0.00%)
occurrences (all)	0	6	0
Musculoskeletal Pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 31 (6.45%)	5 / 34 (14.71%)
occurrences (all)	1	2	7
Bone Pain			
subjects affected / exposed	1 / 22 (4.55%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	1	7	1
Myalgia			
subjects affected / exposed	5 / 22 (22.73%)	6 / 31 (19.35%)	4 / 34 (11.76%)
occurrences (all)	13	13	7
Neck Pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 31 (6.45%)	4 / 34 (11.76%)
occurrences (all)	1	2	4
Pain In Extremity			
subjects affected / exposed	1 / 22 (4.55%)	1 / 31 (3.23%)	4 / 34 (11.76%)
occurrences (all)	2	1	4
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 22 (9.09%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	2	1	0
Influenza			

subjects affected / exposed	0 / 22 (0.00%)	3 / 31 (9.68%)	1 / 34 (2.94%)
occurrences (all)	0	3	1
Nasopharyngitis			
subjects affected / exposed	1 / 22 (4.55%)	4 / 31 (12.90%)	1 / 34 (2.94%)
occurrences (all)	1	6	3
Respiratory Tract Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 22 (9.09%)	4 / 31 (12.90%)	1 / 34 (2.94%)
occurrences (all)	4	6	2
Urinary Tract Infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	8 / 22 (36.36%)	10 / 31 (32.26%)	12 / 34 (35.29%)
occurrences (all)	9	15	15
Dehydration			
subjects affected / exposed	1 / 22 (4.55%)	1 / 31 (3.23%)	3 / 34 (8.82%)
occurrences (all)	1	1	3
Hyperglycaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Hypokalaemia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	2	2	0
Hypomagnesaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 31 (3.23%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2011	This amendment was issued 14 months after study start (09 Nov 2010) and after the inclusion of 116 patients, introduced the following changes: The main purpose of this amendment was to add an additional fifth stratum that would enroll 30 patients with EGFR activating mutations (i.e. exon 18 21), who were less heavily pretreated than patients in the current EGFR stratum (up to two prior lines in comparison to four prior therapies). Preliminary data from the ongoing trial had shown evidence of activity in patients with EGFR activating mutations that had been previously treated with EGFR TKIs. As of 15-Nov-2011, 5/22 evaluable patients had a partial response (four confirmed, one unconfirmed). Because of the efficacy trend observed in the EGFR mutant cohort, 30 additional patients with EGFR mutation were to be enrolled to further assess AUY922 activity in this patient population. In contrast to the previous EGFR mutant stratum, patients enrolled to this new stratum were less heavily pretreated (up to two prior lines), would have no history of CNS metastasis, and would have a performance status of 0 to 1. The reason to enroll less heavily pretreated patients with EGFR mutations was due to the observation that a high number of EGFR mutant patients, nine patients in total, discontinued study participation due to early disease progression prior to completing first radiological assessment (6 ±1weeks), reflecting the fact that most patients had advanced disease, brain metastasis, and had received multiple previous lines of therapies; In addition, all patients to be enrolled to the fifth EGFR mutation stratum were required to undergo baseline biopsy prior to study enrollment in order to understand resistance mechanism to EGFR TKI, as pre-clinical data suggested that HSP90 inhibition may have different sensitivity based on the mutated EGFR, such as T790M (Shimamura et al 2005);
12 January 2012	This amendment was issued 14 months after study start (09 Nov 2010) and after the inclusion of 116 patients, introduced the following changes: The main purpose of this amendment was to add an additional fifth stratum that would enroll 30 patients with EGFR activating mutations (i.e. exon 18 21), who were less heavily pretreated than patients in the current EGFR stratum (up to two prior lines in comparison to four prior therapies). Preliminary data from the ongoing trial had shown evidence of activity in patients with EGFR activating mutations that had been previously treated with EGFR TKIs. As of 15-Nov-2011, 5/22 evaluable patients had a partial response (four confirmed, one unconfirmed). Because of the efficacy trend observed in the EGFR mutant cohort, 30 additional patients with EGFR mutation were to be enrolled to further assess AUY922 activity in this patient population. In contrast to the previous EGFR mutant stratum, patients enrolled to this new stratum were less heavily pretreated (up to two prior lines), would have no history of CNS metastasis, and would have a performance status of 0 to 1. The reason to enroll less heavily pretreated patients with EGFR mutations was due to the observation that a high number of EGFR mutant patients, nine patients in total, discontinued study participation due to early disease progression prior to completing first radiological assessment (6 ±1weeks), reflecting the fact that most patients had advanced disease, brain metastasis, and had received multiple previous lines of therapies; In addition, all patients to be enrolled to the fifth EGFR mutation stratum were required to undergo baseline biopsy prior to study enrollment in order to understand resistance mechanism to EGFR TKI, as pre-clinical data suggested that HSP90 inhibition may have different sensitivity based on the mutated EGFR, such as T790M (Shimamura et al 2005);

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported