Clinical trial results:
Phase I/II study of oral administration of S 49076 given in combination with gefitinib in patients with EGFR mutated advanced non-small-cell lung cancer who have progressed after treatment with EGFR tyrosine kinase inhibitor.

Summary

EudraCT number	2015-002646-31
Trial protocol	ES HU DE
Global end of trial date	07 November 2018

Results information

Result version number	v1 (current)
This version publication date	18 July 2019
First version publication date	18 July 2019

Trial information

Trial identification

Sponsor protocol code	CL1-49076-003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Laboratorios Servier S.L.
Sponsor organisation address	Avenida de los Madronos, 33, Madrid, Spain, 28043
Public contact	Dpto. Investigación y Desarrollo, Laboratorios Servier S.L., +34 917489014, itziar.fernandezgonzalez@servier.com
Scientific contact	Dpto. Investigación y Desarrollo, Laboratorios Servier S.L., +34 917489014, itziar.fernandezgonzalez@servier.com
Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Scientific contact	Center for Therapeutic Innovation in Oncology, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2018
Global end of trial reached?	Yes
Global end of trial date	07 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and activity of S49076 in combination with gefitinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring activating Epidermal Growth Factor Receptor (EGFR) mutations, who had received clinical benefit and then progressed on an EGFR tyrosine kinase inhibitor (TKI) (erlotinib, gefitinib, icotinib, afatinib or dacomitinib).

Protection of trial subjects:

This study was conducted in accordance with Good Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Taiwan: 3
Worldwide total number of subjects	14
EEA total number of subjects	6

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)	9
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The investigators were specialists in Medical Oncology.

Pre-assignment

Screening details:

Male/female patients aged ≥18 years with locally advanced or metastatic stage IIIB/IV NSCLC with measurable tumour disease according to RECIST V1.1, having EGFR Mutation without T790M mutation; with AXL overexpression or MET amplification and/or MET overexpression, who had received clinical benefit, and then progressed on one single agent EGFR TKI

Period 1

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

Arms

Arm title	S 49076

Arm description:

Phase I / Dose-escalation part: patients received S49076 dose level of 500 mg or 600 mg in combination with fixed dose (250 mg) of gefitinib, orally once daily (q.d.), on a continuous schedule during 28-day cycles.
Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

Arm type	Experimental
Investigational medicinal product name	S 49076
Investigational medicinal product code	S 49076
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients took either 5 or 6 tablets of S49076 100 mg once daily on a continuous dosing schedule, during a 28-day cycle.
Patients took one tablet of 250 mg of gefitinib (Non IMP), orally, once daily on a continuous dosing schedule, during a 28-day cycle.

Number of subjects in period 1	S 49076
Started	14
Completed	11
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups

Reporting group title	S 49076

Reporting group description:

Phase I / Dose-escalation part: patients received S49076 dose level of 500 mg or 600 mg in combination with fixed dose (250 mg) of gefitinib, orally once daily (q.d.), on a continuous schedule during 28-day cycles.
Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

Reporting group values	S 49076	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	5	5	
Age continuous Units: years			
arithmetic mean	60.9		
full range (min-max)	35 to 72	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	6	6	

Subject analysis sets

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

Subject analysis set description:

The Safety Set consisted of 14 patients included in the study and who received at least one dose of S49076 or one dose of gefitinib.

Subject analysis set title	DLT Evaluable Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who took at least one dose of S49076 or one dose of gefitinib, and were evaluable for DLT (Dose-Limiting Toxicities) according to the DLT assessment at end of cycle 1.
A patient was not considered evaluable if:
-He/she definitely discontinued during first cycle for a reason other than DLT or
-He/she did not undergo a DLT assessment at the start of cycle 2 or
-He/she did not receive at least 85% (24 doses over 28) of S49076 doses, unless treatment was stopped for a DLT.
-He/she did not receive at least 85% (24 doses over 28) of gefitinib doses, unless treatment was stopped for a DLT.

Reporting group values	Safety Set	DLT Evaluable Set	
Number of subjects	14	10	
Age categorical Units: Subjects			
Adults (18-64 years)	9		
From 65-84 years	5		

Age continuous Units: years			
arithmetic mean	60.9		
full range (min-max)	35 to 72		
Gender categorical Units: Subjects			
Female	8		
Male	6		

End points

End points reporting groups

Reporting group title	S 49076

Reporting group description:

Phase I / Dose-escalation part: patients received S49076 dose level of 500 mg or 600 mg in combination with fixed dose (250 mg) of gefitinib, orally once daily (q.d.), on a continuous schedule during 28-day cycles.
Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

Subject analysis set title	Safety Set
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-He/she did not undergo a DLT assessment at the start of cycle 2 or
-He/she did not receive at least 85% (24 doses over 28) of S49076 doses, unless treatment was stopped for a DLT.
-He/she did not receive at least 85% (24 doses over 28) of gefitinib doses, unless treatment was stopped for a DLT.

Primary: Recommended Phase II Dose (RP2D)

End point title	Recommended Phase II Dose (RP2D)[1]

End point description:

During the dose-escalation (Phase I of the study), two S49076 dose levels were tested in combination with fixed dose gefitinib : 500 mg and 600 mg once daily. DLT was assessed during cycle 1 according to a modified version of Continual Reassessment Method and stopping rules. One DLT at 600 mg (oral mucositis grade 3) was observed in the second cohort including 4 patients. At the end of dose escalation, no Maximum Tolerated Dose was reached, and the RP2D was defined as 600 mg once daily in combination with 250mg once daily of gefitinib.

End point type	Primary

End point timeframe:

See the section description

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: No statistical analyses required for this end point.

End point values	DLT Evaluable Set			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: mg once daily	600			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Emergent adverse events on treatment were defined -as adverse events which occured or worsen (in terms of severity) or became serious between the first S49076 or Gefitinib intake date and the last S49076 / Gefitinib intake date +28 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	500 mg Group

Reporting group description:

Phase I / Dose-escalation part: patients received fixed dose (250 mg) of gefitinib and S 49076 dose level of 500 mg orally once daily (q.d.), on a continuous schedule during 28-day cycles.
Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

Reporting group title	600 mg Group

Reporting group description:

Phase I / Dose-escalation part: patients received fixed dose (250 mg) of gefitinib and S 49076 dose level of 600 mg orally once daily (q.d.), on a continuous schedule during 28-day cycles.
Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

Reporting group title	All patients

Reporting group description:

Phase I / Dose-escalation part: patients received fixed dose (250 mg) of gefitinib and S 49076 (dose level of 500 mg or 600 mg) orally once daily (q.d.), on a continuous schedule during 28-day cycles.
Cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision.

Serious adverse events	500 mg Group	600 mg Group	All patients
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	6 / 10 (60.00%)	9 / 14 (64.29%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Metastases to central nervous system			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related thrombosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug interaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Legionella test positive			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 10 (10.00%)	3 / 14 (21.43%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	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	500 mg Group	600 mg Group	All patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	10 / 10 (100.00%)	14 / 14 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pyogenic granuloma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Pallor			

subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 4 (50.00%)	4 / 10 (40.00%)	6 / 14 (42.86%)
occurrences (all)	2	4	6
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	4 / 10 (40.00%)	5 / 14 (35.71%)
occurrences (all)	2	4	6
Generalised oedema			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	2 / 14 (14.29%)
occurrences (all)	1	1	2
Catheter site oedema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Gait disturbance			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Malaise			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Peripheral swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Reproductive system and breast disorders			
Vulvovaginal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	2 / 14 (14.29%)
occurrences (all)	1	2	3
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Haemoptysis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Lung infiltration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Nasal dryness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Organising pneumonia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 4 (100.00%)	1 / 10 (10.00%)	5 / 14 (35.71%)
occurrences (all)	4	1	5
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 4 (75.00%)	2 / 10 (20.00%)	5 / 14 (35.71%)
occurrences (all)	3	3	6
Blood creatine increased			

subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	2 / 14 (14.29%)
occurrences (all)	1	1	2
Blood albumin decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Body temperature increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Ejection fraction decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Neutrophil count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Troponin I increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	2
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Skin abrasion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Skin wound			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Nervous system disorders			
Allodynia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Central pain syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	3 / 14 (21.43%)
occurrences (all)	2	2	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 4 (75.00%)	4 / 10 (40.00%)	7 / 14 (50.00%)
occurrences (all)	4	11	15
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	3 / 10 (30.00%)	6 / 14 (42.86%)
occurrences (all)	3	4	7
Mouth ulceration			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	3 / 14 (21.43%)
occurrences (all)	1	2	3
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	3 / 14 (21.43%)
occurrences (all)	1	3	4
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	2 / 14 (14.29%)
occurrences (all)	3	1	4
Abdominal distension			

subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	3 / 14 (21.43%)
occurrences (all)	1	4	5
Yellow skin			
subjects affected / exposed	3 / 4 (75.00%)	0 / 10 (0.00%)	3 / 14 (21.43%)
occurrences (all)	3	0	3
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	2 / 14 (14.29%)
occurrences (all)	0	3	3
rash			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Rash papular			

subjects affected / exposed	2 / 4 (50.00%)	0 / 10 (0.00%)	2 / 14 (14.29%)
occurrences (all)	2	0	2
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Hair texture abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Onycholysis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	2
Onychomadesis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Pigmentation disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Skin fissures			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Skin ulcer			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Periarthritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Infections and infestations			
Paronychia			
subjects affected / exposed	3 / 4 (75.00%)	4 / 10 (40.00%)	7 / 14 (50.00%)
occurrences (all)	3	7	10
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Carbuncle			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Cystitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1

Ear infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Genital herpes			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Herpes simplex			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Onychomycosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Staphylococcal infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Wound infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 4 (50.00%)	3 / 10 (30.00%)	5 / 14 (35.71%)
occurrences (all)	4	3	7
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Hypomagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Hyponatraemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Hypophosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Hypoalbuminaemia			
subjects affected / exposed	2 / 4 (50.00%)	3 / 10 (30.00%)	5 / 14 (35.71%)
occurrences (all)	2	3	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2015	Update to the list of treatments prohibited and non-inclusion criteria (related to Investigator Brochure version 5): rosuvastatin is contraindicated. Addition of a new country (Japan) and new centres in the phase I part of the study Corrections of inconsistencies and clarifications
27 January 2016	Concerned Japan : update related to Pharmaceuticals and Medical Devices Agency request.
19 April 2017	Dacomitinib allowed as previous line. Palliative radiotherapy allowed up to 1 week prior to inclusion. A 2-week time window added between biopsy collection and inclusion. Clarification on the reporting of adverse events possibly related to disease progression. The period for LVEF reassessment in case of asymptomatic decreased has been lengthened from 2 to 3 weeks in case of relative LVEF decrease ≥10 units from baseline or absolute LVEF ≥40% and <50%. Addition of herbal product as a prohibited concomitant treatment.
04 June 2018	Update of the list of prohibited treatments and non-inclusion criteria
23 August 2018	Definition of the end of the study and cancellation of the follow-up period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 July 2018	During phase I, the observed frequency of AXL dysregulation was lower than expected. Additionally, the global anti-tumoral preliminary data did not suggest an increase of activity by adding S 49076 to gefitinib. These elements taken together have led the Sponsor not to initiate the phase II part of the study due to feasibility challenges.	-

Notes:

Limitations and caveats

None reported