Clinical trial results:
A Randomized Phase 2 Study of Abemaciclib (LY2835219) versus Docetaxel in Patients with Stage IV Squamous Non-Small Cell Lung Cancer Previously Treated with Platinum-based Chemotherapy

Summary

EudraCT number	2014-004832-20
Trial protocol	DE ES HU IT PL FR RO
Global end of trial date	29 July 2020

Results information

Result version number	v1 (current)
This version publication date	11 August 2021
First version publication date	11 August 2021

Trial information

Trial identification

Sponsor protocol code	I3Y-MC-JPBX

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02450539
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15806

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	29 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the effectiveness of the study drug known as abemaciclib versus docetaxel in participants with stage IV squamous non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	23 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 22
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	159
EEA total number of subjects	97

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	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

Study completers are participants who died due to any cause, were on follow-up at study completion or completed continued access period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Abemaciclib

Arm description:

200 milligram(mg) abemaciclib given orally every 12 hours (Q12H) on days 1 to 21 of each 21 day cycle. Participants may continue to receive treatment until discontinuation criteria are met.

Arm type	Experimental
Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	LY2835219
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally.

Arm title	Docetaxel

Arm description:

75 milligram per meter squared (mg/m²) docetaxel given intravenously (IV) on day 1 of each 21 day cycle. Participants may continue to receive treatment until discontinuation criteria are met.

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

Dosage and administration details:

Administered IV.

Number of subjects in period 1	Abemaciclib	Docetaxel
Started	106	53
Received at least one dose of study drug	106	52
Completed	90	46
Not completed	16	7
Consent withdrawn by subject	12	6
Lost to follow-up	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Abemaciclib
Reporting group description:	
200 milligram(mg) abemaciclib given orally every 12 hours (Q12H) on days 1 to 21 of each 21 day cycle. Participants may continue to receive treatment until discontinuation criteria are met.	
Reporting group title	Docetaxel
Reporting group description:	
75 milligram per meter squared (mg/m²) docetaxel given intravenously (IV) on day 1 of each 21 day cycle. Participants may continue to receive treatment until discontinuation criteria are met.	

Reporting group values	Abemaciclib	Docetaxel	Total
Number of subjects	106	53	159
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.1	64.5	
standard deviation	± 7.8	± 7.1	-
Gender categorical Units: Subjects			
Female	16	9	25
Male	90	44	134
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	3	8
Not Hispanic or Latino	84	48	132
Unknown or Not Reported	17	2	19
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	10	3	13
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	96	50	146
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Romania	18	4	22
Hungary	7	6	13
United States	4	2	6
Ukraine	13	13	26
Russia	11	2	13
Spain	8	6	14
South Korea	8	1	9
Taiwan	2	2	4

Poland	14	10	24
Italy	7	1	8
Australia	4	0	4
France	1	2	3
Germany	9	4	13
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
Participants were stratified at randomization according to the following: Eastern Cooperative Oncology Group (ECOG) PS (0 vs. 1); number of prior therapies (received only platinum-based therapy vs. platinum-based therapy plus immune checkpoint inhibitor) and time since initiation of first line therapy (<=9 months vs >9 months). The ECOG Performance Status:0 - Fully active, able to carry on all pre-disease performance without restriction,1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.			
Units: Subjects			
Zero (0)	22	7	29
One (1)	84	46	130

End points

End points reporting groups

Reporting group title	Abemaciclib
Reporting group description:	
200 milligram(mg) abemaciclib given orally every 12 hours (Q12H) on days 1 to 21 of each 21 day cycle. Participants may continue to receive treatment until discontinuation criteria are met.	
Reporting group title	Docetaxel
Reporting group description:	
75 milligram per meter squared (mg/m²) docetaxel given intravenously (IV) on day 1 of each 21 day cycle. Participants may continue to receive treatment until discontinuation criteria are met.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
PFS was defined as time from the date of randomization to the date of investigator-determined disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or death from any cause. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameters (LD) of target lesions, with reference the smallest sum on study and an absolute increase of at least 5mm, or unequivocal progression of non-target lesions, or 1 or more new lesions. If a participant was not known to have died or have objective progression, PFS time will be censored at the day of their last radiographic tumor assessment (if available) or date of randomization if no post baseline radiographic assessment is available. Analysis Population Description (APD): All participants according to the treatment group to which they were randomized. Participants censored: Abemaciclib=19 and Docetaxel= 15.	
End point type	Primary
End point timeframe:	
Baseline to Objective Progression or Death from Any Cause (Up To 6 Months)	

End point values	Abemaciclib	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	53		
Units: months				
median (confidence interval 95%)	2.53 (1.68 to 2.89)	4.21 (2.79 to 5.65)		

Statistical analyses

Statistical analysis title	Progression Free Survival (PFS)
Statistical analysis description:	
Stratified by baseline ECOG performance status (0 vs 1), number of Prior Therapies (received only platinum-based therapy vs Received platinum-based Therapy plus Immune Checkpoint Inhibitor), and time since initiation of first line therapy (<=9 months vs >9 months).	
Comparison groups	Abemaciclib v Docetaxel

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068
Method	Stratified log-rank test.
Parameter estimate	Hazard ratio (HR)
Point estimate	1.765
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.165
upper limit	2.672

Secondary: Pharmacokinetics (PK): Clearance of Abemaciclib

End point title	Pharmacokinetics (PK): Clearance of Abemaciclib[1]

End point description:

Pharmacokinetics (PK): Clearance of Abemaciclib

Analysis Population Description: All participants who received abemaciclib and had evaluable PK data.

End point type	Secondary

End point timeframe:

Cycle (C) 1 Day (D) 1: Pre-dose; C1D8: 4 and 7 hr Post-dose; C2D1: Pre-dose and 3 hr Post-dose; C3 and C4 D1:Pre-dose

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, statistical analysis (comparison analysis) were not planned for this outcome measure.

End point values	Abemaciclib			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Liters/hour (L/h)				
geometric mean (geometric coefficient of variation)	21.3 (± 36)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Volume of Distribution of Abemaciclib

End point title	PK: Volume of Distribution of Abemaciclib[2]

End point description:

PK: Volume of Distribution of Abemaciclib

Analysis Population Description: All participants who received Abemaciclib and had evaluable PK data.

End point type	Secondary

End point timeframe:

Cycle (C) 1 Day (D) 1: Pre-dose; C1D8: 4 and 7 hr Post-dose; C2D1: Pre-dose and 3 hr Post-dose; C3

and C4 D1:Pre-dose

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, statistical analysis (comparison analysis) were not planned for this outcome measure.

End point values	Abemaciclib			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Liters (L)				
geometric mean (geometric coefficient of variation)	769 (± 51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to the date of death due to any cause. For each participant who is not known to have died as the data inclusion cutoff date for overall survival analysis, OS time was censored on the last date the participant is known to be alive.

Analysis Population Description: All participants according to the treatment group to which they were randomized. Participants censored: Abemaciclib =35 and Docetaxel= 17.

End point type	Secondary

End point timeframe:

Baseline to Date of Death from Any Cause (Up To 27 Months)

End point values	Abemaciclib	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	53		
Units: Months				
median (confidence interval 95%)	7 (5.00 to 8.78)	12.39 (7.13 to 15.98)		

Statistical analyses

Statistical analysis title	Overall Survival

Statistical analysis description:

Stratified by baseline ECOG performance status (0 vs 1), number of Prior Therapies (received only platinum-based therapy vs Received platinum-based Therapy plus Immune Checkpoint Inhibitor), and time since initiation of first line therapy (<=9 months vs >9 months).]

Comparison groups	Abemaciclib v Docetaxel

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.333
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.879
upper limit	2.022

Secondary: Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])

End point title	Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Overall Response Rate [ORR])

End point description:

Overall response was defined as the percentage of randomized participants achieving a best overall response (BoR) of complete response (CR) or partial response (PR) using Response Evaluation Criteria In Solid Tumors (RECIST v1.1) criteria. Participants with unevaluable or unknown response status are considered nonresponders. Complete response (CR) is defined as the disappearance of all target and non-target lesions and no appearance of new lesions. Partial response (PR) is defined as at least a 30% decrease in the sum of the longest diameters (LD) of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions and no appearance of new lesions.

Analysis Population Description: All randomized participants.

End point type	Secondary

End point timeframe:

Baseline to Objective Progression (Up To 6 Months)

End point values	Abemaciclib	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	53		
Units: percentage participants				
number (not applicable)	2.8	20.8		

Statistical analyses

Statistical analysis title	Overall Response Rate (ORR)
Comparison groups	Abemaciclib v Docetaxel

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Rate Difference
Point estimate	-17.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.3
upper limit	-6.6

Notes:

[3] - Confidence intervals are based on the normal approximation to the binomial.

Secondary: Percentage of Participants who Exhibit Stable Disease (SD) or Confirmed Response (CR) or Partial Response (PR): Disease Control Rate (DCR)

End point title	Percentage of Participants who Exhibit Stable Disease (SD) or Confirmed Response (CR) or Partial Response (PR): Disease Control Rate (DCR)

End point description:

DCR is the percentage of randomized participants who achieved a complete response, partial response or stable disease using Response Evaluation Criteria In Solid Tumors (RECIST v1.1) criteria. Complete response (CR) is defined as the disappearance of all target and non-target lesions, and no appearance of new lesions. Partial response (PR) is defined as at least a 30% decrease in the sum of longest diameters (LD) of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions and no appearance of new lesions. Stable disease was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD for target lesions, no progression of non-target lesions, and no appearance of new lesions.

Analysis Population Description: All randomized participants.

End point type	Secondary

End point timeframe:

Baseline through Measured Progressive Disease or Death Due to Any Cause (Up To 6 Months)

End point values	Abemaciclib	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	53		
Units: percentage participants				
number (not applicable)	50.9	64.2		

Statistical analyses

Statistical analysis title	Disease Control Rate (DCR)
Comparison groups	Abemaciclib v Docetaxel

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Stratified Log-rank test
Point estimate	-13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.2
upper limit	2.8

Secondary: Time to Worsening of Eastern Cooperative Oncology Group (ECOG) Performance Status of >/=2

End point title	Time to Worsening of Eastern Cooperative Oncology Group (ECOG) Performance Status of >/=2

End point description:

Worsening of ECOG performance status is the duration from randomization to ECOG PFS of >/=2. Participants without an ECOG PFS >/=2 are censored at last adequate post baseline ECOG Performance Status or randomization date (whichever is last).
The ECOG Performance Status:0 - Fully active, able to carry on all pre-disease performance without restriction,1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours,3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours, 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair, 5 - Dead.

Analysis Population Description: All randomized participants. Participants censored: Abemaciclib =93 and Docetaxel= 43.

End point type	Secondary

End point timeframe:

Randomization to ECOG PFS of >/=2 (Up To 11.5 Months)

End point values	Abemaciclib	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[4]	53[5]		
Units: months				
median (confidence interval 95%)	9999 (6.58 to 9999)	10.52 (4.64 to 9999)		

Notes:

[4] - 9999=NA. Due to insufficient data to support the analysis and the results.

[5] - 9999=NA. Due to insufficient data to support the analysis and the results.

Statistical analyses

Statistical analysis title	Time to Worsening ECOG Performance Status of >/=2

Statistical analysis description:

Stratification factors are baseline ECOG performance status (0 vs 1), Number of Prior Therapies (received only platinum-based therapy vs Received platinum-based Therapy plus Immune Checkpoint Inhibitor), and time since initiation of first line therapy (<=9 months vs >9 months).

Comparison groups	Abemaciclib v Docetaxel

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.7039
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.184
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.502
upper limit	2.792

Notes:

[6] - Stratification factors are baseline ECOG performance status (0 vs 1), Number of Prior Therapies (received only platinum-based therapy vs Received platinum-based Therapy plus Immune Checkpoint Inhibitor), and time since initiation of first line therapy (<=9 months vs >9 months).

Secondary: Change from Baseline in MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC) Scores

End point title	Change from Baseline in MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC) Scores

End point description:

MDASI-LC included 33 items:6 interference and 27 symptom(3 lung-cancer (LC),8 brain tumor (BT),and 3 study-specific(headache,diarrhea, and rash).Analyzed endpoints were 9 constructs:3 single-items (headache,diarrhea,and rash) and 6 composites(interference+core,LC,core+LC,BT, and core+LC worst 5 baseline).Data for all 9 constructs were collected by an 11-point numeric rating scale anchored at 0(not present or does not interfere) and 10(as bad as you can imagine or interfered completely).The measurement range was 10 (maximum score–minimum score). Between-group difference in regression-predicted change from baseline were estimated for each specified construct. MMRM models included independent variables treatment,visit, treatment*visit,and baseline score. Group-level negative change from baseline indicated group improvement.

All randomized participants for cycles which at least 25% of participants in each arm have a score.

End point type	Secondary

End point timeframe:

Baseline through End of Study (Up To 6 Months)

End point values	Abemaciclib	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	43		
Units: units on a scale				
least squares mean (standard error)				
Headache	0.19 (± 0.14)	0.01 (± 0.18)		
Diarrhea	1.01 (± 0.18)	0.15 (± 0.23)		
Mean core symptom severity	0.53 (± 0.14)	0.00 (± 0.18)		
Mean interference	0.50 (± 0.20)	0.18 (± 0.27)		
Mean lung cancer symptom severity	0.20 (± 0.12)	-0.19 (± 0.15)		
Mean core plus lung cancer symptom severity	0.47 (± 0.13)	-0.04 (± 0.17)		
Mean brain tumor symptom severity	0.19 (± 0.11)	0.13 (± 0.15)		
Mean core plus lung worst 5 symptoms severity	-0.25 (± 0.17)	-0.94 (± 0.22)		

Rash	0.28 (± 0.14)	0.18 (± 0.17)		

Statistical analyses

Statistical analysis title	MDASI-LC Scores - Headache
Statistical analysis description: Headache	
Comparison groups	Abemaciclib v Docetaxel
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.62
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:
[7] - Headache

Statistical analysis title	MDASI-LC Scores- Diarrhea
Statistical analysis description: Diarrhea	
Comparison groups	Abemaciclib v Docetaxel
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[8]
Parameter estimate	Mean difference (final values)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.43
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:
[8] - Diarrhea

Statistical analysis title	MDASI-LC Scores - Mean core symptom severity
Statistical analysis description: Mean core symptom severity	
Comparison groups	Abemaciclib v Docetaxel

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[9]
Parameter estimate	Mean difference (final values)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.98
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[9] - Mean core symptom severity

Statistical analysis title	MDASI-LC Scores - Mean interference

Statistical analysis description:

Mean interference

Comparison groups	Abemaciclib v Docetaxel
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[10]
Parameter estimate	Mean difference (final values)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.99
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[10] - Mean interference

Statistical analysis title	MDASI-LC Score - Mean lung cancer symptom severity

Statistical analysis description:

Mean lung cancer symptom severity

Comparison groups	Abemaciclib v Docetaxel
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[11]
Parameter estimate	Mean difference (final values)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.77
Variability estimate	Standard error of the mean
Dispersion value	0.19

Notes:
[11] - Mean lung cancer symptom severity

Statistical analysis title	MDASI-LC Scores - Core plus lung cancer symptom
Statistical analysis description:	
Mean core plus lung cancer symptom severity	
Comparison groups	Abemaciclib v Docetaxel
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[12]
Parameter estimate	Mean difference (final values)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.93
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:
[12] - Mean core plus lung cancer symptom severity

Statistical analysis title	MDASI-LC Scores - Brain tumor symptom
Statistical analysis description:	
Mean brain tumor symptom severity	
Comparison groups	Abemaciclib v Docetaxel
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[13]
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.19

Notes:
[13] - Mean brain tumor symptom severity

Statistical analysis title	MDASI-LC Scores - Lung worst 5 symptoms severity
Statistical analysis description:	
Mean core plus lung worst 5 symptoms severity	
Comparison groups	Abemaciclib v Docetaxel

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[14]
Parameter estimate	Mean difference (final values)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.24
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[14] - Mean core plus lung worst 5 symptoms severity

Statistical analysis title	MDASI-LC Scores - Rash

Statistical analysis description:

Rash

Comparison groups	Abemaciclib v Docetaxel
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[15]
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[15] - Rash

Secondary: Change From Baseline in EuroQol 5-Dimensional 5-Level (EQ-5D-5L) Questionnaire EQ VAS Overall Self-rated Health Score

End point title	Change From Baseline in EuroQol 5-Dimensional 5-Level (EQ-5D-5L) Questionnaire EQ VAS Overall Self-rated Health Score

End point description:

The EQ-5D-5L is a standardized instrument for use as a measure of self-reported health status. Overall self-rated health was measured with a vertical 20 cm visual analog scale (VAS) anchored at 0 (worst health) and ranged through 100 (best health). Between-group differences in regression-predicted change from baseline score were estimated for VAS scores. MMRM models included independent variables treatment, visit, treatment*visit, and baseline score. Group-level negative change from baseline indicated group improvement.

Analysis Population Description: All randomized participants for cycles which at least 25% of participants in each arm have a score.

End point type	Secondary

End point timeframe:

Baseline to Measured Progressive Disease (Up To 6 Months)

End point values	Abemaciclib	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	42		
Units: units on a scale				
least squares mean (standard error)	-5.49 (± 1.28)	-2.36 (± 1.63)		

Statistical analyses

Statistical analysis title	Change From Baseline in EQ5D5L VAS
Statistical analysis description: EQ VAS Overall Self-rated Health Score	
Comparison groups	Abemaciclib v Docetaxel
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	Mean difference (final values)
Point estimate	-3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.26
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	2.07

Notes:

[16] - EQ VAS Overall Self-rated Health Score

Secondary: Change From Baseline in EuroQol 5-Dimensional 5-Level (EQ-5D-5L) Questionnaire Index Value

End point title	Change From Baseline in EuroQol 5-Dimensional 5-Level (EQ-5D-5L) Questionnaire Index Value

End point description:

There are 5 response levels on a good-to-bad continuum of 1-5 corresponding to none, slight, moderate, severe, and extreme/unable to.The EuroQol-developed crosswalk method was used to convert the EQ-5D-5L,using UK weights,health dimensions(mobility,self-care,usual activities,pain/discomfort, and anxiety/depression) into a single index value;the dimensions are not separately scored.The index is marked missing when ≥1 dimensions are missing.The index scores for the response patterns were anchored on full health to dead with negative values assigned to response patterns/health states considered worse than death.The best pattern is assigned the index value of 1.0; the worst pattern is assigned an index value of -0.594. Between-group differences in regression-predicted change from baseline score were estimated for the index .MMRM models included independent variables treatment, visit, treatment*visit, and baseline score.Group-level negative change from baseline indicated group improvement.

End point type	Secondary

End point timeframe:

Baseline to Measured Progressive Disease (Up To 6 Months)

Analysis population description: All randomized participants for cycles which at least 25% of participants in each arm have a score.

End point values	Abemaciclib	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	42		
Units: units on a scale				
least squares mean (standard error)	-0.05 (± 0.02)	-0.01 (± 0.02)		

Statistical analyses

Statistical analysis title	Change From Baseline in EQ-5D-5L Index Value
Statistical analysis description: EQ-5D-5L Index Value	
Comparison groups	Docetaxel v Abemaciclib
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[17]
Parameter estimate	Median difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[17] - EQ-5D-5L Index Value

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline Up To 5 Years	
Adverse event reporting additional description:	
All randomized participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Abemaciclib
Reporting group description:	
200 milligram(mg) abemaciclib given orally every 12 hours (Q12H) on days 1 to 21 of each 21 day cycle. Participants may continue to receive treatment until discontinuation criteria are met.	
Reporting group title	Docetaxel
Reporting group description:	
75 milligram per meter squared (mg/m²) docetaxel given intravenously (IV) on day 1 of each 21 day cycle. Participants may continue to receive treatment until discontinuation criteria are met.	

Serious adverse events	Abemaciclib	Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 106 (27.36%)	17 / 52 (32.69%)	
number of deaths (all causes)	71	35	
number of deaths resulting from adverse events	6	2	
Vascular disorders			
embolism			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 106 (2.83%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
hypotension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (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			
general physical health deterioration			
alternative dictionary used:			

MedDRA 23.1			
subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
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			
dyspnoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoxia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
laryngeal haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
pneumonitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 106 (2.83%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
blood creatinine increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
international normalised ratio increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ankle fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
wrist fracture			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiovascular insufficiency			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
cerebrovascular accident			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 106 (0.00%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
leukopenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 106 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	4 / 52 (7.69%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancytopenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
constipation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 106 (1.89%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric haemorrhage			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
nausea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal fistula			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 106 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
muscular weakness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (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			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 106 (5.66%)	4 / 52 (7.69%)	
occurrences causally related to treatment / all	2 / 6	2 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
myelitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
pleural infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
salmonella bacteraemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper respiratory tract infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
wound infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 106 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Abemaciclib	Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 106 (88.68%)	43 / 52 (82.69%)	
Investigations			
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
blood creatinine increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	13 / 106 (12.26%)	1 / 52 (1.92%)	
occurrences (all)	17	6	
weight decreased			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	12 / 106 (11.32%)	6 / 52 (11.54%)	
occurrences (all)	13	6	
Vascular disorders			
hypotension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 106 (7.55%)	0 / 52 (0.00%)	
occurrences (all)	8	0	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 106 (7.55%)	3 / 52 (5.77%)	
occurrences (all)	10	3	
headache			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 106 (6.60%)	2 / 52 (3.85%)	
occurrences (all)	7	2	
neuropathy			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 106 (2.83%)	7 / 52 (13.46%)	
occurrences (all)	3	9	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	41 / 106 (38.68%)	12 / 52 (23.08%)	
occurrences (all)	47	18	
leukopenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	10 / 106 (9.43%)	14 / 52 (26.92%)	
occurrences (all)	10	48	
neutropenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	18 / 106 (16.98%)	26 / 52 (50.00%)	
occurrences (all)	20	76	
thrombocytopenia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	27 / 106 (25.47%)	2 / 52 (3.85%)	
occurrences (all)	35	2	
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	30 / 106 (28.30%)	7 / 52 (13.46%)	
occurrences (all)	34	10	
non-cardiac chest pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 106 (7.55%)	2 / 52 (3.85%)	
occurrences (all)	9	2	
pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
pyrexia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 106 (4.72%)	4 / 52 (7.69%)	
occurrences (all)	5	4	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 106 (7.55%)	3 / 52 (5.77%)	
occurrences (all)	10	3	
diarrhoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	41 / 106 (38.68%)	5 / 52 (9.62%)	
occurrences (all)	67	5	
nausea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	33 / 106 (31.13%)	7 / 52 (13.46%)	
occurrences (all)	35	10	
vomiting			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	9 / 106 (8.49%)	3 / 52 (5.77%)	
occurrences (all)	11	3	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	11 / 106 (10.38%)	2 / 52 (3.85%)	
occurrences (all)	11	2	
dyspnoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	19 / 106 (17.92%)	6 / 52 (11.54%)	
occurrences (all)	20	6	
laryngeal haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 106 (8.49%)	1 / 52 (1.92%)	
occurrences (all)	9	1	
productive cough			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 106 (5.66%)	2 / 52 (3.85%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 106 (0.94%)	7 / 52 (13.46%)	
occurrences (all)	1	8	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 106 (1.89%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
muscular weakness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	10 / 106 (9.43%)	7 / 52 (13.46%)	
occurrences (all)	12	8	
Metabolism and nutrition disorders			

decreased appetite			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	17 / 106 (16.04%)	7 / 52 (13.46%)	
occurrences (all)	19	7	
hypokalaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 106 (7.55%)	1 / 52 (1.92%)	
occurrences (all)	10	2	
hyponatraemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 106 (6.60%)	1 / 52 (1.92%)	
occurrences (all)	9	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2019	Protocol Amendment a: Added the dose modification guidance for hepatic enzyme alterations.
12 February 2020	Protocol Amendment b: Updates for dose adjustments for Interstitial Lung Disease (ILD)/Pneumonitis are safety-related.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported