



Clinical trial results:

A multicenter, open-label, randomized phase II study to evaluate the efficacy of AUY922 vs. emetrexed or docetaxel in NSCLC patients with EGFR mutations who have progressed on prior EGFR TKI treatment

Summary

EudraCT number	2012-001050-25
Trial protocol	ES GB NO NL FR IT PL
Global end of trial date	25 November 2015

Results information

Result version number	v1 (current)
This version publication date	19 November 2016
First version publication date	19 November 2016

Trial information

Trial identification

Sponsor protocol code	CAUY922A2207
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01646125
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,

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	25 November 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare progression-free survival (PFS) in patients treated with AUY922 versus pemetrexed or docetaxel.

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	23 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	59
EEA total number of subjects	41

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)	36
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 59 patients were randomized in the study: 31 to the AUY922 arm and 28 to the chemotherapy arm. 2 patients from the AUY922 arm & 5 from the chemotherapy arm were not treated.

Pre-assignment

Screening details:

Patients were randomized in a 1:1 ratio to receive either AUY922 or pemetrexed/docetaxel. The control arm treatment was defined as either pemetrexed or docetaxel (at the Investigator's discretion) as they were standard chemotherapeutic agents and were approved for use in patients with advanced NSCLC who had progressed on 1 prior line of treatment

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AUY922 arm

Arm description:

Participants were assigned to one of two treatment arms in a ratio of 1:1. This was the investigational drug arm. AUY922 was to be administered weekly.

Arm type	Experimental
Investigational medicinal product name	AUY922
Investigational medicinal product code	AUY922
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The investigational drug was AUY922 and the mode of administration was intravenous. The dose of AUY922 used in the study was 70 mg/m² once a week.

Arm title	Chemotherapy arm
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Arm description:

Participants were assigned to one of two treatment arms in a ratio of 1:1. This was the control arm drug arm. Pemetrexed or docetaxel was to be given once every three weeks.

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

Dosage and administration details:

Pemetrexed 500 mg/m² every 3 weeks for intravenous use.

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

Dosage and administration details:

Docetaxel 75 mg/m² every 3 weeks for intravenous use.

Number of subjects in period 1	AUY922 arm	Chemotherapy arm
Started	31	28
Completed	0	0
Not completed	31	28
Adverse event, serious fatal	1	1
Physician decision	1	3
Adverse event, non-fatal	2	1
Untreated	2	5
Study terminated by sponsor	2	1
Subject/Guardian decision	1	1
Progressive disease	22	16

Baseline characteristics

Reporting groups

Reporting group title	AUY922 arm
Reporting group description:	
Participants were assigned to one of two treatment arms in a ratio of 1:1. This was the investigational drug arm. AUY922 was to be administered weekly.	
Reporting group title	Chemotherapy arm
Reporting group description:	
Participants were assigned to one of two treatment arms in a ratio of 1:1. This was the control arm drug arm. Pemetrexed or docetaxel was to be given once every three weeks.	

Reporting group values	AUY922 arm	Chemotherapy arm	Total
Number of subjects	31	28	59
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	16	36
From 65-84 years	11	12	23
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	61.8	62.1	
standard deviation	± 10.1	± 10.34	-
Gender, Male/Female			
Units: Subjects			
Female	27	21	48
Male	4	7	11

End points

End points reporting groups

Reporting group title	AUY922 arm
Reporting group description:	
Participants were assigned to one of two treatment arms in a ratio of 1:1. This was the investigational drug arm. AUY922 was to be administered weekly.	
Reporting group title	Chemotherapy arm
Reporting group description:	
Participants were assigned to one of two treatment arms in a ratio of 1:1. This was the control arm drug arm. Pemetrexed or docetaxel was to be given once every three weeks.	

Primary: Progression Free Survival (PFS) at Interim Analysis (IA)

End point title	Progression Free Survival (PFS) at Interim Analysis (IA)
End point description:	
Compared PFS between the treatment of AUY922 to comparators Pemetrexed or Docetaxel. Progression-free survival (PFS) based on local investigator assessment per RECIST 1.1 was 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 had not had an event, progression-free survival is censored at the date of last adequate tumor assessment. Progression was defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions	
End point type	Primary
End point timeframe:	
16 months	

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Months				
median (confidence interval 90%)	1.5 (1.2 to 5.6)	2.3 (1.2 to 4)		

Statistical analyses

Statistical analysis title	Posterior predictive probability for PFS
Comparison groups	Chemotherapy arm v AUY922 arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	0.76

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.35
upper limit	1.63

Secondary: Overall Response Rate (ORR) at Interim analysis

End point title	Overall Response Rate (ORR) at Interim analysis
End point description:	
ORR was to be compared between treatment arms. The ORR was to be based on local investigator assessment per RECIST 1.1. This outcome measure was originally planned to be analyzed up to 24 months.	
End point type	Secondary
End point timeframe:	
16 months	

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: subjects				
Complete Response (CR)	0	0		
Partial Response (PR)	3	2		
ORR (CR + PR)	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from the date of randomization to date of death due to any cause. If a death had not been observed by the date of analysis cutoff, then OS was to be censored at the last known date patient was alive.	
End point type	Secondary
End point timeframe:	
from randomization until death up to death	

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[1]	0 ^[2]		
Units: months				
arithmetic mean (confidence interval 90%)	(to)	(to)		

Notes:

[1] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

[2] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
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End point description:

Duration of DCR was to be compared between treatment arms. The duration of DCR was to be based on local investigator assessment per RECIST 1.1.

End point type	Secondary
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End point timeframe:

baseline, until disease progression up to 24 months

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: subjects				
number (confidence interval 90%)	(to)	(to)		

Notes:

[3] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

[4] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TRR)

End point title	Time to Response (TRR)
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End point description:

TTR was to compare between treatment arms. The TTR was to be based on local investigator assessment per RECIST 1.1

End point type	Secondary
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End point timeframe:

baseline, until disease progression up to 24 months

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[5]	0 ^[6]		
Units: months				
median (confidence interval 90%)	(to)	(to)		

Notes:

[5] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

[6] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
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End point description:

The DOR was to be compared between treatment arms. The DOR was to be based on local investigator assessment per RECIST 1.1

End point type	Secondary
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End point timeframe:

baseline, until disease progression up to 24 months

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: months				
median (confidence interval 90%)	(to)	(to)		

Notes:

[7] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped

[8] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Adverse Events (AEs)

End point title	Rate of Adverse Events (AEs)
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End point description:

To evaluate safety and tolerability of AUY922 compared to chemotherapy agents pemetrexed or docetaxel. See safety section for safety data.

End point type	Secondary
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End point timeframe:

baseline, until disease progression up to 24 months

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	23		
Units: subjects	29	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in laboratory parameters

End point title	Change in laboratory parameters
End point description: Changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs), Dose interruptions, reductions and dose intensity.	
End point type	Secondary
End point timeframe: baseline, until disease progression up to 24 months	

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[9]	0 ^[10]		
Units: subjects				

Notes:

[9] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

[10] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
End point description: TTP was to be compared between treatment arms. The TTP was to be based on local investigator assessment per RECIST 1.1.	
End point type	Secondary
End point timeframe: baseline, until disease progression up to 24 months	

End point values	AUY922 arm	Chemotherapy arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[11]	0 ^[12]		
Units: months				
median (confidence interval 90%)	(to)	(to)		

Notes:

[11] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped

[12] - DMC recommendation at IA was to stop study for futility so collection of efficacy data was stopped.

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Chemotherapy
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Reporting group description:

Chemotherapy

Reporting group title	AUY922
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Reporting group description:

AUY922

Serious adverse events	Chemotherapy	AUY922	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 23 (26.09%)	10 / 29 (34.48%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 23 (4.35%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			

subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 23 (4.35%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 23 (4.35%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISCOMFORT			
subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	1 / 23 (4.35%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eye disorders			
RETINAL DEGENERATION			
subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

VISION BLURRED			
subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	1 / 23 (4.35%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	1 / 23 (4.35%)	0 / 29 (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			
HAEMOPTYSIS			
subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
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	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
LOCALISED INFECTION			
subjects affected / exposed	1 / 23 (4.35%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 23 (4.35%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	1 / 29 (3.45%)	
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	1 / 23 (4.35%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chemotherapy	AUY922	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 23 (91.30%)	28 / 29 (96.55%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 23 (0.00%)	5 / 29 (17.24%)	
occurrences (all)	0	6	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	8 / 23 (34.78%)	8 / 29 (27.59%)	
occurrences (all)	9	9	
AXILLARY PAIN			
subjects affected / exposed	0 / 23 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
FATIGUE			
subjects affected / exposed	5 / 23 (21.74%)	10 / 29 (34.48%)	
occurrences (all)	7	14	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 23 (4.35%)	2 / 29 (6.90%)	
occurrences (all)	1	2	

OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 4	1 / 29 (3.45%) 1	
PYREXIA subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 4	2 / 29 (6.90%) 2	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) DYSPNOEA subjects affected / exposed occurrences (all) HAEMOPTYSIS subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3 7 / 23 (30.43%) 8 2 / 23 (8.70%) 2 2 / 23 (8.70%) 2	7 / 29 (24.14%) 7 2 / 29 (6.90%) 2 0 / 29 (0.00%) 0 0 / 29 (0.00%) 0	
Psychiatric disorders DEPRESSION subjects affected / exposed occurrences (all) INSOMNIA subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 0 / 23 (0.00%) 0	2 / 29 (6.90%) 2 3 / 29 (10.34%) 4	
Investigations ASPARTATE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all) GAMMA-GLUTAMYLTRANSFERASE INCREASED subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 0 / 23 (0.00%) 0	2 / 29 (6.90%) 2 3 / 29 (10.34%) 3	
Nervous system disorders			

DIZZINESS subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 29 (6.90%) 2	
HEADACHE subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	9 / 29 (31.03%) 16	
PARAESTHESIA subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 29 (6.90%) 2	
PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 29 (6.90%) 2	
VISUAL FIELD DEFECT subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 29 (6.90%) 2	
VISUAL PERSEVERATION subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 29 (6.90%) 2	
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	5 / 29 (17.24%) 6	
LYMPHOPENIA subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	2 / 29 (6.90%) 2	
NEUTROPENIA subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 7	0 / 29 (0.00%) 0	
Eye disorders ACCOMMODATION DISORDER subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 29 (6.90%) 2	
NIGHT BLINDNESS subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 29 (6.90%) 3	
PHOTOPSIA			

subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	10 / 29 (34.48%) 11	
VISION BLURRED subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	6 / 29 (20.69%) 7	
VISUAL ACUITY REDUCED subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 29 (6.90%) 2	
VISUAL IMPAIRMENT subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	6 / 29 (20.69%) 8	
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	2 / 29 (6.90%) 2	
CONSTIPATION subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 4	6 / 29 (20.69%) 6	
DIARRHOEA subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	21 / 29 (72.41%) 44	
DRY MOUTH subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	1 / 29 (3.45%) 1	
NAUSEA subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 6	10 / 29 (34.48%) 15	
STOMATITIS subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 4	1 / 29 (3.45%) 1	
VOMITING subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 6	3 / 29 (10.34%) 4	
Hepatobiliary disorders			
HEPATOCELLULAR INJURY			

subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 29 (6.90%) 2	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	6 / 23 (26.09%)	0 / 29 (0.00%)	
occurrences (all)	6	0	
NAIL DISORDER			
subjects affected / exposed	2 / 23 (8.70%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
PRURITUS			
subjects affected / exposed	2 / 23 (8.70%)	6 / 29 (20.69%)	
occurrences (all)	2	10	
RASH			
subjects affected / exposed	4 / 23 (17.39%)	2 / 29 (6.90%)	
occurrences (all)	4	2	
Renal and urinary disorders			
POLLAKIURIA			
subjects affected / exposed	0 / 23 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 23 (0.00%)	6 / 29 (20.69%)	
occurrences (all)	0	6	
BACK PAIN			
subjects affected / exposed	3 / 23 (13.04%)	5 / 29 (17.24%)	
occurrences (all)	3	6	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 23 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 23 (0.00%)	5 / 29 (17.24%)	
occurrences (all)	0	5	
MYALGIA			
subjects affected / exposed	3 / 23 (13.04%)	4 / 29 (13.79%)	
occurrences (all)	9	5	
PAIN IN EXTREMITY			

subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3	3 / 29 (10.34%) 3	
Infections and infestations			
CONJUNCTIVITIS			
subjects affected / exposed	3 / 23 (13.04%)	0 / 29 (0.00%)	
occurrences (all)	3	0	
RHINITIS			
subjects affected / exposed	0 / 23 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	3	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 23 (4.35%)	3 / 29 (10.34%)	
occurrences (all)	1	4	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 23 (8.70%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	3 / 23 (13.04%)	4 / 29 (13.79%)	
occurrences (all)	4	7	
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	3 / 29 (10.34%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2013	The primary purpose of this amendment was to implement an interim analysis for futility, in order to stop the study earlier in the event that the efficacy of the AUY922 arm was unlikely to be better than that of the chemotherapy comparator arm.
03 March 2014	A planned interim analysis was conducted per the protocol on May 23, 2014, and the DMC recommendation based on the IA results was to terminate the study due to futility. There were no new safety concerns from the data. Following the DMC recommendations, enrollment was stopped on 05 Jun 2014. In addition, patients will no longer be followed-up for survival. The study continued to offer study medication (AUY and Pemetrexed) and perform safety follow-up for the 6 patients remaining in the trial, whom the investigator deemed were benefiting from the treatment.
03 November 2014	This amendment was a global amendment. The main purpose of this amendment was to change the fresh baseline tumor biopsy from mandatory to optional for patients because this requirement appeared to impact the ability for patients to join the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

IA futility criterion was met based on estimated IA PFS HR = 0.76 (90% CI: 0.35, 1.63) & posterior predictive probability $P(HR_{\text{final}} \leq 0.7 \mid HR_{\text{interim}}) = 0.421$, below predefined threshold of a posterior predictive probability >85% to continue study

Notes: