Clinical trial results:
LUX-Lung IO: A phase II, open label, non-randomised study of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous cell carcinoma of the lung

Summary

EudraCT number	2016-005042-37
Trial protocol	ES FR
Global end of trial date	13 January 2020

Results information

Result version number	v2 (current)
This version publication date	08 June 2022
First version publication date	06 January 2021
Version creation reason	• Correction of full data set Correction of previously posted information.

Trial information

Trial identification

Sponsor protocol code	1200-0283

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03157089
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany,
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2020
Global end of trial reached?	Yes
Global end of trial date	13 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC) who progressed during or after firstline platinum-based treatment, with efficacy measured by objective response (OR).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all subjects as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	28
EEA total number of subjects	18

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)	15
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A phase II, open-label, non-randomised, single arm study. Patients with locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC), who progressed during or after first line platinum-based standard therapy and had no prior treatment with an immune checkpoint inhibitor or Epidermal Growth Factor Receptor (EGFR) targeted therapy.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group, if any of the entry criteria were violated.

Period 1

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

Blinding implementation details:

This was an open label trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib 40 mg + pembrolizumab 200 mg

Arm description:

40 milligram (mg) of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily + pembrolizumab 200 mg, intravenous infusion, once every 3 weeks. Both afatinib and pembrolizumab were to be given until documented disease progression, or unacceptable adverse events, or other reasons requiring treatment discontinuation, or for up to 35 cycles of 21 days (i.e. the approved pembrolizumab monotherapy duration). In case of early discontinuation of one agent, the other agent could be continued as monotherapy for altogether up to 35 cycles.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg, intravenous infusion, once every 3 weeks.

Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	Gilotrif®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40 milligram (mg) of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily.

Arm title	Afatinib 30 mg + pembrolizumab 200 mg

Arm description:

30 mg of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily + pembrolizumab 200 mg, intravenous infusion, once every 3 weeks. Both afatinib and pembrolizumab were to be given until documented disease progression, or unacceptable adverse events, or other reasons requiring treatment

discontinuation, or for up to 35 cycles of 21 days (i.e. the approved pembrolizumab monotherapy duration). In case of early discontinuation of one agent, the other agent could be continued as monotherapy for altogether up to 35 cycles.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg, intravenous infusion, once every 3 weeks.

Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	Gilotrif®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

30 milligram (mg) of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily.

Number of subjects in period 1[1]	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg
Started	12	12
Treated with afatinib+pembrolizumab	12	12
Completed	0	0
Not completed	12	12
Adverse event, non-fatal	5	4
Treated only with pembrolizumab	1	-
Progressive disease	6	8

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 28 patients had been enrolled, 24 patients thereof were entered into the trial and treated with at least 1 dose of study medication.

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib 40 mg + pembrolizumab 200 mg
Reporting group description:	
40 milligram (mg) of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily + pembrolizumab 200 mg, intravenous infusion, once every 3 weeks. Both afatinib and pembrolizumab were to be given until documented disease progression, or unacceptable adverse events, or other reasons requiring treatment discontinuation, or for up to 35 cycles of 21 days (i.e. the approved pembrolizumab monotherapy duration). In case of early discontinuation of one agent, the other agent could be continued as monotherapy for altogether up to 35 cycles.	
Reporting group title	Afatinib 30 mg + pembrolizumab 200 mg
Reporting group description:	
30 mg of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily + pembrolizumab 200 mg, intravenous infusion, once every 3 weeks. Both afatinib and pembrolizumab were to be given until documented disease progression, or unacceptable adverse events, or other reasons requiring treatment discontinuation, or for up to 35 cycles of 21 days (i.e. the approved pembrolizumab monotherapy duration). In case of early discontinuation of one agent, the other agent could be continued as monotherapy for altogether up to 35 cycles.	

Reporting group values	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg	Total
Number of subjects	12	12	24
Age categorical			
Treated Set (TS) included all participants, who received at least one dose of afatinib or pembrolizumab.			
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)	8	6	14
From 65-84 years	4	6	10
85 years and over	0	0	0
Age Continuous			
Treated Set (TS) included all participants, who received at least one dose of afatinib or pembrolizumab.			
Units: years			
arithmetic mean	62.8	63.3	
standard deviation	± 10.0	± 7.3	-
Sex: Female, Male			
Treated Set (TS) included all participants, who received at least one dose of afatinib or pembrolizumab.			
Units: Participants			
Female	4	1	5
Male	8	11	19
Race (NIH/OMB)			
Treated Set (TS) included all participants, who received at least one dose of afatinib or pembrolizumab. Unknown or Not Reported represents participants from France where information on race could not be collected for legal reasons.			

Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	5	0	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	6	8	14
More than one race	0	0	0
Unknown or Not Reported	1	4	5
Ethnicity (NIH/OMB)			
Treated Set (TS) included all participants, who received at least one dose of afatinib or pembrolizumab. Ethnicity was not collected.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	0	0	0
Unknown or Not Reported	12	12	24

End points

End points reporting groups

Reporting group title	Afatinib 40 mg + pembrolizumab 200 mg

Reporting group description:

40 milligram (mg) of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily + pembrolizumab 200 mg, intravenous infusion, once every 3 weeks. Both afatinib and pembrolizumab were to be given until documented disease progression, or unacceptable adverse events, or other reasons requiring treatment discontinuation, or for up to 35 cycles of 21 days (i.e. the approved pembrolizumab monotherapy duration). In case of early discontinuation of one agent, the other agent could be continued as monotherapy for altogether up to 35 cycles.

Reporting group title	Afatinib 30 mg + pembrolizumab 200 mg

Reporting group description:

30 mg of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily + pembrolizumab 200 mg, intravenous infusion, once every 3 weeks. Both afatinib and pembrolizumab were to be given until documented disease progression, or unacceptable adverse events, or other reasons requiring treatment discontinuation, or for up to 35 cycles of 21 days (i.e. the approved pembrolizumab monotherapy duration). In case of early discontinuation of one agent, the other agent could be continued as monotherapy for altogether up to 35 cycles.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

Objective response rate is defined as percentage of participants with best overall response of complete response (CR, disappearance of all target lesions) or confirmed partial response (PR, at least a 30% decrease in sum of diameter (SoD, longest diameter (LD) measured for all lesions except lymph nodes, where shortest diameter (ShD) was used) of target lesions, reference is baseline SoD). Tumour response was assessed based on local radiological image (Computerised tomography (CT) or Magnetic resonance imaging (MRI)) evaluation by the investigators according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. The treated set (TS) included all participants who received at least one dose of afatinib or pembrolizumab.

End point type	Primary

End point timeframe:

Tumour assessment performed at screening (-28 days), week 9 (day 56-63) after study treatment (afatinib or pembrolizumab) start and every 9th week thereafter, up to 556 days.

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: 28 patients had been enrolled, 24 patients thereof were entered into the trial and treated with at least 1 doseof study medication.

End point values	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[2]	12[3]		
Units: Percentage of Participants				
number (not applicable)	16.7	8.3		

Notes:

[2] - TS

[3] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Recommended Phase II Dose (RP2D)

End point title	Recommended Phase II Dose (RP2D)

End point description:

Recommended Phase II Dose (RP2D) was to be calculated through a Bayesian logistic regression model (BLRM) with overdose control that was to be fitted to binary toxicity outcomes. After 12 patients had completed at least one cycle (one cycle equals 21 days and consists of one time infusion of pembrolizumab at Day 1 + daily intake of afatinib) of treatment, the prior distributions were to be updated through Gibbs sampling procedures with the accumulated dose limiting toxicity (DLT) data from the first treatment cycle. The estimate of parameters was to be updated as data were accumulated using the BLRM. At the end of the dose confirmation, the toxicity probability at each dose level was to be calculated to determine an estimate of the RP2D. Posterior probabilities for the rate of DLT were to be summarised from BLRM. Confirmation of the RP2D by the Safety Monitoring Committee (SMC) was to be based on these probabilities as well as on the review of other safety and laboratory data.

End point type	Secondary

End point timeframe:

21 days (1 treatment cycle) from study treatment (afatinib and pembrolizumab) administration.

End point values	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: milligram				
number (not applicable)				

Notes:

[4] - TS, the decision on RP2D was not performed, because the trial was stopped according to the protocol.
[5] - TS, the decision on RP2D was not performed, because the trial was stopped according to the protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease control rate was calculated as percentage of participants with CR, PR, or stable disease (SD, neither sufficient shrinkage to qualify for PR, taking as reference the baseline sum of diameters (SoD), nor sufficient increase to qualify for progressive disease (PD, at least a 20% increase in the SoD of target lesions, taking as reference the smallest SoD recorded on study (including baseline), together with an absolute increase in the SoD of at least 5 millimeter (mm) or the appearance of one or more new lesions). Tumour response was assessed based on local radiological image (Computerised tomography (CT) or Magnetic resonance imaging (MRI)) evaluation by the investigators according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. The treated set (TS) included all participants who received at least one dose of afatinib or pembrolizumab.

End point type	Secondary

End point timeframe:

Tumour assessment performed at screening (-28 days), week 9 (day 56-63) after study treatment (afatinib or pembrolizumab) start and every 9th week thereafter, up to 556 days.

End point values	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[6]	12[7]		
Units: Percentage of participants				
number (not applicable)	50	58.3		

Notes:

[6] - TS

[7] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response (DoR)

End point title	Duration of objective response (DoR)

End point description:

For participants who showed objective response, duration of objective response (DoR), was defined as the time from first documented complete response (CR, disappearance of all target lesions) or partial response (PR, at least a 30% decrease in the sum of diameter (SoD) of target lesions taking as reference the baseline SoD until the earliest of disease progression (PD, at least a 20% increase in the SoD of target lesions, taking as reference the smallest SoD recorded on study (including baseline), together with an absolute increase in the SoD of at least 5 mm or the appearance of one or more new lesions) or death. Tumour response was assessed based on local radiological image (CT or MRI) evaluation by the investigators according to RECIST version 1.1. The number of participants with objective response who experienced the event "disease progression or death (whatever came first)" is reported.

End point type	Secondary

End point timeframe:

Tumour assessment performed at screening (-28 days), week 9 (day 56-63) after study treatment (afatinib or pembrolizumab) start and every 9th week thereafter, up to 436 days.

End point values	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[8]	1[9]		
Units: Participants	2	1		

Notes:

[8] - All participants who received at least one dose of study drug and showed objective response.

[9] - All participants who received at least one dose of study drug and showed objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival was defined as the time (weeks) from the date of the first afatinib or pembrolizumab administration to the date of disease progression (at least a 20% increase in the sum of diameter (SoD, longest diameter (LD) measured for all lesions except lymph nodes, where shortest diameter (ShD) was used) of target lesions, taking as reference the smallest SoD recorded on study (including baseline), together with an absolute increase in the SoD of at least 5 mm or the appearance of one or more new lesions) or death (if the patient died without progression). The date of progression for the primary analyses was determined based on investigator assessment. Tumour response was assessed based on local radiological image (Computerised tomography (CT) or Magnetic resonance imaging (MRI)) evaluation by the investigators according to RECIST version 1.1. Median and 95% Confidence Interval were calculated using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

Tumour assessment performed at screening (-28 days), week 9 (day 56-63) after study treatment (afatinib or pembrolizumab) start and every 9th week thereafter, up to 556 days.

End point values	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[10]	12[11]		
Units: weeks				
median (confidence interval 95%)	9.0 (4.6 to 27.1)	14.4 (5.0 to 26.1)		

Notes:

[10] - TS, all participants who received at least one dose of afatinib or pembrolizumab.

[11] - TS, all participants who received at least one dose of afatinib or pembrolizumab.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival is defined as the time from the date of treatment start date to the date of death. Participants without event were censored. Median and 95% Confidence Interval were calculated using Kaplan-Meier estimates. The treated set (TS) included all participants who received at least one dose of afatinib or pembrolizumab.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment (afatinib or pembrolizumab) administration up to a total of 574 days.

End point values	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[12]	12[13]		
Units: weeks				
median (confidence interval 95%)	37.9 (15.0 to 59.3)	26.6 (8.6 to 53.6)		

Notes:

[12] - TS

[13] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour shrinkage

End point title	Tumour shrinkage

End point description:

Tumour shrinkage (in millimeters) is defined as the difference between the minimum post-baseline sum of diameters of target lesions (SoD, longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions. Tumour shrinkage is reported as percentage change from baseline and represents the maximum decrease or the minimum increase from baseline in SoD in percentage of the baseline SoD. Negative values indicate a reduction in the SoD; positive values indicate an increase in the SoD. Tumour response was assessed based on local radiological image (CT or MRI) evaluation by the investigators according to RECIST 1.1. The treated set (TS) included all participants who received at least one dose of afatinib or pembrolizumab

End point type	Secondary

End point timeframe:

Tumour assessment performed at screening (-28 days), week 9 (day 56-63) after study treatment (afatinib or pembrolizumab) start and every 9th week thereafter, up to 556 days.

End point values	Afatinib 40 mg + pembrolizumab 200 mg	Afatinib 30 mg + pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[14]	12[15]		
Units: Percentage change				
arithmetic mean (standard deviation)	-7.7 (± 29.83)	22.0 (± 71.84)		

Notes:

[14] - TS

[15] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

[All-Cause Mortality]: From Day 1 of study treatment administration up to a total of 574 days. [Serious and Other Adverse Events]: From the time of first drug administration up to 558 days.

Adverse event reporting additional description:

The treated set (TS) included all participants, who received at least one dose of afatinib or pembrolizumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Afatinib 30 mg + pembrolizumab 200 mg

Reporting group description:

30 mg of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily + pembrolizumab 200 mg, intravenous infusion, once every 3 weeks. Both afatinib and pembrolizumab were to be given until documented disease progression, or unacceptable adverse events, or other reasons requiring treatment discontinuation, or for up to 35 cycles of 21 days (i.e. the approved pembrolizumab monotherapy duration). In case of early discontinuation of one agent, the other agent could be continued as monotherapy for altogether up to 35 cycles.

Reporting group title	Afatinib 40 mg + pembrolizumab 200 mg

Reporting group description:

40 milligram (mg) of afatinib film-coated tablet, given orally with a glass of water (without food consumption 3 hours (h) prior and 1h post afatinib administration), once daily + pembrolizumab 200 mg, intravenous infusion, once every 3 weeks. Both afatinib and pembrolizumab were to be given until documented disease progression, or unacceptable adverse events, or other reasons requiring treatment discontinuation, or for up to 35 cycles of 21 days (i.e. the approved pembrolizumab monotherapy duration). In case of early discontinuation of one agent, the other agent could be continued as monotherapy for altogether up to 35 cycles.

Serious adverse events	Afatinib 30 mg + pembrolizumab 200 mg	Afatinib 40 mg + pembrolizumab 200 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)	4 / 12 (33.33%)	
number of deaths (all causes)	10	10	
number of deaths resulting from adverse events	0	1	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Extremity necrosis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Immune-mediated hepatitis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated pneumonitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 12 (25.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Afatinib 30 mg + pembrolizumab 200 mg	Afatinib 40 mg + pembrolizumab 200 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	12 / 12 (100.00%)	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Asthenia			
subjects affected / exposed	3 / 12 (25.00%)	2 / 12 (16.67%)	
occurrences (all)	5	2	
Face oedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	4 / 12 (33.33%)	3 / 12 (25.00%)	
occurrences (all)	6	6	
Mucosal inflammation			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Non-cardiac chest pain			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Vessel puncture site swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Prostatitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dysphonia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	2 / 12 (16.67%)	2 / 12 (16.67%)	
occurrences (all)	3	2	
Haemoptysis			

subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Pleuritic pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Restrictive pulmonary disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	2	3	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	4	
Amylase increased			
subjects affected / exposed	1 / 12 (8.33%)	3 / 12 (25.00%)	
occurrences (all)	2	10	
Blood creatinine increased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
International normalised ratio increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	3	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 10	3 / 12 (25.00%) 9	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 12 (8.33%) 1	
Cheilitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 12 (16.67%) 2	
Constipation subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	7 / 12 (58.33%) 20	11 / 12 (91.67%) 35	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	
Gastritis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	
Nausea subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 8	1 / 12 (8.33%) 1	
Vomiting subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 5	3 / 12 (25.00%) 5	
Stomatitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	4 / 12 (33.33%) 8	
Hepatobiliary disorders			

Hepatic pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Cholestasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Dermatitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Dermatitis acneiform			
subjects affected / exposed	5 / 12 (41.67%)	2 / 12 (16.67%)	
occurrences (all)	8	3	
Dermatitis bullous			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	1 / 12 (8.33%)	5 / 12 (41.67%)	
occurrences (all)	1	12	
Xeroderma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin erosion			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 12 (16.67%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Hypothyroidism			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	3	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Tendon pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Hepatitis viral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Tracheobronchitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Subcutaneous abscess			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			

subjects affected / exposed	3 / 12 (25.00%)	6 / 12 (50.00%)	
occurrences (all)	3	7	
Hypercalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Hyperglycaemia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Hypomagnesaemia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2019	Safety Monitoring Committee (SMC) recommended after the safety run-in to stop the trial and not open the main part. Modifications in the trial conduct, such as cancellation of the biomarker assessment, modified tumour assessment, Eastern Cooperative Oncology Group (ECOG) performance score evaluation no longer required. New or modified text was introduced in the respective sections of the Clinical Trial Protocol (CTP). After the decision to stop the trial, the definition of the end of the trial was adapted. In addition, new text described that patients were to be discontinued from the trial treatment after completing 35 cycles with pembrolizumab and/or afatinib. Patients were not to be followed up for disease progression or overall survival after discontinuation from trial treatment. Additional information from the Summary of Product Pharacteristics (SmPC) of pembrolizumab was added concerning dose modifications in patients with liver metastases at baseline, myocarditis, and other immune-related Adverse Events (AEs) of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3; dose interruption for reasons other than treatment-related AE; supportive care; and management of infusion reaction. Imaging during the trial was clarified.

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.

After the safety run-in, the Safety Monitoring Committee (SMC) decided that the benefit-risk ratio was not favorable and recommended stopping the trial. The main part of the trial did not open.

Notes: