



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 | v1 |
| This version publication date | 19 May 2024 |
| First version publication date | 19 May 2024 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | J2G-MC-JZJC |
|-----------------------|-------------|

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) |
|------------------|---|

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) | | |
|----------------------------------|-----------------------|-----------------------|--|--|

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] |
|-----------------|--|

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 |
|----------------|---------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|--|

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] |
|-----------------|--|

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) | | |
|----------------------------------|-----------------------|---------------------|--|--|

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] |
|-----------------|--|

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 |
|----------------|-----------|

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] |
|-----------------|--|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|--|

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 |
|----------------|-----------|

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] |
|-----------------|--|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|--|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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:

All randomized participants who received at least 1 dose (including a partial dose) of study treatment. Analysis of safety data will be based on the actual treatment a participant received on the first study treatment administration regardless of which treatment they were randomized to receive ("as treated").

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

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

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.

| | |
|-----------------------|-----------------------|
| Reporting group title | Selpercatinib (TRT A) |
|-----------------------|-----------------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastritis erosive | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haematemesis | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ileus | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| inguinal hernia | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| intestinal obstruction | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 2 / 98 (2.04%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| small intestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| 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 | 0 / 98 (0.00%) 0 / 0 0 / 0 | 1 / 158 (0.63%) 0 / 3 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 | 1 / 98 (1.02%) 0 / 1 0 / 0 | 0 / 158 (0.00%) 0 / 0 0 / 0 | |
| volvulus alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 98 (0.00%) 0 / 0 0 / 0 | 1 / 158 (0.63%) 0 / 1 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 | 0 / 98 (0.00%) 0 / 0 0 / 0 | 3 / 158 (1.90%) 1 / 3 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 | 0 / 98 (0.00%) 0 / 0 0 / 0 | 4 / 158 (2.53%) 4 / 4 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 | 0 / 98 (0.00%) 0 / 0 0 / 0 | 2 / 158 (1.27%) 5 / 5 0 / 0 | |
| Skin and subcutaneous tissue disorders dermatitis alternative dictionary used: MedDRA 26.0 | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| drug eruption | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| 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 | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| 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 | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| covid-19 | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| covid-19 pneumonia | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| erysipelas | | | |
| alternative dictionary used: MedDRA 26.0 | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| herpes zoster | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infectious pleural effusion | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| meningitis | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sepsis | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia viral | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| peritonitis | | | |
| alternative dictionary used: MedDRA 26.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| 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 | 2 / 98 (2.04%) 1 / 2 0 / 0 | 3 / 158 (1.90%) 1 / 4 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 | 0 / 98 (0.00%) 0 / 0 0 / 0 | 2 / 158 (1.27%) 0 / 2 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 | 0 / 98 (0.00%) 0 / 0 0 / 0 | 1 / 158 (0.63%) 1 / 1 0 / 0 | |
| urosepsis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 98 (0.00%) 0 / 0 0 / 0 | 1 / 158 (0.63%) 0 / 1 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 | 0 / 98 (0.00%) 0 / 0 0 / 0 | 2 / 158 (1.27%) 2 / 2 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 | 1 / 98 (1.02%) 1 / 1 0 / 0 | 0 / 158 (0.00%) 0 / 0 0 / 0 | |
| hyperglycaemia alternative dictionary used: MedDRA 26.0 | | | |

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

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

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

| | | | |
|--|--|---|--|
| <p>oedema peripheral</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>13 / 98 (13.27%)</p> <p>15</p> | <p>41 / 158 (25.95%)</p> <p>57</p> | |
| <p>pyrexia</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>22 / 98 (22.45%)</p> <p>41</p> | <p>21 / 158 (13.29%)</p> <p>39</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>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>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>Psychiatric disorders</p> <p>insomnia</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 98 (5.10%)</p> <p>5</p> | <p>10 / 158 (6.33%)</p> <p>10</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>39 / 98 (39.80%)</p> <p>108</p> | <p>95 / 158 (60.13%)</p> <p>324</p> | |

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

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

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

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

| | | | |
|---|--|---|--|
| Hepatobiliary disorders hepatic function abnormal alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 3 | 10 / 158 (6.33%) 41 | |
| 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) | 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 | 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 | |
| Endocrine disorders hyperthyroidism alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) hypothyroidism | 7 / 98 (7.14%) 7 | 4 / 158 (2.53%) 8 | |

| | | | |
|--|--|---|--|
| alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 6 / 98 (6.12%) 10 | 5 / 158 (3.16%) 7 | |
| 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) | 9 / 98 (9.18%) 10 12 / 98 (12.24%) 19 7 / 98 (7.14%) 8 6 / 98 (6.12%) 8 | 17 / 158 (10.76%) 22 14 / 158 (8.86%) 22 10 / 158 (6.33%) 10 12 / 158 (7.59%) 16 | |
| 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: | 5 / 98 (5.10%) 15 18 / 98 (18.37%) 18 5 / 98 (5.10%) 9 | 3 / 158 (1.90%) 3 30 / 158 (18.99%) 34 9 / 158 (5.70%) 15 | |

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

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

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