EU Clinical Trials Register

Clinical trial results:
Phase II, randomized, open-label study of the IGF-1R inhibitor AXL1717 compared to docetaxel in patients with previously treated, locally advanced, or metastatic squamous cell carcinoma or adenocarcinoma of the lung

Summary

EudraCT number	2011-002007-15
Trial protocol	HU
Global end of trial date	11 November 2014

Results information

Result version number	v1 (current)
This version publication date	04 May 2016
First version publication date	04 May 2016

Trial information

Trial identification

Sponsor protocol code	AXL-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01561456
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Axelar AB
Sponsor organisation address	Karolinska Institutet Science Park, Fogdevreten 2, Solna, Sweden, 171 65
Public contact	Ulrika Wennberg, Axelar AB, +48 70 722 6332, ulrika.wennberg@axelar.se
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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	23 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2013
Global end of trial reached?	Yes
Global end of trial date	11 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the rate of progression-free survival (PFS) at 12 weeks between patients treated with AXL1717 (AXL) and patients treated with docetaxel (DCT) in the total study population and in the squamous cell carcinoma (SCC) and adenocarcinoma (AC) subtypes of non-small cell lung cancer (NSCLC).

Protection of trial subjects:

Good Clinical Practice; informed consent required; maximum 4 treatment cycles in primary treatment period; extension treatment offered to patients with stable disease or better, only if initiated by investigator; disease progression monitored regularly according to RECIST through death or end of study.
Following 12 deaths early in the study, enrollment was suspended while the cases were reviewed. Recommended changes to the protocol were implemented as Amendment 2. The opinion of the Data Safety Monitoring Committee (DSMC) was that steroids should be avoided in neutropenic patients because steroids may stimulate the growth of microorganisms by causing immunosuppression, may mask fever and symptoms of infection, and do not stimulate host defense against microorganisms. Prophylactic antibiotics should be used in all Grade 4 neutropenic patients, irrespective of the presence of fever or other symptoms. Guidelines with respect to prophylactic antibiotic treatment of neutropenic patients were provided to all centers. Guidelines from ASCO were also issued with respect to use of hematologic growth factors for treating neutropenia in patients in the AXL group. Neutropenic patients should be followed daily. The DSMC recommended direct contact between the patient and the study center for all future cases involving events of fever and/or neutropenia.

Background therapy:

None.

Evidence for comparator:

Docetaxel is standard therapy for advanced NSCLC.

Actual start date of recruitment	15 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	14 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belarus: 2
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Ukraine: 50
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Poland: 5

Worldwide total number of subjects	99
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	85
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient randomized on 27Dec2011. The last patient randomized on 29Apr2013. The recruitment put on hold on 19Jul2012 (until Protocol Amendment approved in each country) -due to additional safety actions in order to decrease the numbers of neutropenia development.
During the study the patients were observed at multifunctional hospitals.

Pre-assignment

Screening details:

138 screened; 37 screen failures due to: hematology (7), non-measurable disease (RECIST) (6), randomization on hold (5), CNS malignancy (4), ECOG status >2 (2), mixed histology of NSCLC (2), infection/other major disease (2), coexisting medical condition (1), history of cancer in 5 years (1), lack of suitability for participation (1), other (6).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AXL1717

Arm description:

Test Arm; The Per Protocol set consisted of 101 randomized patients, 2 of whom were not treated (patient 101-008 withdrew consent; patient 305-007 was mistakenly randomized despite the presence of an exclusion criterion), and therefore the full analysis set (FAS) (also used for safety) consisted of 99 treated patients (58 AXL, 41 DCT).

Arm type	Experimental
Investigational medicinal product name	Picropodophyllin
Investigational medicinal product code	AXL1717(H2O)
Other name	AXL1717, BVT.51004, BVT.51004G
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

300 mg or 400 mg BID (twice daily)

Arm title	Docetaxel

Arm description:

Active comparator

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard 75 mg/m2 in 100 mL of normal saline solution with IV infusion over 60 minutes

Number of subjects in period 1	AXL1717	Docetaxel
Started	58	41
Completed	19	24
Not completed	39	17
Consent withdrawn by subject	5	1
On treatment as of data cut off	1	-
Death	10	1
Other	2	-
AE (any)	4	1
Progressive disease	17	13
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	AXL1717
Reporting group description:	

Test Arm; The Per Protocol set consisted of 101 randomized patients, 2 of whom were not treated (patient 101-008 withdrew consent; patient 305-007 was mistakenly randomized despite the presence of an exclusion criterion), and therefore the full analysis set (FAS) (also used for safety) consisted of 99 treated patients (58 AXL, 41 DCT).

Reporting group title	Docetaxel
Reporting group description:	

Active comparator

Reporting group values	AXL1717	Docetaxel	Total
Number of subjects	58	41	99
Age categorical			
Patients were similar in age, with median ages of 57 years (range 42 to 81 years) for the AXL group and 59 years (range 44 to 73 years) for the DCT group. The majority of patients were male (69.0% AXL group vs. 75.6% DCT group). All treated patients were Caucasian.			
Units: Subjects			
Adults (18-64 years)	52	33	85
From 65-84 years	6	8	14
Age continuous			
Units: years			
median	57	58	
full range (min-max)	42 to 81	44 to 73	-
Gender categorical			
Units: Subjects			
Female	18	10	28
Male	40	31	71
ECOG performance status			
Eastern Cooperative Oncology Group performance status			
Units: Subjects			
ECOG 0	12	12	24
ECOG 1	43	28	71
ECOG 2	3	1	4
ECG status			
Electrocardiogram status			
Units: Subjects			
ECG abnormal	35	28	63
ECG normal	23	13	36
Respiratory status			
Units: Subjects			
Respiratory abnormal	38	29	67
Respiratory normal	20	12	32
Time since diagnosis			
Time since diagnosis of NSCLC			
Units: years			
arithmetic mean	1.1	1.6	
standard deviation	± 0.8	± 1.87	-

End points

End points reporting groups

Reporting group title	AXL1717

Reporting group description:

Test Arm; The Per Protocol set consisted of 101 randomized patients, 2 of whom were not treated (patient 101-008 withdrew consent; patient 305-007 was mistakenly randomized despite the presence of an exclusion criterion), and therefore the full analysis set (FAS) (also used for safety) consisted of 99 treated patients (58 AXL, 41 DCT).

Reporting group title	Docetaxel

Reporting group description:

Active comparator

Primary: Rate of PFS - by squamous cell carcinoma (SCC) subtype

End point title	Rate of PFS - by squamous cell carcinoma (SCC) subtype

End point description:

The primary efficacy parameter in this study was the assessment of tumor response as evaluated by RECIST 1.1. The PFS rate was defined as the proportion of surviving, non-progressing patients at 12 weeks. Only patients with a tumor assessment performed during the protocol-defined window for the 12-week assessment were included in the analysis of the primary endpoint. To objective was to compare the rate of PFS at 12 weeks between patients treated with AXL1717 and patients treated with docetaxel in the total study population and in the squamous cell carcinoma (SCC) and adenocarcinoma (AC) subtypes of NSCLC.

End point type	Primary

End point timeframe:

12 weeks following first dose of study drug

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	21		
Units: Percent				
number (confidence interval 95%)				
PFS at 12 weeks	20.7 (8 to 39.7)	38.1 (18.1 to 61.6)		

Statistical analyses

Statistical analysis title	The PFS rate - SCC subtype

Statistical analysis description:

The PFS rate is defined as the proportion of surviving, non-progressing patients at 12 weeks. Only patients with a tumor assessment performed during the protocol-defined window for the 12-week assessment were included in the analysis of the primary endpoint.
The PFS rate and associated 95% confidence interval are presented for each treatment group. Difference in PFS rates between treatment groups are presented along with the exact 95% CI.

Comparison groups	AXL1717 v Docetaxel

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.213
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.6
upper limit	10.6

Primary: Rate of PFS - adenocarcinoma (AC) subtype

End point title	Rate of PFS - adenocarcinoma (AC) subtype

End point description:

The primary efficacy parameter in this study was the assessment of tumor response as evaluated by RECIST 1.1. The PFS rate was defined as the proportion of surviving, non-progressing patients at 12 weeks. Only patients with a tumor assessment performed during the protocol-defined window for the 12-week assessment were included in the analysis of the primary endpoint. To objective was to compare the rate of PFS at 12 weeks between patients treated with AXL1717 and patients treated with docetaxel in the total study population and in the squamous cell carcinoma (SCC) and adenocarcinoma (AC) subtypes of NSCLC.

End point type	Primary

End point timeframe:

12 weeks following first dose of study drug

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	21		
Units: Percent				
number (confidence interval 95%)				
PFS at 12 weeks	31 (15.3 to 50.8)	40 (19.1 to 63.9)		

Statistical analyses

Statistical analysis title	The PFS rate - AC subtype

Statistical analysis description:

The PFS rate is defined as the proportion of surviving, non-progressing patients at 12 weeks. Only patients with a tumor assessment performed during the protocol-defined window for the 12-week assessment were included in the analysis of the primary endpoint.
The PFS rate and associated 95% confidence interval are presented for each treatment group. Difference in PFS rates between treatment groups are presented along with the exact 95% CI.

Comparison groups	Docetaxel v AXL1717

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.555
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.7
upper limit	19.2

Primary: Rate of PFS

End point title	Rate of PFS

End point description:

The primary efficacy parameter in this study was the assessment of tumor response as evaluated by RECIST 1.1. The PFS rate was defined as the proportion of surviving, non-progressing patients at 12 weeks. Only patients with a tumor assessment performed during the protocol-defined window for the 12-week assessment were included in the analysis of the primary endpoint. To objective was to compare the rate of PFS at 12 weeks between patients treated with AXL1717 and patients treated with docetaxel in the total study population and in the squamous cell carcinoma (SCC) and adenocarcinoma (AC) subtypes of NSCLC.

End point type	Primary

End point timeframe:

12 weeks following first dose of study drug

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	41		
Units: Percent				
number (confidence interval 95%)				
PFS at 12 weeks	25.9 (15.3 to 39)	39 (24.2 to 55.5)		

Statistical analyses

Statistical analysis title	The PFS rate at 12 weeks following first drug dose

Statistical analysis description:

The PFS rate is defined as the proportion of surviving, non-progressing patients at 12 weeks. Only patients with a tumor assessment performed during the protocol-defined window for the 12-week assessment were included in the analysis of the primary endpoint.
The PFS rate and associated 95% confidence interval are presented for each treatment group. Difference in PFS rates between treatment groups are presented along with the exact 95% CI.

Comparison groups	AXL1717 v Docetaxel

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.4
upper limit	6.8

Secondary: Survival rates

End point title	Survival rates

End point description:

The survival rate was defined as the percentage of patients in the study who had survived for a period of time from randomization. The 12-week and 1-year survival rates and associated 95% CIs were planned for each treatment group. Differences in survival rates between treatment groups were to be presented along with the exact 95% CIs.

End point type	Secondary

End point timeframe:

12 weeks and 1 year

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	41		
Units: Percent				
number (confidence interval 95%)				
12-week survival rate	78.6 (65.4 to 87.2)	87.5 (72.5 to 94.6)		
1-year survival rate	46.7 (32.7 to 59.6)	43.6 (26.4 to 59.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Survival rates – SCC subtype

End point title	Survival rates – SCC subtype

End point description:

The survival rate was defined as the percentage of patients in the study who had survived for a period of time from randomization. The 12-week and 1-year survival rates and associated 95% CIs were planned for each treatment group. Differences in survival rates between treatment groups were to be presented along with the exact 95% CIs.

End point type	Secondary

End point timeframe:
12 weeks and 1 year

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	21		
Units: Percent				
number (confidence interval 95%)				
12-week survival rate	77.9 (57.2 to 89.4)	85 (60.4 to 94.9)		
1-year survival rate	34.3 (15.4 to 54.4)	36.9 (12.3 to 62.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Survival rates – AC subtype

End point title	Survival rates – AC subtype

End point description:

The survival rate was defined as the percentage of patients in the study who had survived for a period of time from randomization. The 12-week and 1-year survival rates and associated 95% CIs were planned for each treatment group. Differences in survival rates between treatment groups were to be presented along with the exact 95% CIs.

End point type	Secondary

End point timeframe:
12 weeks and 1 year

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	20		
Units: Percent				
number (confidence interval 95%)				
12-week survival rate	79.3 (59.6 to 90.1)	90 (65.6 to 97.4)		
1-year survival rate	55.2 (35.6 to 71)	45 (23.1 to 64.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was defined as the time from randomization to death from any cause. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the date of the data cut-off were censored at that date.

End point type	Secondary

End point timeframe:

Through cutoff date of analyses.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	41		
Units: Weeks				
number (confidence interval 95%)				
Kaplan-Meier estimate of median overall survival	32.7 (21.1 to 69.6)	40.9 (21.4 to 74.3)		

Attachments (see zip file)	Graphical Representation.pdf

Statistical analyses

Statistical analysis title	Kaplan-Meier estimate of median OS

Statistical analysis description:

Overall survival was defined as the time from randomization to death from any cause. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the date of the data cut-off were censored at that date.

Comparison groups	Docetaxel v AXL1717
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.907
Method	Logrank

Secondary: Overall survival – SCC subtype

End point title	Overall survival – SCC subtype

End point description:

Overall survival was defined as the time from randomization to death from any cause. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the date of the data cut-off were censored at that date.

End point type	Secondary

End point timeframe:

Through cutoff date of analyses.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	21		
Units: Weeks				
number (confidence interval 95%)				
Kaplan-Meier estimate of median overall survival	28.4 (16.9 to 57.9)	40.9 (23 to 65.3)		

Statistical analyses

Statistical analysis title	Kaplan-Meier estimate of median OS – SCC subtype
Statistical analysis description:	

Overall survival was defined as the time from randomization to death from any cause. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the date of the data cut-off were censored at that date.

Comparison groups	AXL1717 v Docetaxel
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.626
Method	Logrank

Secondary: Overall survival – AC subtype

End point title	Overall survival – AC subtype
End point description:	

Overall survival was defined as the time from randomization to death from any cause. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the date of the data cut-off were censored at that date.
Kaplan-Meier estimate of median OS, weeks [95% CI] for AC Subtype:
AXL1717 - 57.3 [18.0, NA]
Docetaxel - 24.8 [15.0, NA]

End point type	Secondary
End point timeframe:	

Through cutoff date of analyses.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[1]	20[2]		
Units: Percent				
number (confidence interval 95%)				
Kaplan-Meier estimate of median overall survival	57.3 (18 to 9999.9)	24.8 (15 to 9999.9)		

Notes:

[1] - AC subtype of NSCLC covers 29 subjects from AXL1717 group

[2] - AC subtype of NSCLC covers 20 subjects from Decetaxel group

Statistical analyses

Statistical analysis title	Kaplan-Meier estimate of median OS – AC subtype

Statistical analysis description:

Overall survival was defined as the time from randomization to death from any cause. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the date of the data cut-off were censored at that date.

Comparison groups	AXL1717 v Docetaxel
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.745
Method	Logrank

Secondary: Kaplan-Meier estimate of median PFS

End point title	Kaplan-Meier estimate of median PFS

End point description:

Using the same definition as for the primary endpoint, PFS was defined as the time from randomization to the first observation of disease progression according to the RECIST criteria or death due to any cause.

End point type	Secondary

End point timeframe:

Through cutoff date of analyses.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[3]	20[4]		
Units: Weeks				
number (confidence interval 95%)				
Kaplan-Meier estimate of median PFS	13 (6.3 to 15.4)	12.4 (6.1 to 20.3)		

Notes:

[3] - AC subtype of NSCLC covers 29 subjects from AXL1717 group

[4] - AC subtype of NSCLC covers 20 subjects from Decetaxel group

Attachments (see zip file)	Graphical Representation_2.pdf

Statistical analyses

Statistical analysis title	Kaplan-Meier estimate of median PFS

Statistical analysis description:

PFS was defined as the time from randomization to the first observation of disease progression according to the RECIST criteria or death due to any cause.

Comparison groups	AXL1717 v Docetaxel
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.615
Method	Logrank

Secondary: Kaplan-Meier estimate of median PFS – SCC subtype

End point title	Kaplan-Meier estimate of median PFS – SCC subtype

End point description:

Using the same definition as for the primary endpoint, PFS was defined as the time from randomization to the first observation of disease progression according to the RECIST criteria or death due to any cause.

End point type	Secondary

End point timeframe:

Through cutoff date of analyses.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	21		
Units: Weeks				
number (confidence interval 95%)				
Kaplan-Meier estimate of median PFS	12.3 (6.1 to 13)	12.4 (6.3 to 30.6)		

Attachments (see zip file)	Graphical Representation_3.pdf

Statistical analyses

Statistical analysis title	Kaplan-Meier estimate of median PFS – SCC subtype
Comparison groups	Docetaxel v AXL1717
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082
Method	Logrank

Secondary: Kaplan-Meier estimate of median PFS – AC subtype

End point title	Kaplan-Meier estimate of median PFS – AC subtype

End point description:

Using the same definition as for the primary endpoint, PFS was defined as the time from randomization to the first observation of disease progression according to the RECIST criteria or death due to any cause.

End point type	Secondary

End point timeframe:

Through cutoff date of analyses.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	20		
Units: Percent				
number (confidence interval 95%)				
Kaplan-Meier estimate of median PFS	13 (6.3 to 15.4)	12.4 (6.1 to 20.3)		

Attachments (see zip file)	Graphical Representation_4.pdf

Statistical analyses

Statistical analysis title	Kaplan-Meier estimate of median PFS – AC subtype

Statistical analysis description:

PFS was defined as the time from randomization to the first observation of disease progression according to the RECIST criteria or death due to any cause.

Comparison groups	AXL1717 v Docetaxel
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.615
Method	Logrank

Secondary: Tumor response – combined local/central reader	
End point title	Tumor response – combined local/central reader

End point description:

A secondary endpoint of the study was to compare the rate of CR, PR, SD, PD, disease control (CR + PR + SD), and objective response (CR + PR) at 12 weeks between the AXL and DCT groups in the total study population and in the SCC and AC subtypes. Results are presented combining the RECIST tumor response assessments of central readers and local readers.

End point type	Secondary

End point timeframe:

12 weeks

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	41		
Units: Subjects				
number (not applicable)				
Complete response	0	0		
Partial response	0	5		
Stable disease	15	10		
No measurable disease	0	3		
Non CR / Non PD	0	2		
Progressive disease	12	8		
No assessment	31	13		

Statistical analyses

Statistical analysis title	Tumor response – Combined Local/Central reader

Statistical analysis description:

Tumor response after four cycles will be summarized descriptively using response categories based on RECIST criteria: PD, SD, PR, CR, or Not Evaluable (NE). Separate analysis will be performed for Central reader and for Local reader data.
The rates for disease control and objective response will be calculated based on the best tumor response during four cycles.

Comparison groups	AXL1717 v Docetaxel
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	Fisher exact

Secondary: Tumor response – combined local/central reader

End point title	Tumor response – combined local/central reader

End point description:

A secondary endpoint of the study was to compare the rate of CR, PR, SD, PD, disease control (CR + PR + SD), and objective response (CR + PR) at 12 weeks between the AXL and DCT groups in the total study population and in the SCC and AC subtypes. Results are presented combining the RECIST tumor response assessments of central readers and local readers.

End point type	Secondary

End point timeframe:

12 weeks.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	41		
Units: Percent				
number (confidence interval 95%)				
Objective response rate (CR+PR)	0 (0 to 0)	12.2 (4.1 to 26.2)		
Disease control rate (CR+PR+SD)	25.9 (15.3 to 39)	36.6 (22.1 to 53.1)		

Statistical analyses

Statistical analysis title	Tumor response – Combined Local/Central reader

Statistical analysis description:

Tumor response after four cycles will be summarized descriptively using response categories based on RECIST criteria: PD, SD, PR, CR, or Not Evaluable (NE). Separate analysis will be performed for Central reader and for Local reader data.
The rates for disease control and objective response will be calculated based on the best tumor response during four cycles.

Comparison groups	AXL1717 v Docetaxel
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	Fisher exact

Secondary: Time to progression

End point title	Time to progression

End point description:

Time to progression was defined as the time from randomization to the first observation of disease progression according to the RECIST criteria or death due to progression.
A patient who stopped treatment with the study drug and received alternative therapy prior to documentation of disease progression was censored on the date that the alternative therapy started. If a patient had not progressed, TTP was censored on the date of the last tumor assessment.

End point type	Secondary

End point timeframe:

Through cutoff date of analyses.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	41		
Units: Weeks				
number (confidence interval 95%)				
Kaplan-Meier estimate of median PFS	13 (11.9 to 14.7)	12.7 (12.1 to 20.1)		

Attachments (see zip file)	Graphical Representation_5.pdf

Statistical analyses

Statistical analysis title	Time to progression

Statistical analysis description:

Time to progression (TTP) is defined as the time from randomization to the first observation of disease progression according to the RECIST criteria or death due to progression.

Comparison groups	AXL1717 v Docetaxel
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.662
Method	Logrank

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

Time to treatment failure was defined as the time from randomization to the first observation of discontinuation of treatment, PD, or death.
A patient who stopped treatment with the study drug and received alternative therapy prior to documentation of disease progression was censored on the date that the alternative therapy started. If a patient had not progressed, TTF was censored on the date of the last tumor assessment.

End point type	Secondary

End point timeframe:

Through cutoff date of analyses.

End point values	AXL1717	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	41		
Units: Percent				
number (confidence interval 95%)				
Kaplan-Meier estimate of median PFS	10.8 (6.3 to 12.3)	12.4 (10.4 to 16.3)		

Statistical analyses

Statistical analysis title	Time to treatment failure

Statistical analysis description:

TTF is defined as the time from randomization to the first observation of discontinuation of treatment, PD or death.

Comparison groups	Docetaxel v AXL1717
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.129
Method	Logrank

Comparison groups	Docetaxel v AXL1717
Number of subjects included in analysis	99

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Signing of informed consent through no later than 30 days after last date of study drug exposure.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15,0

Reporting groups

Reporting group title	AXL1717
Reporting group description:	
subjects who received AXL1717	
Reporting group title	Docetaxel
Reporting group description:	
Subjects who received docetaxel	

Serious adverse events	AXL1717	Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 58 (24.14%)	5 / 41 (12.20%)	
number of deaths (all causes)	33	23	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	2 / 58 (3.45%)	4 / 41 (9.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 4	
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	2 / 58 (3.45%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 58 (8.62%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Febrile neutropenia		
subjects affected / exposed	1 / 58 (1.72%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Agranulocytosis		
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Anaemia		
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancytopenia		
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0
General disorders and administration site conditions		
Fatigue		
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
General physical health deterioration		
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Gastrointestinal disorders		
Diarrhoea		
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	2 / 58 (3.45%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 58 (3.45%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AXL1717	Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 58 (70.69%)	34 / 41 (82.93%)	
Blood and lymphatic system disorders			

Neutropenia		
subjects affected / exposed	11 / 58 (18.97%)	19 / 41 (46.34%)
occurrences (all)	16	21
Leukopenia		
subjects affected / exposed	12 / 58 (20.69%)	9 / 41 (21.95%)
occurrences (all)	15	9
Anemia		
subjects affected / exposed	12 / 58 (20.69%)	12 / 41 (29.27%)
occurrences (all)	13	12
General disorders and administration site conditions		
Asthenia		
subjects affected / exposed	7 / 58 (12.07%)	9 / 41 (21.95%)
occurrences (all)	7	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2012	Protocol Amendment 1 addressed safety concerns. A summary of changes included: Added: -additional biomarker evaluation -clarification of inclusion criteria related to radiation therapy -clarification to the exclusion criteria for men who are capable of fathering a child -that AXL patients could be treated with WBC growth factors while in the study. Per Amendment 1, WBC growth factors could be used in the management of patients in the AXL group, according to ASCO guidelines. Investigators were encouraged to use G-CSF for treatment of nonfebrile Grade 3 neutropenia. Upon development of febrile neutropenia or nonfebrile Grade 4 neutropenia, G-CSF use was required in the AXL group -an additional biopsy procedure and evaluation -Appendix 2 to clarify the procedures for both AXL treatment groups -additional safety testing to evaluate the need for dose delays or adjustments -Appendix 9 to include TNM classification -Appendix 10 for clarification of BSA calculation used for DCT dose calculation -Appendix 11 for clarification of list of the CYP3A4 substrate with narrow therapeutic index and CYP2C9 inhibitors Clarified -parameters for WBC with or without differential counts to evaluate safety related to dose delays or interruptions -AXL dose interruptions/adjustment procedures -DCT dose procedures & dose interruption procedures -protocol procedures for toxicity criteria for patient withdrawal -patient withdrawal procedures -local standard of care among clinical sites -end of study procedures -protocol procedures for exploratory assessments, AEs, clinical laboratory, and biomarker evaluations Included a list of medications that were to be avoided Provided an alternate treatment schedule based on safety Patients receiving DCT were to be premedicated with corticosteroids to account for local standard of care among clinical sites

| 07 October 2012 | Protocol Amendment 2 addressed safety concerns and implemented clarifications throughout the protocol. Changes included:
• Clinical update summarizing recruitment, which was temporarily stopped on 19 July 2012 due to safety concerns, as noted above; dose-limiting events; and fatalities.
• Implemented a revised treatment regimen based on safety recommendation from the DSMC. The starting dose of AXL was reduced to 300 mg for the first 28 days; then, depending on ANC levels measured during the first 28 days, subsequent doses could be increased to 400 mg BID, remain at 300 mg BID, or be temporarily interrupted and, when ANC levels recovered to an acceptable level, be resumed at the same dose or 1 dose level lower.
• Revised the exclusion criteria based on safety recommendations from the DSMC. SCC patients with involvement of major vessels (diagnosis as confirmed by a radiologist) were excluded.
• Updated and provided additional safety data and information.
• Clarified storage and handling procedures for AXL.
• Implementation of procedural changes based on safety recommendations from the DSMC.
• Appendix 7 clarified guidelines for the use of WBC growth factors.
• Appendix 12 was added as a safety recommendation from the DSMB to provide standard recommendations and procedures for the management of patients who developed neutropenia while treated with AXL. Appendix 12 included guidelines for use of WBC growth factors in the treatment of patients in the AXL group.
After implementation of the amended protocol, 1 patient died due to an SAE of clinically suspected pneumonia with neutropenic sepsis. The DSMC investigated the case in detail and decided to recommend to permanently abandon the 400 mg BID dose for the remainder of the study. The 300 mg BID dose of AXL was thus instituted as the recommended Phase II dose for continuous treatment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

| 19 July 2012 | Following the deaths of 12 patients in the study (9 in the AXL group and 3 in the DCT group), with 7 patients dying within 4 weeks of entry into the study, recruitment into the study was temporarily stopped on 19July2012 to allow the DSMC to review the cases. The DSMC monitoring the trial convened 3 times (26Jul2012, 03Aug2012, 13Aug2012) and recommended changes to the conduct of the study and the Sponsor implemented Protocol Amendment 2 (07Oc2012). At the time recruitment was suspended, 75 patients had been treated (46 AXL & 29 DCT). During the review by the DSMC, 23 patients (14 AXL & 9 DCT) already randomized continued receiving study treatment.
7 fatal cases in AXL group and 3 in DCT group were assessed as related to tumor progression. 2 fatal cases in AXL group were directly attributable to neutropenia or leukopenia, 2 cases were reported as disease progression in the clinical setting of neutropenia or leukopenia, 3 cases were reported as disease progression without any known neutropenia or leukopenia, and 2 patients experienced fatal pulmonary hemorrhage.
There were 4 fatal cases connected with neutropenia. Three patients were treated with corticosteroids (dexamethasone) during the neutropenic periods.
According to DSMC it was not possible to exclude that the treatment with steroids may have contributed to the outcome in these 3 fatal cases.
The 2 fatal events of pulmonary hemorrhage were reported as starting 14 & 28 days after the first dose of AXL, respectively. Both of the patients had central squamous NSCLC tumors with tumor involvement of major blood vessels on CT as assessed by the DSMC. The DSMC determined it was not possible to exclude that possible tumor shrinkage could have contributed to the bleeding. The DSMC therefore recommended that patients with central tumors and/or involvement of major blood vessels should be excluded from enrollment into the study; however, patients already randomized were to continue as planned. | 03 December 2012 |

Notes:

Limitations and caveats

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

Following implementation of Protocol Amendment 2, the Sponsor curtailed enrollment in the study from a planned 140 treated patients to the 99 patients described in this report.

Notes: