



Clinical trial results:

A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

Summary

EudraCT number	2019-001979-36
Trial protocol	DE CZ GR FR PL NL GB ES BE IT RO
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	07 July 2024
First version publication date	19 May 2024
Version creation reason	<ul style="list-style-type: none">Correction of full data setRevision to AE reporting group description requested per CTgov comment.

Trial information

Trial identification

Sponsor protocol code	J2G-MC-JZJC
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04194944
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 17479

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center , Indianapolis, Estonia, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company , 1 877-CTLilly,
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	Interim
Date of interim/final analysis	01 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2023
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare PFS of LOXO-292 and platinum- based (carboplatin or cisplatin) and pemetrexed therapy with or without pembrolizumab in patients with advanced or metastatic RET fusion-positive NSCLC

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	17 February 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	48 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Japan: 25
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Türkiye: 8
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	China: 90
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 6

Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 32
Worldwide total number of subjects	261
EEA total number of subjects	76

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)	157
From 65 to 84 years	102
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

If a participant has a recorded death on study, or is alive and being followed but off treatment, then the participant can be considered to be study completer.

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	Selpercatinib (TRT A)

Arm description:

160 milligram (mg) Selpercatinib administered orally, twice daily (BID) continuously in 21-day cycles.

Arm type	Experimental
Investigational medicinal product name	Selpercatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

160 milligram (mg) Selpercatinib administered orally, twice daily (BID) continuously in 21-day cycles.

Arm title	Pemetrexed and Platinum With or Without Pembrolizumab (TRT B)
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Arm description:

Pemetrexed 500 milligrams per meter squared (mg/m²) administered intravenously (IV) on Day 1, every 3 weeks (Q3W), plus at the investigator's choice of carboplatin area under the concentration versus time curve 5 (AUC 5 [maximum dose of 750 mg] IV), or cisplatin (75 mg/m² cisplatin IV) on Day 1 Q3W for 4 cycles, plus investigator's choice with or without 200 mg pembrolizumab IV on Day 1 Q3W up to 35 cycles.

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

Dosage and administration details:

Pemetrexed 500 mg/m², IV on Day 1, every 3 Q3W

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin AUC 5 (maximum dose of 750 mg) IV on Day 1 Q3W for 4 cycles.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Cisplatin 75 mg/m ² , IV on Day 1 Q3W for 4 cycles.	
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
200 mg Pembrolizumab, IV on Day 1, Q3W up to 35 cycles.	

Number of subjects in period 1	Selpercatinib (TRT A)	Pemetrexed and Platinum With or Without Pembrolizumab (TRT B)
Started	159	102
Received at Least One Dose of Study Drug	158	98
Completed	61	70
Not completed	98	32
On Treatment	93	30
Withdrawal by Subject	2	2
Lost to follow-up	3	-

Baseline characteristics

Reporting groups

Reporting group title	Selpercatinib (TRT A)
Reporting group description: 160 milligram (mg) Selpercatinib administered orally, twice daily (BID) continuously in 21-day cycles.	
Reporting group title	Pemetrexed and Platinum With or Without Pembrolizumab (TRT B)
Reporting group description: Pemetrexed 500 milligrams per meter squared (mg/m ²) administered intravenously (IV) on Day 1, every 3 weeks (Q3W), plus at the investigator's choice of carboplatin area under the concentration versus time curve 5 (AUC 5 [maximum dose of 750 mg] IV), or cisplatin (75 mg/m ² cisplatin IV) on Day 1 Q3W for 4 cycles, plus investigator's choice with or without 200 mg pembrolizumab IV on Day 1 Q3W up to 35 cycles.	

Reporting group values	Selpercatinib (TRT A)	Pemetrexed and Platinum With or Without Pembrolizumab (TRT B)	Total
Number of subjects	159	102	261
Age categorical Units: Subjects			

Age continuous			
Intent to Treat Population (ITT): All randomized participants, even if a participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.			
Units: years			
arithmetic mean	60.2	60.8	
standard deviation	± 11.3	± 11.4	-
Gender categorical Units: Subjects			
Female	86	57	143
Male	73	45	118
Race Units: Subjects			
American Indian or Alaska Native	2	1	3
Asian	92	52	144
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	0	2
White	58	43	101
More than one race	1	0	1
Unknown or Not Reported	4	6	10
Region of Enrollment Units: Subjects			
Hong Kong	4	1	5
Russian Federation	1	2	3
Korea, Republic of	8	8	16
Brazil	7	1	8
Argentina	2	0	2
Japan	15	10	25

Ukraine	0	5	5
Canada	2	1	3
Turkiye	8	0	8
Taiwan	2	4	6
Mexico	4	1	5
Israel	1	4	5
Australia	2	2	4
China	62	28	90
Netherlands	2	1	3
Poland	0	1	1
Spain	7	9	16
Belgium	3	3	6
Czechia	0	1	1
France	2	4	6
Germany	5	4	9
Greece	2	0	2
Italy	20	12	32

End points

End points reporting groups

Reporting group title	Selpercatinib (TRT A)
Reporting group description: 160 milligram (mg) Selpercatinib administered orally, twice daily (BID) continuously in 21-day cycles.	
Reporting group title	Pemetrexed and Platinum With or Without Pembrolizumab (TRT B)
Reporting group description: Pemetrexed 500 milligrams per meter squared (mg/m ²) administered intravenously (IV) on Day 1, every 3 weeks (Q3W), plus at the investigator's choice of carboplatin area under the concentration versus time curve 5 (AUC 5 [maximum dose of 750 mg] IV), or cisplatin (75 mg/m ² cisplatin IV) on Day 1 Q3W for 4 cycles, plus investigator's choice with or without 200 mg pembrolizumab IV on Day 1 Q3W up to 35 cycles.	
Subject analysis set title	Pemetrexed with Pembrolizumab (TRT B)
Subject analysis set type	Per protocol
Subject analysis set description: 500 milligrams per meter squared (mg/m ²) Pemetrexed administered intravenously (IV) on Day 1, every 3 weeks (Q3W), plus at the investigator's discretion, area under the concentration versus time curve 5 (maximum dose of 750 mg) carboplatin IV, or 75 mg/m ² cisplatin IV Day 1 Q3W for 4 cycles, and with 200 mg pembrolizumab IV on Day 1 Q3W up to 35 cycles.	
Subject analysis set title	Pemetrexed With or Without Pembrolizumab (TRT B)
Subject analysis set type	Per protocol
Subject analysis set description: 500 mg/m ² Pemetrexed administered IV on Day 1, Q3W, plus at the investigator's discretion, area under the concentration versus time curve 5 (maximum dose of 750 mg) carboplatin IV, or 75 mg/m ² cisplatin IV Day 1, Q3W for 4 cycles, and with or without 200 mg pembrolizumab IV on Day 1, Q3W up to 35 cycles.	

Primary: Progression Free Survival (PFS) by Blinded Independent Central Review (BICR) (With Pembrolizumab)

End point title	Progression Free Survival (PFS) by Blinded Independent Central Review (BICR) (With Pembrolizumab) ^[1]
End point description: PFS is defined as the time from randomization until the occurrence of documented disease progression by the BICR, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, or death from any cause in the absence of BICR-documented progressive disease. Analysis Population Description: Intent to Treat (ITT) Pembrolizumab: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment. Participants censored: TRT A: 80, TRT B: 34.	
End point type	Primary
End point timeframe: Baseline to Progressive Disease or Death from Any Cause Up to 31 Months	

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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	129 ^[2]	83		
Units: Months				

median (confidence interval 95%)	24.84 (16.89 to 9999)	11.17 (8.77 to 16.76)		
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Notes:

[2] - 9999 = N/A: Upper limit of 95% confidence interval is not evaluable due to high censoring.

Statistical analyses

Statistical analysis title	Selpercatinib, Pemetrexed with Pembrolizumab
Comparison groups	Selpercatinib (TRT A) v Pemetrexed with Pembrolizumab (TRT B)
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.465
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.309
upper limit	0.699

Primary: PFS by BICR (With or Without Pembrolizumab)

End point title	PFS by BICR (With or Without Pembrolizumab) ^[3]
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End point description:

PFS is defined as the time from randomization until the occurrence of documented disease progression by the BICR, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, or death from any cause in the absence of BICR-documented progressive disease.

APD: ITT Population: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Participants were analyzed according to the treatment arm they were assigned to regardless of what actual treatment they received. Participants censored: TRT A: 98, TRT B:45.

End point type	Primary
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End point timeframe:

Baseline to Progressive Disease or Death from Any Cause Up to 31 Months

Notes:

[3] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	159 ^[4]	102		
Units: Months				
median (confidence interval 95%)	24.84 (17.31	11.17 (8.77 to		

Notes:

[4] - 9999 = N/A: Upper limit of 95% confidence interval is not evaluable due to high censoring.

Statistical analyses

Statistical analysis title	Selpercatinib, Pemetrexed with or without Pembro
Comparison groups	Selpercatinib (TRT A) v Pemetrexed With or Without Pembrolizumab (TRT B)
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.482
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.331
upper limit	0.7

Secondary: Percentage of Participant With Disease Control Rate (DCR) by BICR (With Pembrolizumab)

End point title	Percentage of Participant With Disease Control Rate (DCR) by BICR (With Pembrolizumab) ^[5]
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End point description:

DCR by BICR (with Pembrolizumab) is defined as the number of participants who achieve a BOR of clinical response (CR), partial response (PR), or stable disease (SD) lasting 16 or more weeks divided by the total number of participants randomized to each treatment arm.

APD: ITT Pembrolizumab: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment.

End point type	Secondary
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End point timeframe:

Baseline to Progressive Disease or Death from Any Cause Up to 31 Months

Notes:

[5] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	129	83		
Units: Percentage of participants				
number (confidence interval 95%)	89.1 (82.5 to 93.9)	84.3 (74.7 to 91.4)		

Statistical analyses

Statistical analysis title	Selpercatinib (TRT A) Pemetrexed + Pembro (TRT B)
Comparison groups	Selpercatinib (TRT A) v Pemetrexed with Pembrolizumab (TRT B)
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3996
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	3.4

Secondary: Percentage of Participant With DCR by BICR (With or Without Pembrolizumab)

End point title	Percentage of Participant With DCR by BICR (With or Without Pembrolizumab) ^[6]
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End point description:

DCR by BICR (with or without Pembrolizumab) is defined as the number of participants who achieve a BOR of CR, PR, or SD lasting 16 or more weeks divided by the total number of participants randomized to each treatment arm.

APD: ITT Population: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Participants were analyzed according to the treatment arm they were assigned to regardless of what actual treatment they received.

End point type	Secondary
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End point timeframe:

Baseline to Progressive Disease or Death from Any Cause Up to 31 Months

Notes:

[6] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	159	102		
Units: Percentage of participants				
number (confidence interval 95%)	89.3 (83.4 to 93.7)	82.4 (73.6 to 89.2)		

Statistical analyses

Statistical analysis title	Selpercatinib (TRT A), With/Without Pembro (TRT B)
Comparison groups	Selpercatinib (TRT A) v Pemetrexed With or Without Pembrolizumab (TRT B)
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.6

Secondary: PFS2 (With Pembrolizumab)

End point title	PFS2 (With Pembrolizumab) ^[7]
End point description:	
PFS2 is defined as the time from randomization to disease progression on the next line of treatment or death from any cause in the absence of observed disease progression.	
APD: ITT Pembrolizumab: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment. Participants censored: TRT A: 103; TRT B: 62.	
End point type	Secondary
End point timeframe:	
Baseline to Second Disease Progression or Death from Any Cause Up to 38 Months.	

Notes:

[7] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	129 ^[8]	83 ^[9]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[8] - 9999 = N/A: Data not available due to high censoring.

[9] - 9999= N/A: Data not available due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS2 (With or Without Pembrolizumab)

End point title	PFS2 (With or Without Pembrolizumab) ^[10]
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End point description:

PFS2 is defined as the time from randomization to disease progression on the next line of treatment or death from any cause in the absence of observed disease progression.

APD: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Participants were analyzed according to the treatment arm they were assigned to regardless of what actual treatment they received. Participants censored: TRT A: 126; TRT B: 77.

End point type	Secondary
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End point timeframe:

Baseline to Second Disease Progression or Death from Any Cause Up to 38 Months

Notes:

[10] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	159 ^[11]	102 ^[12]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[11] - 9999 = NA: Data not available due to high censoring.

[12] - 9999 = NA: Data not available due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR): Percentage of Participants With Complete Response (CR) or Partial Response (PR) by BICR (With Pembrolizumab)

End point title	Overall Response Rate (ORR): Percentage of Participants With
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End point description:

ITT Pembrolizumab: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment.

APD: ITT Pembrolizumab: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment.

End point type	Secondary
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End point timeframe:

Baseline through Disease Progression or Death Up to 31 Months

Notes:

[13] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	129	83		
Units: Percentage of participants				
number (confidence interval 95%)	83.7 (76.2 to 89.6)	65.1 (53.8 to 75.2)		

Statistical analyses

Statistical analysis title	Selpercatinib (TRT A), Pemetrexed + Pembro (TRT B)
Comparison groups	Selpercatinib (TRT A) v Pemetrexed with Pembrolizumab (TRT B)
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0028
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	5.1

Secondary: ORR: Percentage of Participants With CR or PR by BICR (With or Without Pembrolizumab)

End point title	ORR: Percentage of Participants With CR or PR by BICR (With or Without Pembrolizumab) ^[14]
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End point description:

ORR: Percentage of Participants with CR or PR by BICR (with or without Pembrolizumab)

APD: ITT Population: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Participants were analyzed according to the treatment arm they were assigned to regardless of what actual treatment they received.

End point type	Secondary
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End point timeframe:

Baseline through Disease Progression or Death Up to 31 Months

Notes:

[14] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	159	102		
Units: Percentage of participants				
number (confidence interval 95%)	83.6 (77.0 to 89.0)	62.7 (52.6 to 72.1)		

Statistical analyses

Statistical analysis title	Selpercatinib (TRT A), With/Without Pembro (TRT B)
Comparison groups	Selpercatinib (TRT A) v Pemetrexed With or Without Pembrolizumab (TRT B)
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	5.2

Secondary: Duration of Response (DoR) by BICR (With Pembrolizumab)

End point title	Duration of Response (DoR) by BICR (With Pembrolizumab) ^[15]
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End point description:

DoR was defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) were first met until the first date that disease was recurrent or documented disease

progression was observed, or the date of death from any cause in the absence of documented disease progression or recurrence. The DOR according to both BICR and investigator-assessed BOR was evaluated per RECIST 1.1 criteria.

APD: ITT Pembrolizumab: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment. Participants censored: TRT A:74; TRT B: 25.

End point type	Secondary
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End point timeframe:

Date of CR or PR to Date of Disease Progression or Death Due to Any Cause Up to 31 Months

Notes:

[15] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	108 ^[16]	54		
Units: Months				
median (confidence interval 95%)	24.18 (17.94 to 9999)	11.47 (9.66 to 23.26)		

Notes:

[16] - 9999 = N/A: Upper limit of 95% confidence interval not available due to high censoring.

Statistical analyses

Statistical analysis title	Selpercatinib (TRT A), Pemetrexed + Pembro (TRT B)
Comparison groups	Selpercatinib (TRT A) v Pemetrexed with Pembrolizumab (TRT B)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.377
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.224
upper limit	0.633

Secondary: DOR by BICR (With or Without Pembrolizumab)

End point title	DOR by BICR (With or Without Pembrolizumab) ^[17]
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End point description:

DoR was defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) were first met until the first date that disease was recurrent or documented disease progression was observed, or the date of death from any cause in the absence of documented disease progression or recurrence. The DOR according to both BICR and investigator-assessed BOR was

evaluated per RECIST 1.1 criteria.

APD: ITT Population: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Participants were analyzed according to the treatment arm they were assigned to regardless of what actual treatment they received. Participants censored: TRT A: 90; TRT B: 33.

End point type	Secondary
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End point timeframe:

Date of CR or PR to Date of Disease Progression or Death Due to Any Cause Up to 31 Months

Notes:

[17] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	133 ^[18]	64		
Units: Monts				
median (confidence interval 95%)	24.18 (17.94 to 9999)	11.99 (9.69 to 23.26)		

Notes:

[18] - 9999 = N/A: Upper limit of 95% Confidence Interval unavailable due to high censoring.

Statistical analyses

Statistical analysis title	Selpercatinib (TRT A), With/Without Pembro (TRT B)
Comparison groups	Selpercatinib (TRT A) v Pemetrexed With or Without Pembrolizumab (TRT B)
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.418
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.256
upper limit	0.684

Secondary: Overall Survival (OS) (With Pembrolizumab)

End point title	Overall Survival (OS) (With Pembrolizumab) ^[19]
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End point description:

Overall survival was defined as the time from randomization until death from any cause. If the participant was alive or lost to follow-up at the time of data analysis, OS data was censored on the last date the participant is known to be alive.

APD: ITT Pembrolizumab: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment. Participants censored: TRT A: 104; TRT B: 68.

End point type	Secondary
End point timeframe:	
Baseline to Date of Death from Any Cause Up to 38 Months	

Notes:

[19] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	129 ^[20]	83 ^[21]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[20] - 9999 = NA: Median OS data not available due to high censoring

[21] - 9999 = N/A: Median OS data not available due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: OS (With or Without Pembrolizumab)

End point title	OS (With or Without Pembrolizumab) ^[22]
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End point description:

Overall survival was defined as the time from randomization until death from any cause. If the participant was alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the participant is known to be alive.

APD: ITT Population: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Participants were analyzed according to the treatment arm they were assigned to regardless of what actual treatment they received. Participants censored: TRT A: 127; TRT B: 84.

End point type	Secondary
End point timeframe:	
Baseline to Date of Death from Any Cause Up to 38 Months	

Notes:

[22] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	159 ^[23]	102 ^[24]		
Units: Months				

median (confidence interval 95%)	33.05 (33.05 to 9999)	9999 (9999 to 9999)		
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Notes:

[23] - 9999 = N/A: Upper limit of 95% Confidence Interval unavailable due to high censoring.

[24] - 9999 = N/A: Data not available due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial ORR: Percentage of Participants With Intracranial CR or PR Per RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 by BICR (With Pembrolizumab)

End point title	Intracranial ORR: Percentage of Participants With Intracranial CR or PR Per RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 by BICR (With Pembrolizumab) ^[25]
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End point description:

Intracranial ORR: Percentage of Participants with Intracranial CR or PR per RECIST 1.1 by BICR (with Pembrolizumab)

APD: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment who had baseline CNS assessment and who had CNS metastasis at baseline.

End point type	Secondary
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End point timeframe:

Baseline through Central Nervous System (CNS) Progression or Death up to 31 Months

Notes:

[25] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: Percentage of participants				
number (confidence interval 95%)	81.0 (58.1 to 94.6)	57.1 (34.0 to 78.2)		

Statistical analyses

Statistical analysis title	Selpercatinib (TRT A), With Pembrolizumab (TRT B)
Comparison groups	Selpercatinib (TRT A) v Pemetrexed with Pembrolizumab (TRT B)

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1809
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	12.8

Secondary: Intracranial ORR: Percentage of Participants With Intracranial CR or PR Per RECIST 1.1 by BICR (With or Without Pembrolizumab)

End point title	Intracranial ORR: Percentage of Participants With Intracranial CR or PR Per RECIST 1.1 by BICR (With or Without Pembrolizumab) ^[26]
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End point description:

Intracranial ORR: Percentage of Participants with Intracranial CR or PR per RECIST 1.1 by BICR (with or without Pembrolizumab).

APD: All participants included in the ITT population who had baseline CNS assessment and who had CNS metastasis at baseline.

End point type	Secondary
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End point timeframe:

Baseline through CNS Progression or Death Up to 31 Months

Notes:

[26] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	26		
Units: Percentage of participants				
median (confidence interval 95%)	84.0 (63.9 to 95.5)	50.0 (29.9 to 70.1)		

Statistical analyses

Statistical analysis title	Selpercatinib (TRT A), With/Without Pembro (TRT B)
Comparison groups	Selpercatinib (TRT A) v Pemetrexed With or Without Pembrolizumab (TRT B)

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0167
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	19.6

Secondary: Median Intracranial DOR Per RECIST 1.1 by BICR (With Pembrolizumab)

End point title	Median Intracranial DOR Per RECIST 1.1 by BICR (With Pembrolizumab) ^[27]
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End point description:

Intracranial DOR is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or documented disease progression is observed, or the date of death from any cause in the absence of documented disease progression or recurrence).

APD: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment who had baseline CNS assessment and who had CNS metastasis at baseline. Participants censored: TRT A: 13; TRT B: 9.

End point type	Secondary
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End point timeframe:

Date of Intracranial CR or PR to Date of CNS Progression or Death Due to Any Cause Up to 31 Months

Notes:

[27] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	17 ^[28]	12 ^[29]		
Units: Months				
median (confidence interval 95%)	9999 (14.75 to 9999)	9999 (8.74 to 9999)		

Notes:

[28] - 9999 = N/A: Median and upper limit of 95% CI unavailable due to high censoring.

[29] - 9999 = N/A: Median and upper limit of 95% CI unavailable due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Intracranial DOR Per RECIST 1.1 by BICR (With or Without Pembrolizumab)

End point title	Median Intracranial DOR Per RECIST 1.1 by BICR (With or Without Pembrolizumab) ^[30]
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End point description:

Intracranial DOR is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or documented disease progression is observed, or the date of death from any cause in the absence of documented disease progression or recurrence).

APD: All participants included in the ITT population who had baseline CNS assessment and who had CNS metastasis at baseline. Participants censored: TRT A: 15; TRT B: 9.

End point type	Secondary
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End point timeframe:

Date of Intracranial CR or PR to Date of CNS Progression or Death Due to Any Cause Up to 31 Months

Notes:

[30] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21 ^[31]	13 ^[32]		
Units: Median				
median (confidence interval 95%)	9999 (9.53 to 9999)	13.40 (4.17 to 9999)		

Notes:

[31] - 9999 = N/A: Median and upper limit of 95% Confidence Interval unavailable due to high censoring.

[32] - 9999 = N/A: Upper limit of 95% Confidence Interval unavailable due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration of Pulmonary Symptoms (With Pembrolizumab)

End point title	Time to Deterioration of Pulmonary Symptoms (With Pembrolizumab) ^[33]
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End point description:

Time to Deterioration of Pulmonary Symptoms Measured by the NSCLC-Symptom Assessment Questionnaire (SAQ) (with Pembrolizumab).

APD: ITT Pembrolizumab: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment. Participants censored: TRT A: 99; TRT B: 47.

End point type	Secondary
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End point timeframe:

Baseline to Deterioration of Pulmonary Symptoms Up to 31 Months

Notes:

[33] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	129 ^[34]	83		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	1.9 (0.7 to 6.6)		

Notes:

[34] - 9999 = N/A: Data not available due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration of Pulmonary Symptoms (With or Without Pembrolizumab)

End point title	Time to Deterioration of Pulmonary Symptoms (With or Without Pembrolizumab) ^[35]
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End point description:

Time to Deterioration of Pulmonary Symptoms Measured by the NSCLC-SAQ (with or without Pembrolizumab).

APD: ITT Population: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Participants were analyzed according to the treatment arm they were assigned to regardless of what actual treatment they received. Participants censored: TRT A: 121; TRT B: 58.

End point type	Secondary
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End point timeframe:

Baseline to Deterioration of Pulmonary Symptoms Up to 31 Months

Notes:

[35] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	159 ^[36]	102		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	1.6 (0.7 to 4.9)		

Notes:

[36] - 9999 = N/A: Data not available due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to CNS Progression Per RECIST 1.1 by BICR (With Pembrolizumab)

End point title	Median Time to CNS Progression Per RECIST 1.1 by BICR (With Pembrolizumab) ^[37]
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End point description:

Time to CNS Progression is defined as the time from randomization to the occurrence of documented CNS progression by the BICR. Central nervous system progression is defined as progression due to newly developed intracranial lesions and/or progression of pre-existing intracranial lesions per RECIST 1.1.

APD: Participants included in the ITT population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment who had baseline CNS assessment and who had CNS metastasis at baseline. Number of participants censored: TRT A = 112; TRT B = 59.

End point type	Secondary
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End point timeframe:

Baseline through CNS Progression or Death Up to 31 Months

Notes:

[37] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed with Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	120 ^[38]	72 ^[39]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[38] - 9999 = N/A: Data not available due to high censoring.

[39] - 9999 = N/A: Data not available due to high censoring.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to CNS Progression Per RECIST 1.1 by BICR (With or Without Pembrolizumab)

End point title	Median Time to CNS Progression Per RECIST 1.1 by BICR (With or Without Pembrolizumab) ^[40]
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End point description:

Time to CNS Progression is defined as the time from randomization to the occurrence of documented CNS progression by the BICR. Central nervous system progression is defined as progression due to newly developed intracranial lesions and/or progression of pre-existing intracranial lesions per RECIST 1.1.

APD: All participants included in the ITT population who had baseline CNS assessment and who had CNS metastasis at baseline. Participants censored: TRT A: 137; TRT B: = 73.

End point type	Secondary
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End point timeframe:

Baseline through CNS Progression or Death Up to 31 Months

Notes:

[40] - 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: Participants in the Treatment B arm were in one of two subject analysis sets: "With

Pembrolizumab" arm or "With or Without Pembrolizumab" arm.

End point values	Selpercatinib (TRT A)	Pemetrexed With or Without Pembrolizumab (TRT B)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	146 ^[41]	88 ^[42]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (999 to 9999)		

Notes:

[41] - 9999 = N/A: Data not available due to high censoring.

[42] - 9999 = N/A: Data not available due to high censoring.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline Up to 38 Months

Adverse event reporting additional description:

Safety population is defined as all participants who received study drug regardless of strata and as pre-specified, adverse events were collected for the TRT B treatment arm as a whole. Analysis of safety data will be based on the actual treatment a participant received on the first study treatment administration regardless of allocation.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Selpercatinib (TRT A)
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Reporting group description:

160 milligram (mg) Selpercatinib administered orally, twice daily (BID continuously in 21-day cycles.

Reporting group title	Carboplatin or Cisplatin + Pemetrexed+/-Pembrolizumab (TRT B)
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Reporting group description:

Pemetrexed 500 milligrams per meter squared (mg/m²) administered intravenously (IV) on Day 1, every 3 weeks (Q3W), plus at the investigator's choice of carboplatin area under the concentration versus time curve 5 (AUC 5 [maximum dose 750 mg]) IV, or cisplatin 75mg/m² IV on Day 1 Q3W for 4 cycles, plus investigator's choice with or without 200 mg pembrolizumab IV on Day 1 Q3W up to 35 cycles.

Serious adverse events	Selpercatinib (TRT A)	Carboplatin or Cisplatin + Pemetrexed+/-Pembrolizumab (TRT B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 158 (34.81%)	23 / 98 (23.47%)	
number of deaths (all causes)	32	17	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
malignant pleural effusion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 158 (1.27%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
transitional cell carcinoma			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
jugular vein thrombosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
venous thrombosis limb			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
chest pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
asthenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
malaise			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 158 (1.27%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
oedema peripheral			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sudden death			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			
anaphylactic shock			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypersensitivity			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
acute respiratory failure			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
chylothorax				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	2 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
dyspnoea				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	2 / 158 (1.27%)	1 / 98 (1.02%)		
occurrences causally related to treatment / all	1 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
interstitial lung disease				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
respiratory failure				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
pulmonary embolism				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	1 / 98 (1.02%)		
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 26.0				
subjects affected / exposed	7 / 158 (4.43%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	1 / 11	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood creatinine increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
electrocardiogram t wave abnormal			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic enzyme increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutrophil count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
platelet count decreased			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 158 (0.63%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	1 / 1	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
femur fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
procedural haemorrhage			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiac arrest			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
cardiac failure			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial fibrillation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
angina pectoris			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 158 (1.27%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
myocardial ischaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericardial effusion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 158 (1.27%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebral infarction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal cord compression			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 158 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ascites			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 158 (1.90%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	5 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterocolitis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastritis erosive			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematemesis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
inguinal hernia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal obstruction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal haemorrhage			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

pancreatitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 158 (0.63%) 0 / 3 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
pancreatitis acute alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 158 (0.00%) 0 / 0 0 / 0	1 / 98 (1.02%) 0 / 1 0 / 0	
volvulus alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 158 (0.63%) 0 / 1 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
Hepatobiliary disorders cholecystitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 158 (1.90%) 1 / 3 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
hepatic function abnormal alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 158 (2.53%) 4 / 4 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
immune-mediated hepatic disorder alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 158 (1.27%) 5 / 5 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
Skin and subcutaneous tissue disorders dermatitis alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
drug eruption			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (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			
covid-19			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
covid-19 pneumonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
erysipelas			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
herpes zoster				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
infectious pleural effusion				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
meningitis				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
sepsis				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
pneumonia viral				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
peritonitis				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)		
occurrences causally related to treatment / all	2 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

pneumonia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 158 (1.90%) 1 / 4 0 / 0	2 / 98 (2.04%) 1 / 2 0 / 0	
urinary tract infection alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 158 (1.27%) 0 / 2 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
soft tissue infection alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 158 (0.63%) 1 / 1 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
urosepsis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 158 (0.63%) 0 / 1 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 158 (1.27%) 2 / 2 0 / 0	0 / 98 (0.00%) 0 / 0 0 / 0	
electrolyte imbalance alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 158 (0.00%) 0 / 0 0 / 0	1 / 98 (1.02%) 1 / 1 0 / 0	
hyperglycaemia alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 158 (0.63%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypomagnesaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 158 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
malnutrition			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 158 (0.63%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

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

Non-serious adverse events	Selpercatinib (TRT A)	Carboplatin or Cisplatin + Pemetrexed+/- Pembrolizumab (TRT B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 158 (98.73%)	97 / 98 (98.98%)	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	76 / 158 (48.10%)	7 / 98 (7.14%)	
occurrences (all)	167	18	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	20 / 158 (12.66%)	25 / 98 (25.51%)	
occurrences (all)	53	73	
chest pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	8 / 158 (5.06%)	13 / 98 (13.27%)	
occurrences (all)	9	15	
face oedema			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	12 / 158 (7.59%)	4 / 98 (4.08%)	
occurrences (all)	14	4	
fatigue			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	24 / 158 (15.19%)	26 / 98 (26.53%)	
occurrences (all)	40	47	
malaise			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	8 / 158 (5.06%)	5 / 98 (5.10%)	
occurrences (all)	9	8	
oedema			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	9 / 158 (5.70%)	8 / 98 (8.16%)	
occurrences (all)	16	10	

<p>oedema peripheral</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>41 / 158 (25.95%)</p> <p>57</p>	<p>13 / 98 (13.27%)</p> <p>15</p>	
<p>pyrexia</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>21 / 158 (13.29%)</p> <p>39</p>	<p>22 / 98 (22.45%)</p> <p>41</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>dyspnoea</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>cough</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>hiccups</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>oropharyngeal pain</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 158 (3.16%)</p> <p>9</p> <p>16 / 158 (10.13%)</p> <p>19</p> <p>0 / 158 (0.00%)</p> <p>0</p> <p>9 / 158 (5.70%)</p> <p>10</p>	<p>14 / 98 (14.29%)</p> <p>18</p> <p>15 / 98 (15.31%)</p> <p>22</p> <p>6 / 98 (6.12%)</p> <p>11</p> <p>4 / 98 (4.08%)</p> <p>4</p>	
<p>Psychiatric disorders</p> <p>insomnia</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 158 (6.33%)</p> <p>10</p>	<p>5 / 98 (5.10%)</p> <p>5</p>	
<p>Investigations</p> <p>alanine aminotransferase increased</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>95 / 158 (60.13%)</p> <p>324</p>	<p>39 / 98 (39.80%)</p> <p>108</p>	

aspartate aminotransferase increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	97 / 158 (61.39%) 322	39 / 98 (39.80%) 94	
blood thyroid stimulating hormone increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 158 (6.33%) 14	6 / 98 (6.12%) 8	
electrocardiogram qt prolonged alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	32 / 158 (20.25%) 58	1 / 98 (1.02%) 1	
blood bilirubin increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	59 / 158 (37.34%) 230	1 / 98 (1.02%) 1	
blood alkaline phosphatase increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	20 / 158 (12.66%) 36	8 / 98 (8.16%) 12	
bilirubin conjugated increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	19 / 158 (12.03%) 54	1 / 98 (1.02%) 1	
blood creatinine increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	36 / 158 (22.78%) 76	15 / 98 (15.31%) 38	
gamma-glutamyltransferase increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	20 / 158 (12.66%) 56	10 / 98 (10.20%) 15	
lymphocyte count decreased			

alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	7 / 158 (4.43%) 21	6 / 98 (6.12%) 28	
weight decreased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 158 (6.33%) 31	9 / 98 (9.18%) 11	
neutrophil count decreased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	31 / 158 (19.62%) 126	25 / 98 (25.51%) 90	
platelet count decreased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	32 / 158 (20.25%) 92	18 / 98 (18.37%) 46	
weight increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	23 / 158 (14.56%) 44	7 / 98 (7.14%) 20	
white blood cell count decreased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	32 / 158 (20.25%) 142	25 / 98 (25.51%) 72	
Nervous system disorders dizziness alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	11 / 158 (6.96%) 12	8 / 98 (8.16%) 13	
dysgeusia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	8 / 158 (5.06%) 10	12 / 98 (12.24%) 22	
headache alternative dictionary used: MedDRA 26.0			

subjects affected / exposed occurrences (all)	22 / 158 (13.92%) 30	10 / 98 (10.20%) 13	
Blood and lymphatic system disorders			
anaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	18 / 158 (11.39%) 35	57 / 98 (58.16%) 209	
leukopenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	11 / 158 (6.96%) 22	8 / 98 (8.16%) 37	
neutropenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	6 / 158 (3.80%) 13	18 / 98 (18.37%) 61	
thrombocytopenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	11 / 158 (6.96%) 17	10 / 98 (10.20%) 20	
Eye disorders			
lacrimation increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	3 / 158 (1.90%) 5	13 / 98 (13.27%) 16	
Gastrointestinal disorders			
abdominal pain upper alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	20 / 158 (12.66%) 31	13 / 98 (13.27%) 30	
ascites alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	9 / 158 (5.70%) 10	0 / 98 (0.00%) 0	
abdominal distension alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	8 / 158 (5.06%)	3 / 98 (3.06%)
occurrences (all)	11	3
abdominal discomfort		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	9 / 158 (5.70%)	3 / 98 (3.06%)
occurrences (all)	9	3
abdominal pain		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	18 / 158 (11.39%)	7 / 98 (7.14%)
occurrences (all)	34	11
diarrhoea		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	69 / 158 (43.67%)	24 / 98 (24.49%)
occurrences (all)	218	33
dry mouth		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	61 / 158 (38.61%)	6 / 98 (6.12%)
occurrences (all)	73	6
constipation		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	34 / 158 (21.52%)	39 / 98 (39.80%)
occurrences (all)	46	67
nausea		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	20 / 158 (12.66%)	43 / 98 (43.88%)
occurrences (all)	26	93
stomatitis		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	19 / 158 (12.03%)	9 / 98 (9.18%)
occurrences (all)	28	13
vomiting		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	20 / 158 (12.66%)	23 / 98 (23.47%)
occurrences (all)	38	35

Hepatobiliary disorders hepatic function abnormal alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 158 (6.33%) 41	1 / 98 (1.02%) 3	
Skin and subcutaneous tissue disorders alopecia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) dermatitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) dry skin alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) pruritus alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) rash alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) rash maculo-papular alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	11 / 158 (6.96%) 12 8 / 158 (5.06%) 11 8 / 158 (5.06%) 10 16 / 158 (10.13%) 27 35 / 158 (22.15%) 54 6 / 158 (3.80%) 16	6 / 98 (6.12%) 6 1 / 98 (1.02%) 2 6 / 98 (6.12%) 6 22 / 98 (22.45%) 26 21 / 98 (21.43%) 30 5 / 98 (5.10%) 7	
Endocrine disorders hyperthyroidism alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) hypothyroidism	4 / 158 (2.53%) 8	7 / 98 (7.14%) 7	

alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	5 / 158 (3.16%) 7	6 / 98 (6.12%) 10	
Musculoskeletal and connective tissue disorders arthralgia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) back pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) myalgia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) pain in extremity alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	 17 / 158 (10.76%) 22 14 / 158 (8.86%) 22 10 / 158 (6.33%) 10 12 / 158 (7.59%) 16	 9 / 98 (9.18%) 10 12 / 98 (12.24%) 19 7 / 98 (7.14%) 8 6 / 98 (6.12%) 8	
Infections and infestations conjunctivitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) covid-19 alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) nasopharyngitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) paronychia alternative dictionary used:	 3 / 158 (1.90%) 3 30 / 158 (18.99%) 34 9 / 158 (5.70%) 15	 5 / 98 (5.10%) 15 18 / 98 (18.37%) 18 5 / 98 (5.10%) 9	

MedDRA 26.0			
subjects affected / exposed	9 / 158 (5.70%)	0 / 98 (0.00%)	
occurrences (all)	10	0	
pneumonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	10 / 158 (6.33%)	6 / 98 (6.12%)	
occurrences (all)	14	8	
upper respiratory tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	9 / 158 (5.70%)	3 / 98 (3.06%)	
occurrences (all)	12	3	
urinary tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	14 / 158 (8.86%)	4 / 98 (4.08%)	
occurrences (all)	24	4	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	27 / 158 (17.09%)	33 / 98 (33.67%)	
occurrences (all)	35	56	
hyperglycaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	5 / 158 (3.16%)	9 / 98 (9.18%)	
occurrences (all)	8	17	
hyperuricaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	10 / 158 (6.33%)	6 / 98 (6.12%)	
occurrences (all)	15	20	
hypoalbuminaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	23 / 158 (14.56%)	6 / 98 (6.12%)	
occurrences (all)	63	9	
hypocalcaemia			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	13 / 158 (8.23%)	0 / 98 (0.00%)	
occurrences (all)	34	0	
hypokalaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	23 / 158 (14.56%)	8 / 98 (8.16%)	
occurrences (all)	33	25	
hypomagnesaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	8 / 158 (5.06%)	5 / 98 (5.10%)	
occurrences (all)	24	8	
hyponatraemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	14 / 158 (8.86%)	6 / 98 (6.12%)	
occurrences (all)	47	10	
hypoproteinaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	8 / 158 (5.06%)	3 / 98 (3.06%)	
occurrences (all)	24	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2019	Amendment A: This amendment incorporates changes requested by regulatory authorities to the inclusion/exclusion criteria, dose modifications and the addition of a secondary objective to assess/evaluation performance of RET local laboratory tests compared to a single, central test. In addition, this amendment includes changes made to correct and clarify information for sites.
10 June 2020	Amendment B: This amendment incorporates changes to the primary endpoint to satisfy certain country-specific regulatory and payer expectations. In response to regulatory agency feedback and additional data gleaned from LIBRETTO-001, changes to the sample size and randomization ratio were made to minimize the number of patients treated on the control arm, while still maintaining the ability to test the central hypothesis. In addition, this amendment includes changes to align with the latest version of the IB, incorporate feedback from EC/IRBs, and to correct and clarify information in order for sites to improve the conduct to the study.
26 June 2020	Amendment C: This amendment clarifies key secondary analyses and supportive secondary analyses. In addition, it corrects typographical errors and inconsistencies that were noted in JZJC amendment (b).
18 November 2020	Amendment D: This amendment incorporates changes to include additional endpoints to further characterize the intracranial activity of selpercatinib compared to the control arm. In addition, this amendment includes changes made to correct and clarify information for sites. This amendment also corrects typographical errors and inconsistencies that were noted in JZJC amendment (c).
15 August 2023	Amendment E: The primary purpose of this amendment is to update as per the latest Investigator Brochure (IB) and to align with EU Clinical Trial Regulation (EU-CTR) requirements. In addition, this amendment includes changes made to correct and clarify information for sites. This amendment also corrects typographical errors and inconsistencies that were noted in JZJC amendment(d).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported