# Supplementary Appendix

Supplement to: Zhou C, Solomon B, Loong HH, et al. First-line selpercatinib or chemotherapy and pembrolizumab in *RET* fusion–positive NSCLC. N Engl J Med 2023;389:1839-50. DOI: 10.1056/NEJMoa2309457

This appendix has been provided by the authors to give readers additional information about the work.

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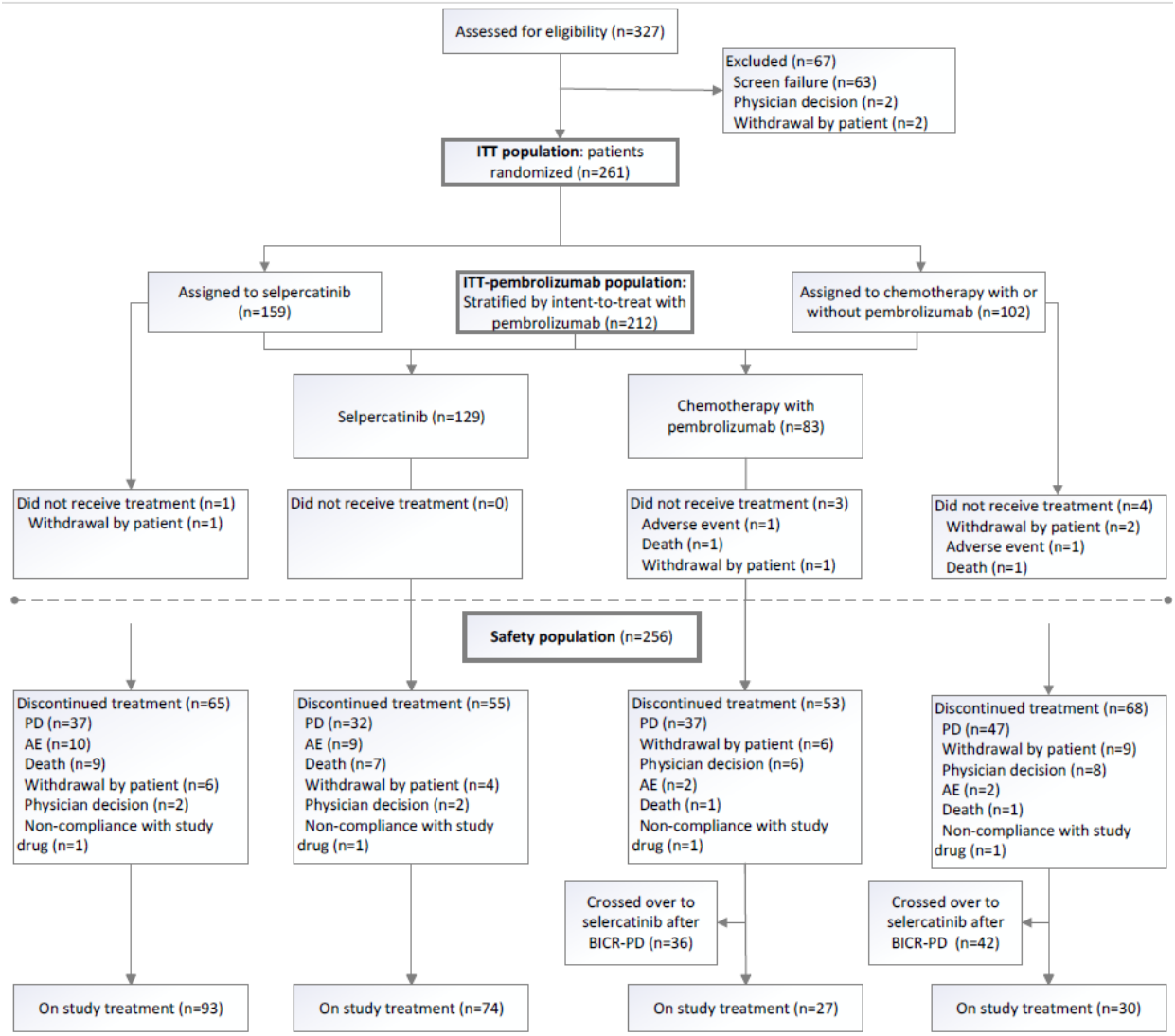
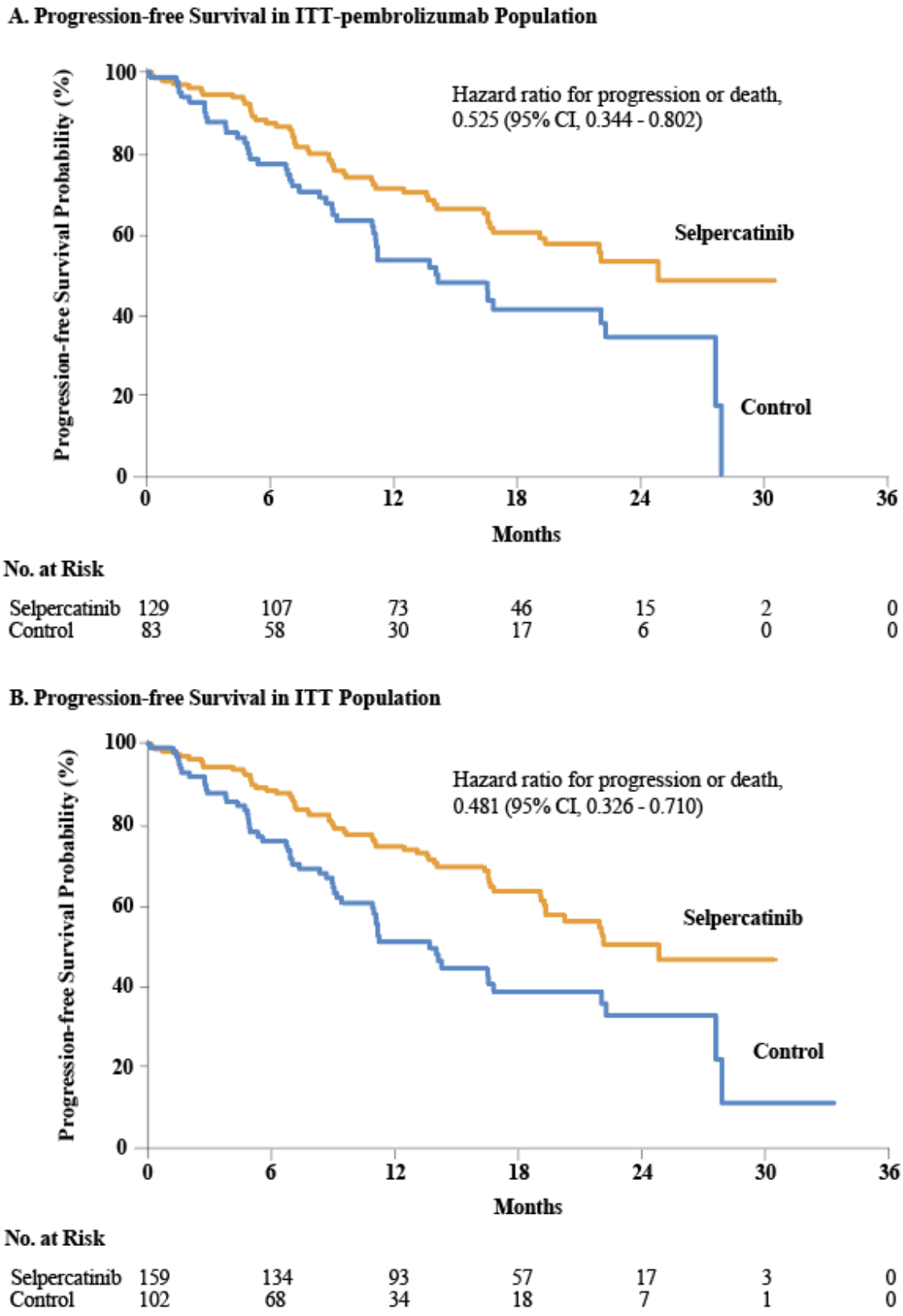
Figure S1: CONSORT diagram




Abbreviations: AE, adverse events; BICR, blinded independent central review; ITT, intention to treat; ITT-pembrolizumab, intent-to-treat with pembrolizumab in the event patients were randomized to the control arm; PD, progressive disease; Safety population, randomized patients who took at least 1 dose of the assigned study treatment.

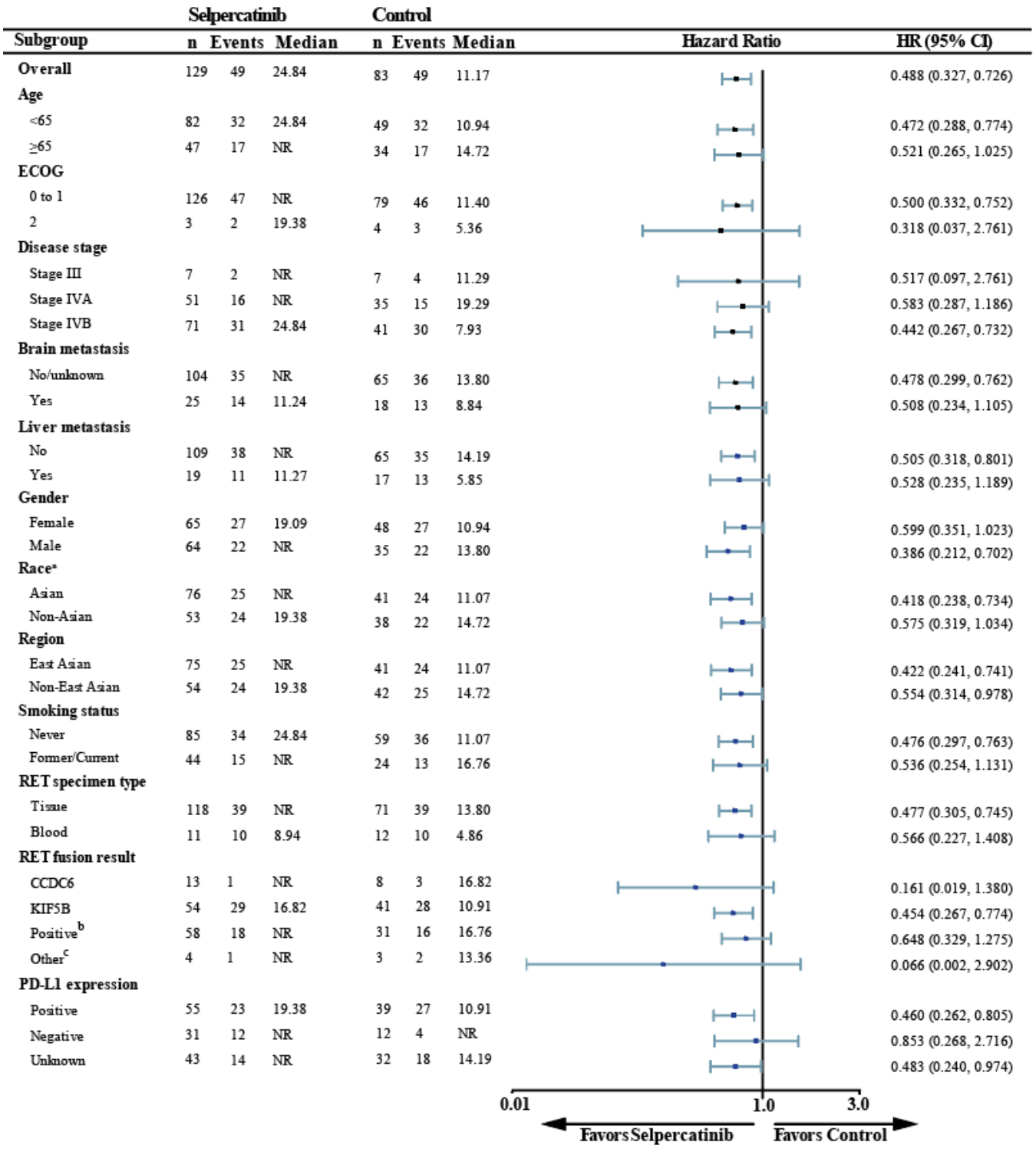
Data cutoff date: 01 May 2023

Figure S2. Progression-free Survival by Investigator



Panel A shows Kaplan-Meier estimates of progression-free-survival by investigator assessment in the ITT-pembrolizumab population. Panel B shows Kaplan-Meier estimates of progression-free-survival by investigator assessment in the ITT population. Tick marks on the survival curves indicate censoring of data.

Figure S3. Subgroup Analysis of Progression-free Survival in the ITT-pembrolizumab Population



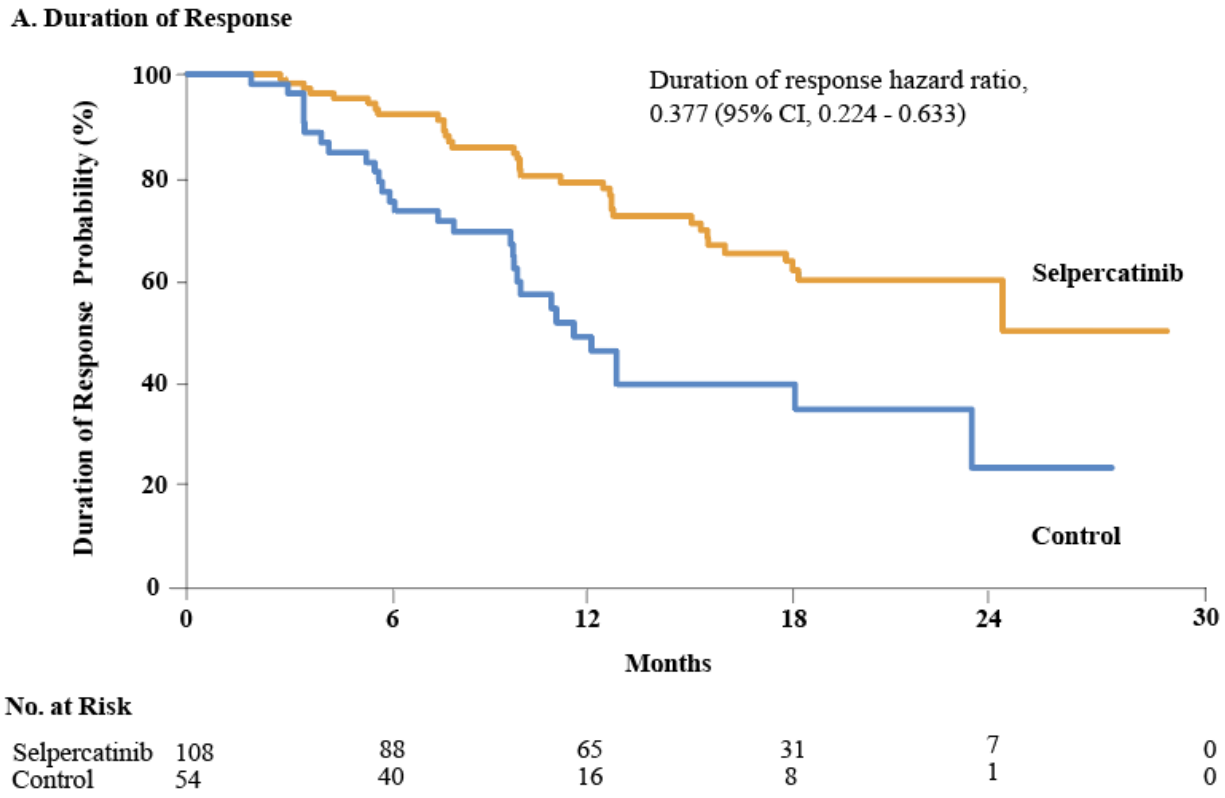
Note that confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

[a] Race was reported by the patients.

[b] *RET* fusion was indicated by molecular analysis, but the *RET* fusion partner was not identified.

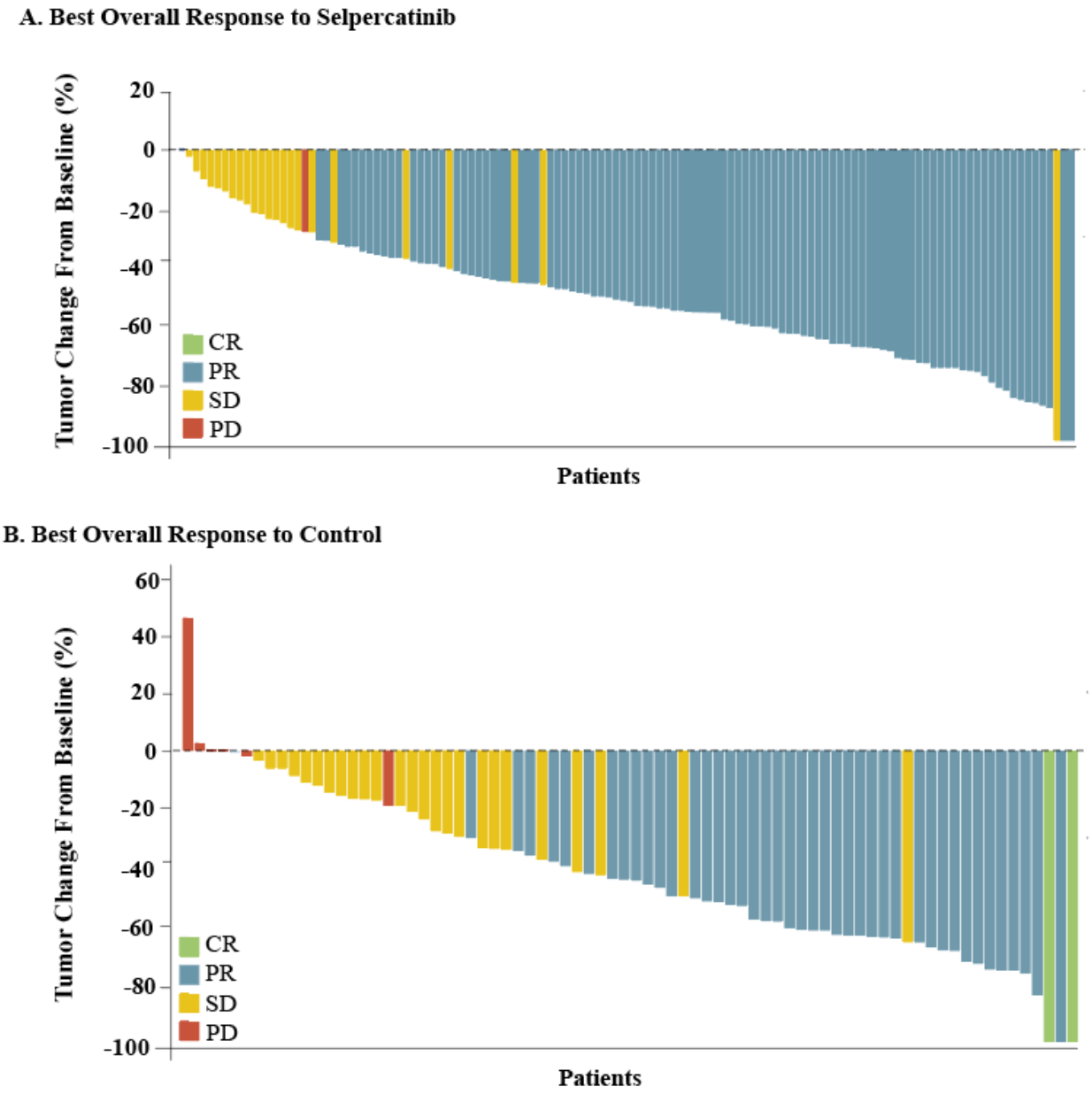
[c] Other included *NCOA4-RET, KIF13A-RET, KIAA1468-RET, KIAA1549L-RET, PRKAR1A-RET* and multiple results with *KIF5B-RET, CDKAL1-RET* and *NCOA4-RET, ZNF32-AS3-RET*.

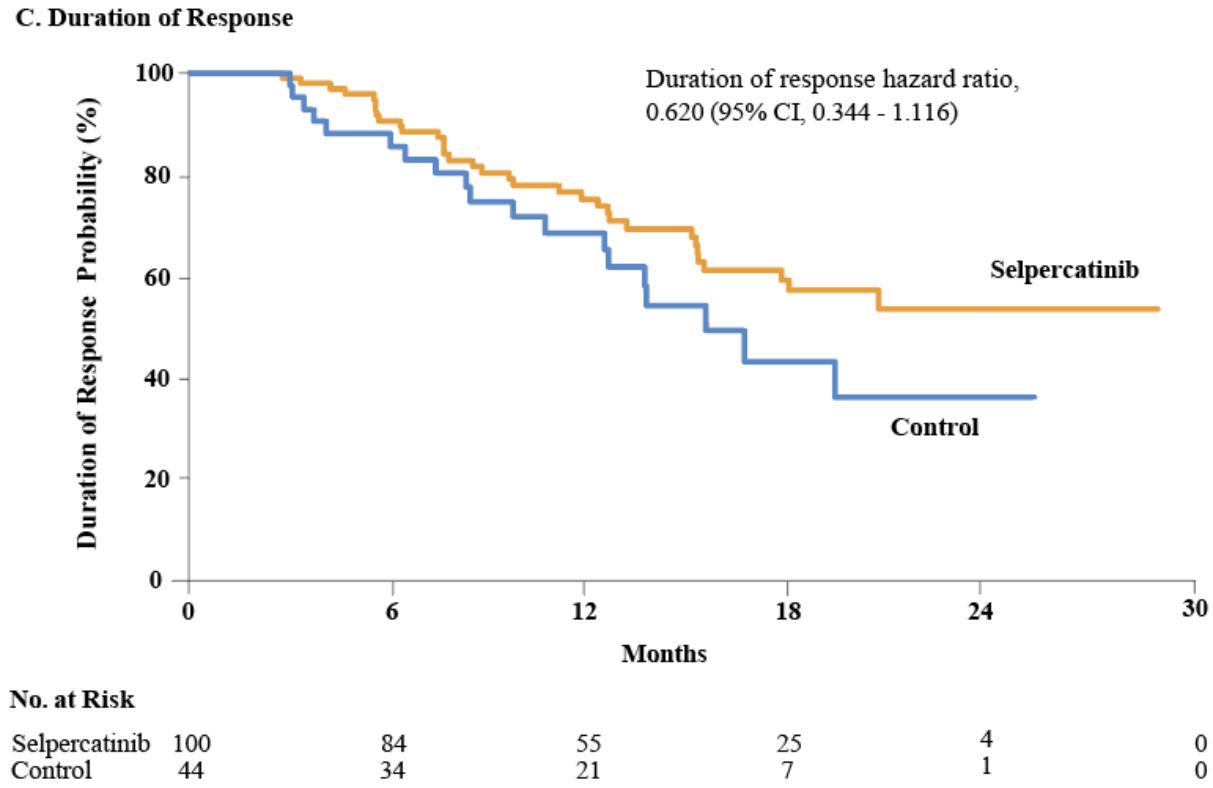
Figure S4. Duration of Responses by BICR in ITT-pembrolizumab Population




Shown are data for duration of response by BICR among 162 patients in the ITT-pembrolizumab population with confirmed responses, including 108 in the selpercatinib arm and 54 in the control arm.

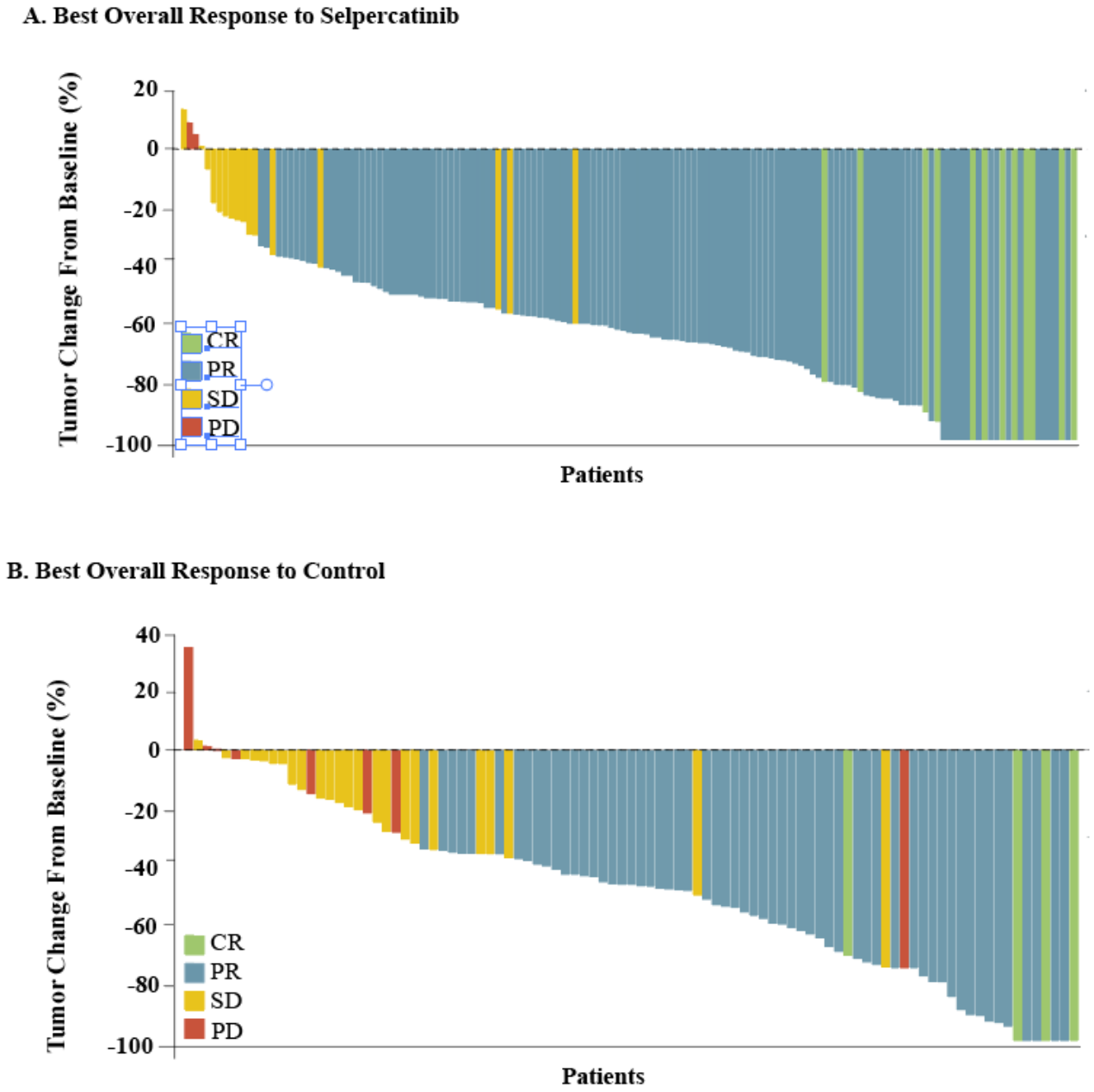
Figure S5. Responses by Investigator in ITT-pembrolizumab Population



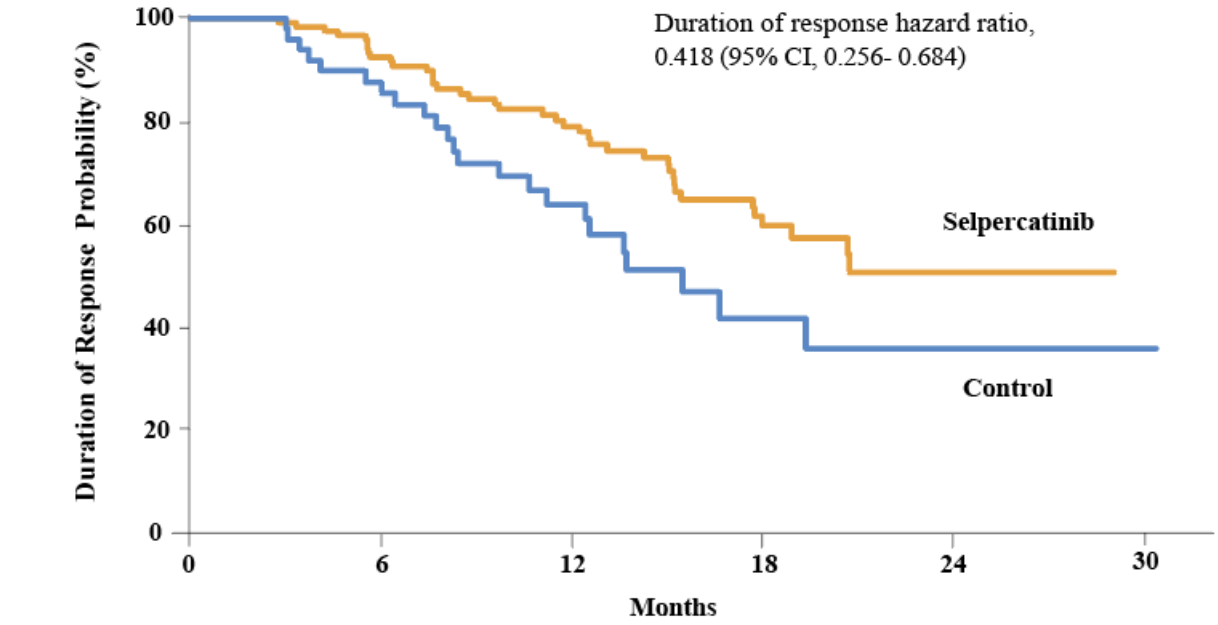



Shown are data according to investigator assessment of best overall responses and duration of response in the ITT-pembrolizumab population. Panels A and B show waterfall plots of the maximum change in tumor size for 100 patients on selpercatinib and 44 patients on control respectively. Panel C shows duration of response among 144 patients with a confirmed response.

Figure S6. Responses by BICR in ITT Population



**C. Duration of Response**

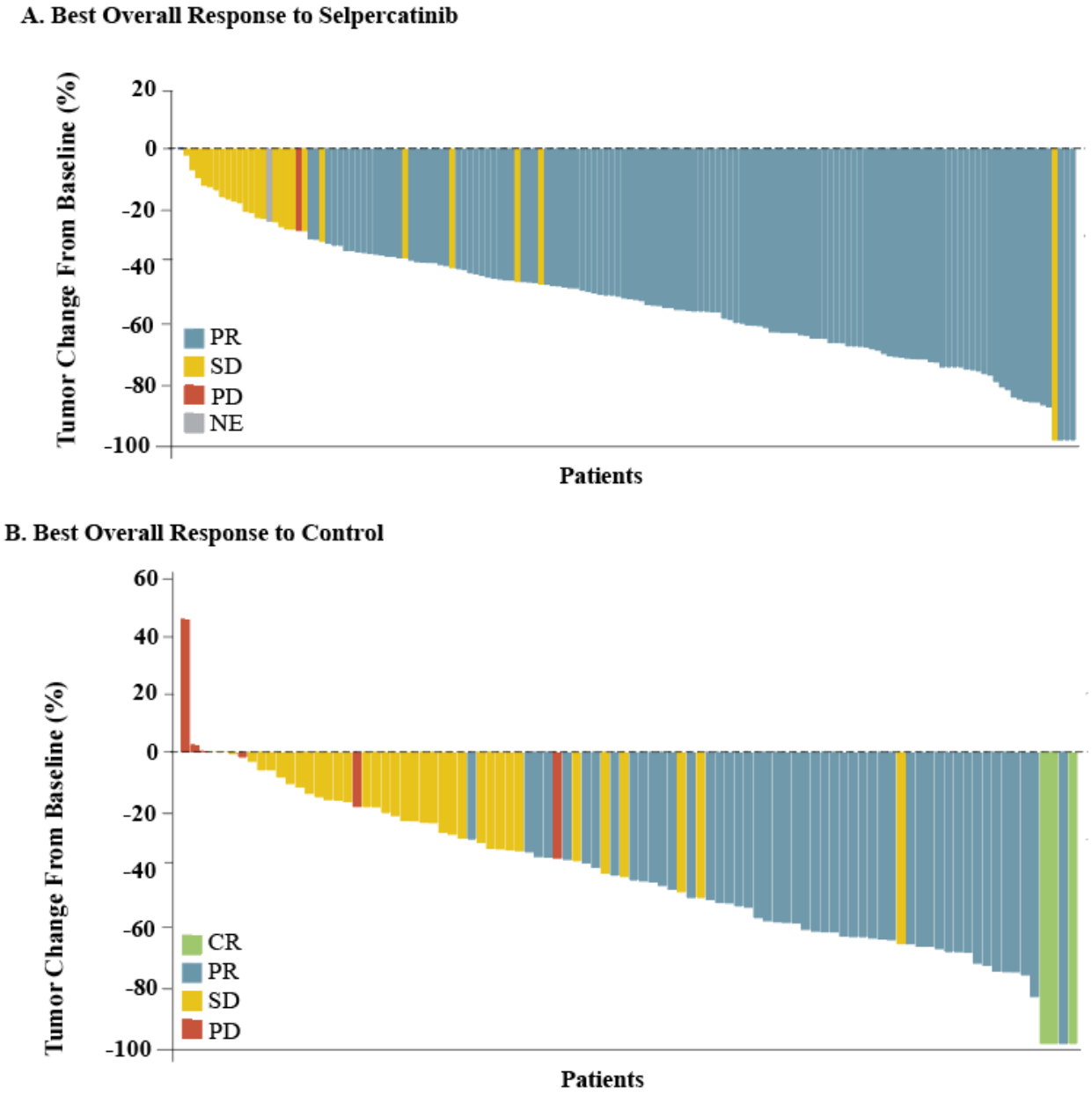


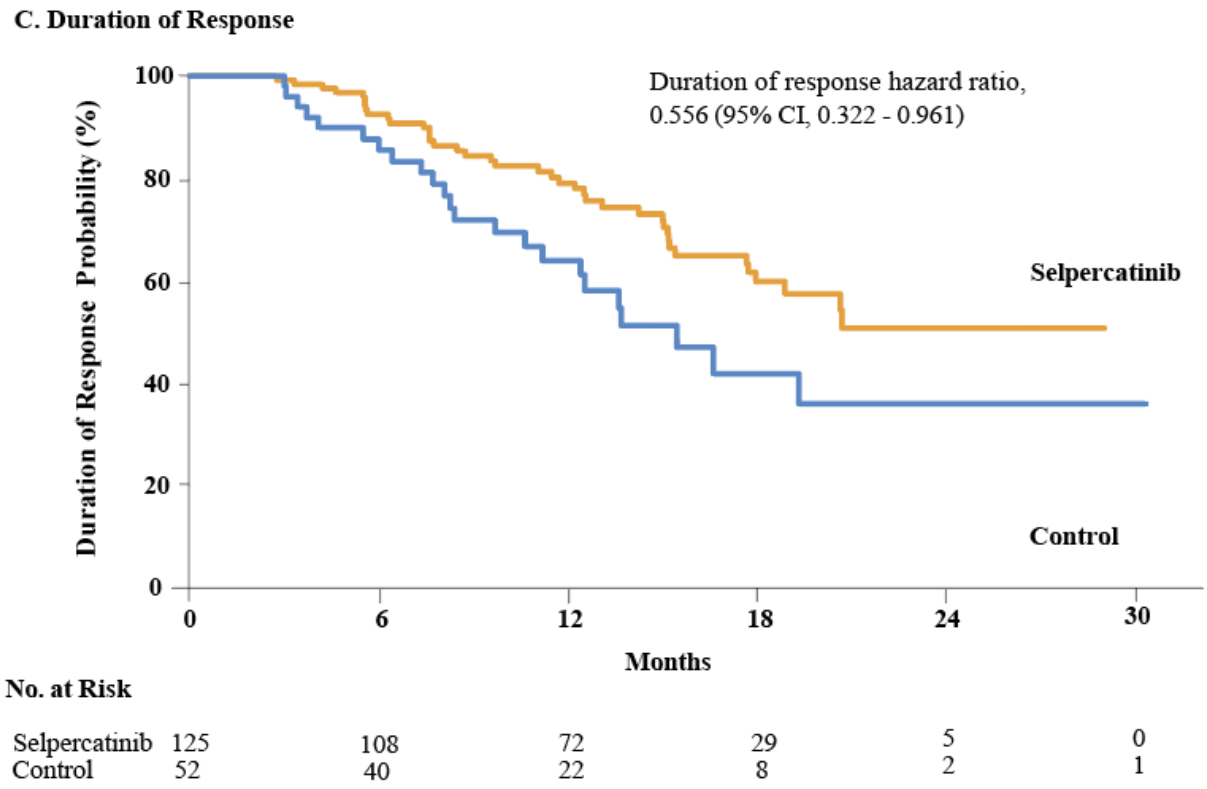

**No. at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Selpercatinib | 133 | 109 | 80 | 35 | 8 | 0 |
| Control | 64 | 46 | 17 | 9 | 2 | 1 |

Shown are data by BICR of best overall responses and duration of response in the ITT population. Panels A and B show waterfall plots of the maximum change in tumor size for 133 patients on selpercatinib and 64 patients on control respectively. Panel C shows duration of response among 197 patients with a confirmed response.

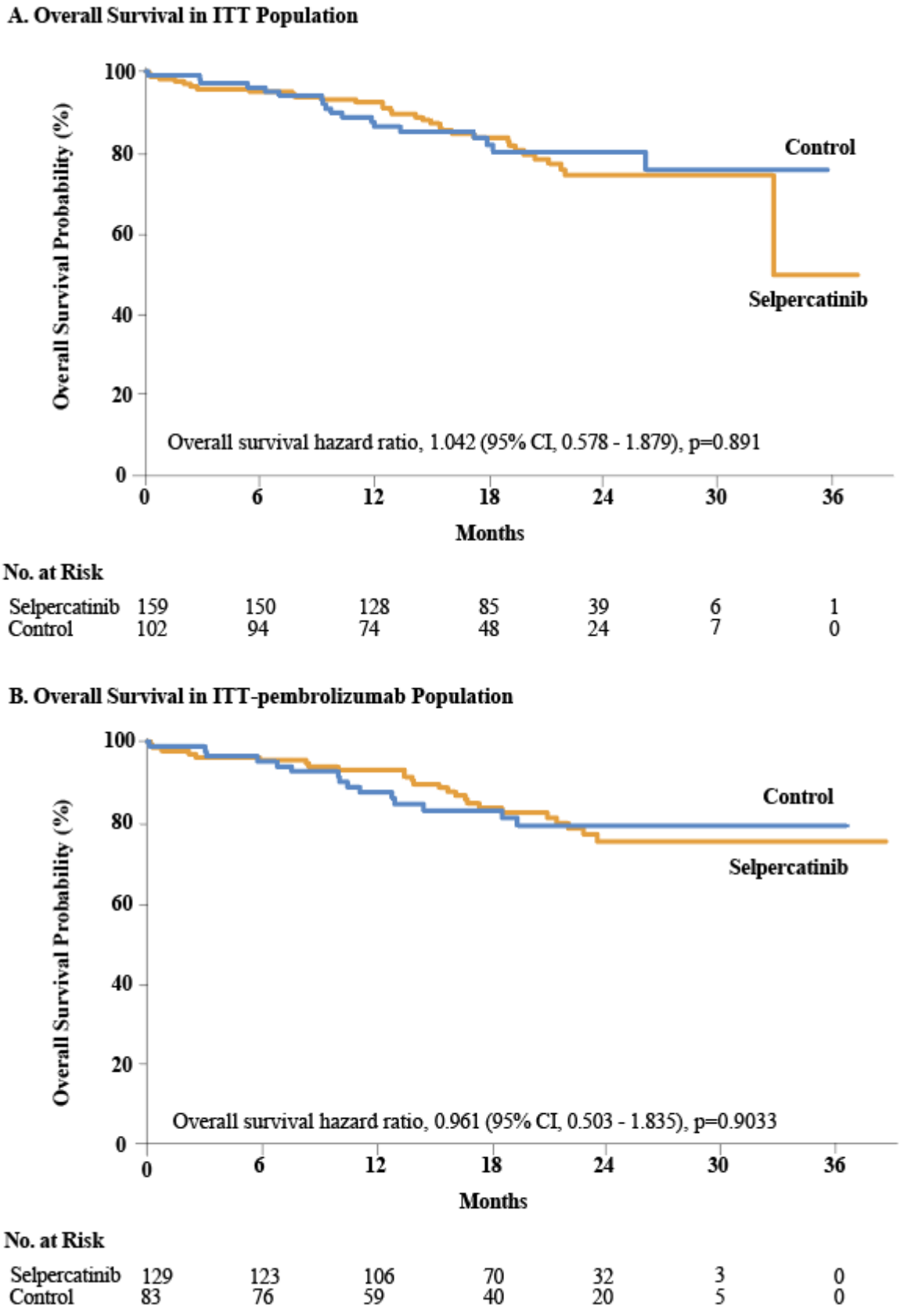
Figure S7. Investigator-assessed Responses in ITT Population





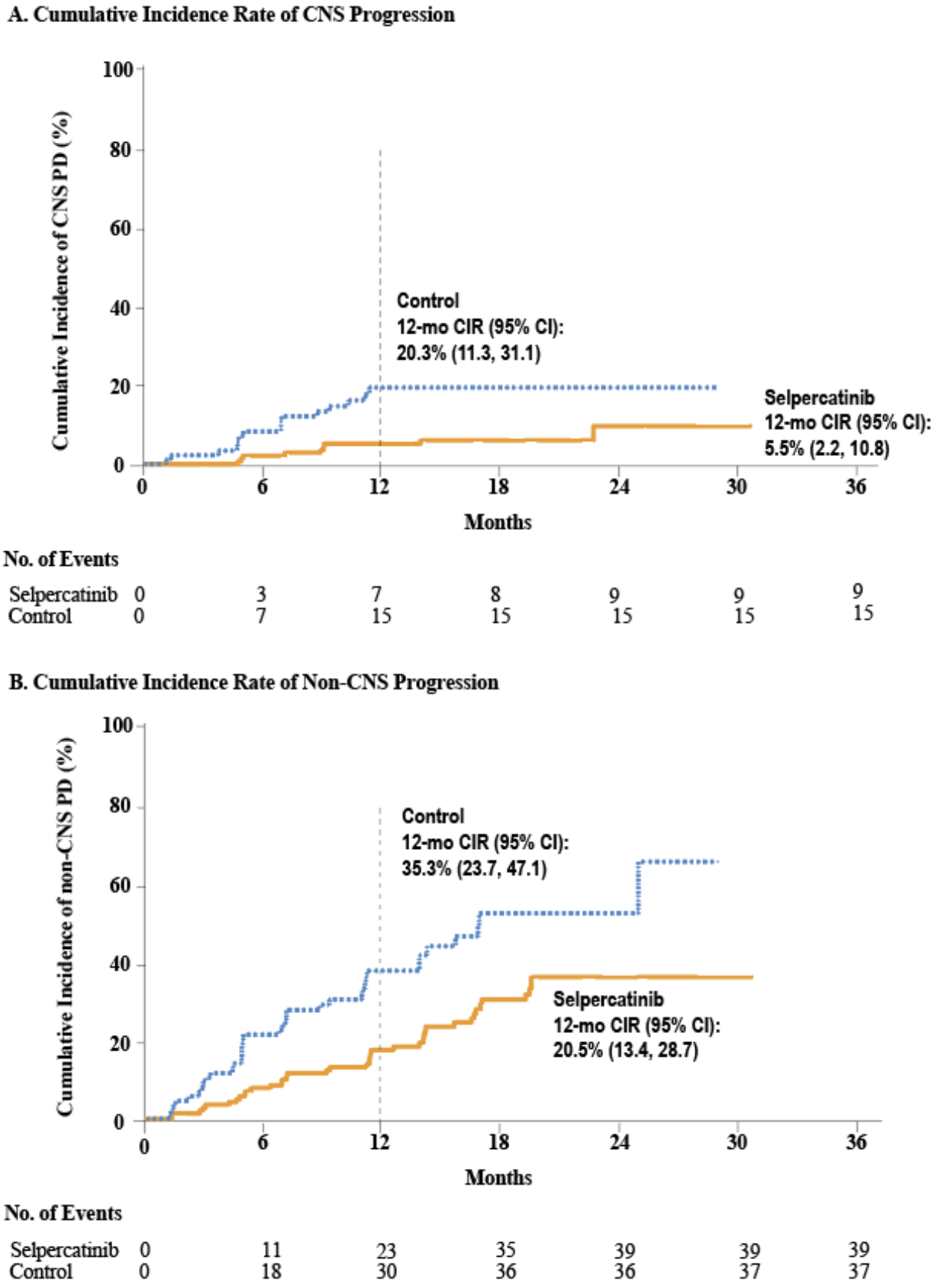

Shown are data according to investigator assessment of best overall responses and duration of response in the ITT population. Panels A and B show waterfall plots of the maximum change in tumor size for 125 patients on selpercatinib and 52 patients on control respectively. Panel C shows duration of response among 177 patients with a confirmed response.

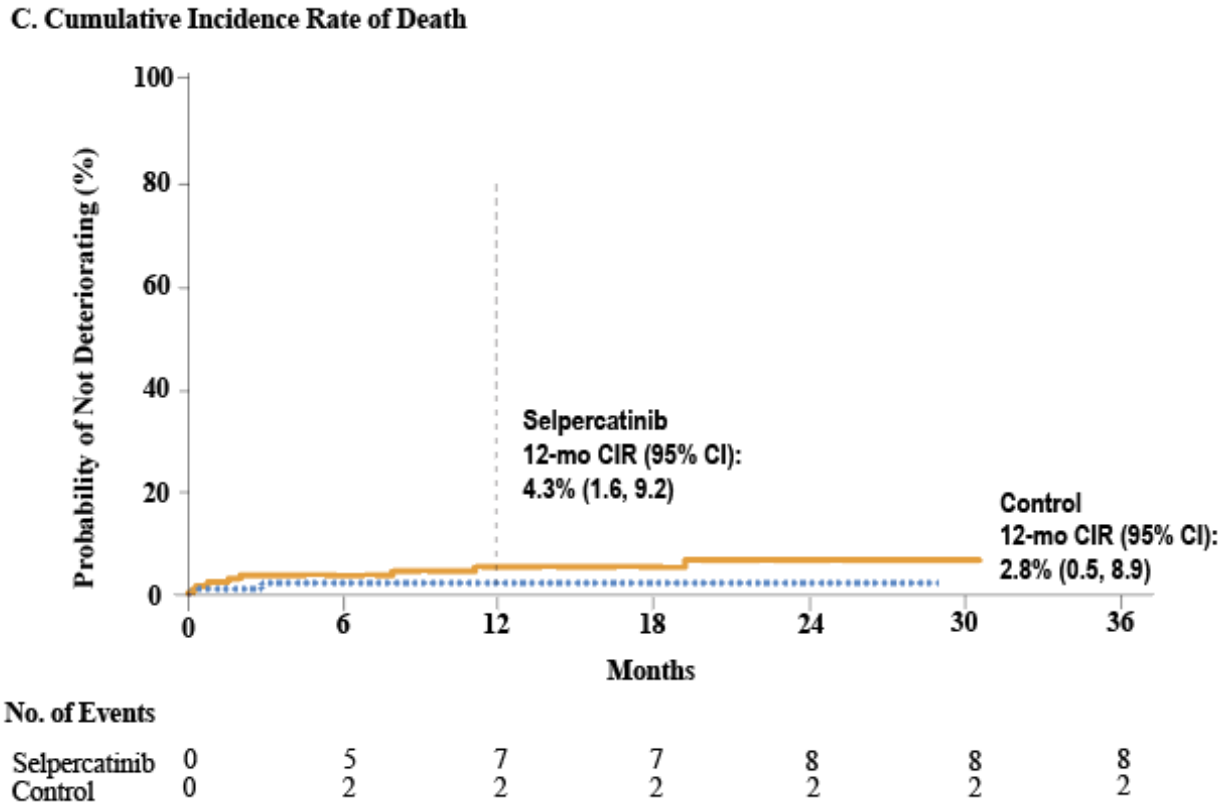
Fig. S8. Overall Survival



Panels A and B show Kaplan-Meier estimates of overall survival in the ITT population and ITT-pembrolizumab population respectively.

Fig. S9. Cumulative Incidence Rate in CNS-pembrolizumab Population

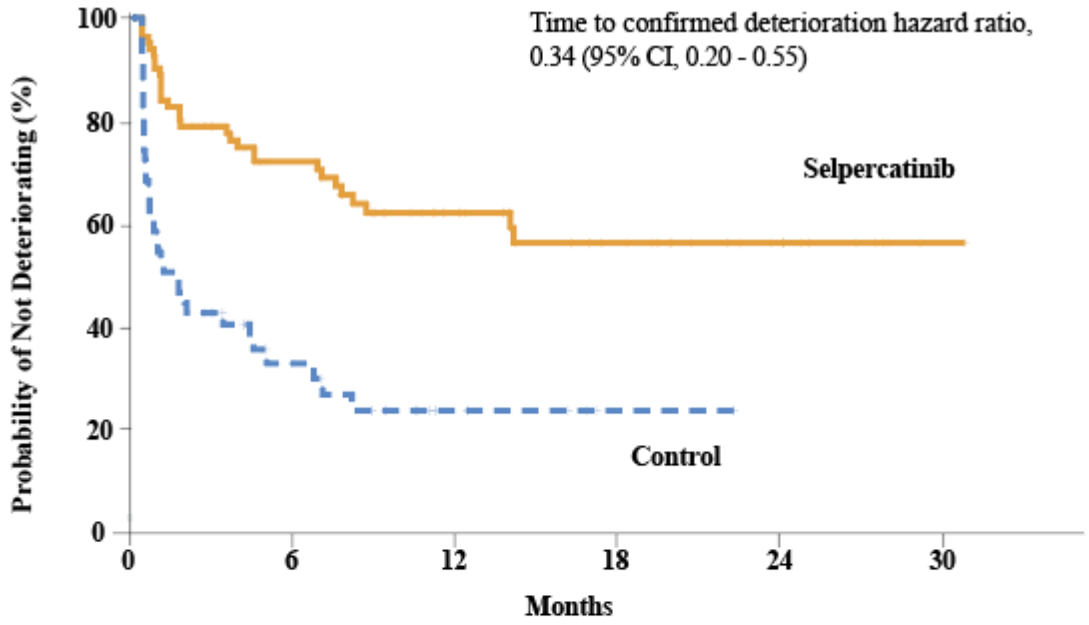





Shown are Kaplan-Meier estimates of cumulative incidence rates for the competing risks of (Panel A) CNS progressive disease, (Panel B) non-CNS progressive disease and (Panel C) death, in the CNS-pembrolizumab population.

Fig. S10. Time to Confirmed Deterioration of Pulmonary Symptoms, Measured by the NSCLC-SAQ Total Score

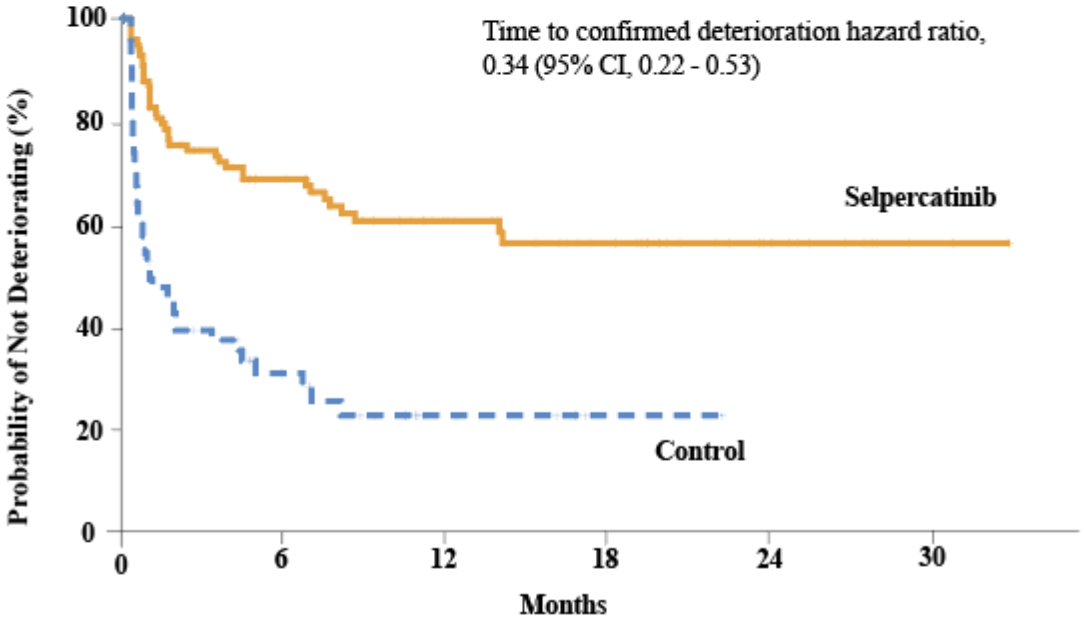
**A. Time to Confirmed Deterioriation in the ITT-pembrolizumab Population**




**No. at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Selpercatinib | 129 | 57 | 32 | 20 | 10 | 2 |
| Control | 83 | 16 | 6 | 2 | 0 | 0 |

**B. Time to Confirmed Deterioriation in the ITT Population**




**No. at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Selpercatinib | 159 | 68 | 40 | 26 | 12 | 3 |
| Control | 102 | 17 | 6 | 2 | 0 | 0 |

Shown are Kaplan-Meier estimates for time to confirmed deterioration, assessed by the NSCLC-SAQ Total Score.

Table S1. Summary of Investigator-Assessed Outcomes [a]

| | ITT-Pembrolizumab Population | | ITT Population | |
|---|---|---|---|---|
| | **Selpercatinib n = 129** | **Control n = 83** | **Selpercatinib n = 159** | **Control n = 102** |
| **Progression-free Survival** | | | | |
| Median PFS, months (95% CI) | 24.8 (19.1, NE) | 14.0 (10.9, 22.3) | 24.8 (19.4, NE) | 13.7 (9.4, 16.8) |
| Median duration of follow-up, months (95% CI) | 19.4 (16.7, 19.7) | 18.9 (14.1, 22.3) | 19.4 (16.7, 19.6) | 16.7 (13.8, 21. 3) |
| **Objective Response Rate, % (95% CI)** | 77.5 (69.3-84.4) | 53.0 (41.7-64.1) | 78.6 (71.4-84.7) | 51.0 (40.9-61.0) |
| **Best Overall Response** | | | | |
| Complete response, n (%) | 0 (0) | 2 (2.4) | 0 (0) | 3 (2.9) |
| Partial response, n (%) | 100 (77.5) | 42 (50.6) | 125 (78.6) | 49 (48.0) |
| Stable disease, n (%) | 24 (18.6) | 30 (36.1) | 26 (16.4) | 38 (37.3) |
| Progressive disease, n (%) | 1 (0.8) | 4 (4.8) | 1 (0.6) | 6 (5.9) |
| Non-evaluable, n (%) | 4 (3.1) | 5 (6.0) | 7 (4.4) | 6 (5.9) |
| **Duration of Response** | | | | |

| | ITT-Pembrolizumab Population | | ITT Population | |
|---|---|---|---|---|
| | **Selpercatinib n = 129** | **Control n = 83** | **Selpercatinib n = 159** | **Control n = 102** |
| Responders, n | 100 | 44 | 125 | 52 |
| Censored, n (%) | 66 (51.2) | 25 (30.1) | 85 (53.5) | 29 (28.4) |
| Median, months<br>(95% CI) | NE<br>(15.4, NE) | 15.5<br>(12.4, NE) | NE<br>(18.0, NE) | 15.5<br>(11.2, NE) |
| Median Duration of Follow-up, months (95% CI) | 18.0<br>(15.1, 18.2) | 15.2<br>(12.5, 19.6) | 17.4<br>(15.2, 18.0) | 14.6<br>(11.8, 19.3) |

Percentages may not total to 100 because of rounding. Note that confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects

NE denotes could not be evaluated.

[a] Efficacy outcomes were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by blinded independent radiologic review

Table S2. Summary of CNS Progression in CNS-pembrolizumab Population

| | **Selpercatinib n = 120** | **Control n= 72** |
|---|---|---|
| CNS progression without prior non-CNS progressive disease, n (%) [a] | 8 (6.7) | 13 (18.1) |
| Non-CNS progression without prior CNS progressive disease, n (%) | 33 (27.5) | 30 (41.7) |
| Death without prior CNS or non-CNS progressive disease, n (%) | 5 (4.2) | 2 (2.8) |

[a] Includes patients who had both CNS and non-CNS PD within a 7-day window

Table S3. Intracranial Outcomes by BICR in Patients with Measurable Baseline Metastases

| | **Selpercatinib n = 17** | **Control n= 12** |
|---|---|---|
| **CNS Overall Response Rate, % (95% CI)** | 82.4<br>(56.6, 96.2) | 58.3<br>(27.7, 84.8) |
| **CNS Best Overall Response** | | |
| Complete response, n (%) | 6 (35.3) | 2 (16.7) |
| Partial response, n (%) | 8 (47.1) | 5 (41.7) |
| Stable disease, n (%) | 1 (5.9) | 3 (25.0) |
| Progressive disease, n (%) | 0 (0.0) | 1 (8.3) |
| Non-evaluable, n (%) | 2 (11.8) | 1 (8.3) |
| **CNS Duration of Response** | | |
| Responders, n (%) | 14 (82.4) | 7 (58.3) |
| Censored, n (%) | 10 (58.8) | 4 (33.3) |
| Median, months (95% CI) | NR (7.6, NE) | 13.4 (3.5, NE) |
| 12-month survival rate, % (95% CI) | 76.0 (42.2, 91.6) | 62.5 (14.2, 89.3) |

Note that confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

Abbreviations: CNS, central nervous system; NE, not able to be evaluated; NR, not reached.

Table S4. Summary of Safety

| | **Selpercatinib n = 158** | **Control n= 98** |
|---|---|---|
| Median time on treatment, months | 16.7 ± 8.3 | 9.8 ± 7.2 |
| Any AE, n (%) | 158 (100.0) | 97 (99.0) |
| AE Grade ≥3, n (%) | 111 (70.3) | 56 (57.1) |
| Any SAE, n (%) | 55 (34.8) | 23 (23.5) |
| AE leading to dose reduction, n (%) | 81 (51.3) | 28 (28.6) |
| AE leading to permanent treatment discontinuation, n (%) | 16 (10.1) | 2 (2.0) |
| SAE leading to permanent treatment discontinuation, n (%) | 8 (5.1) | 1 (1.0) |
| Fatal AE[a], n (%) | 7 (4.4) | 0 |
| Fatal AE on study treatment, n (%) | 6 (3.8) | 0 |
| Fatal AE within 30 days of the last dose, n (%) | 1 (0.6) | 0 |

Abbreviations: AE = adverse event; SAE = serious adverse event.

[a] Deaths are also included as SAEs and discontinuations due to AEs.

Table S5. Summary of Adverse Events by Region (East Asian vs. Non-East Asian)

| | Selpercatinib n = 158 | | Control n = 98 | |
|---|---|---|---|---|
| | East Asian n = 91 | Non-East Asian n = 67 | East Asian n = 49 | Non-East Asian n = 49 |
| Any AE, n (%) | 91 (100.0) | 67 (100.0) | 49 (100.0) | 48 (98.0) |
| Grade ≥3 AE, n (%) | 70 (76.9) | 41 (61.2) | 25 (51.0) | 31 (63.3) |
| Any SAE, n (%) | 35 (38.5) | 20 (29.9) | 13 (26.5) | 10 (20.4) |
| AE leading to permanent treatment discontinuation, n (%) | 11 (12.1) | 5 (7.5) | 1 (2.0) | 1 (2.0) |
| SAE leading to permanent treatment discontinuation, n (%)[a] | 4 (4.4) | 4 (6.0) | 1 (2.0) | 0 (0.0) |
| Fatal AE[a], n (%) | 2 (2.2) | 6 (9.0) | 0 (0.0) | 0 (0.0) |
| Fatal AE on study treatment, n (%) | 2 (2.2) | 5 (7.5) | 0 (0.0) | 0 (0.0) |
| Fatal AE within 30 days of the last dose, n (%) | 0 (0.0) | 1 (1.5) | 0 (0.0) | 0 (0.0) |

Abbreviations: AE = adverse event; SAE = serious adverse event.

[a] Deaths are also included as SAEs and discontinuations due to AEs.

Table S6. Summary of Fatal AEs

| Demographics<br><br>Age/Sex/Race | Study Day of Death | BICR Best Overall Response | AE (MedDRA PT) | Comorbidities/Comment |
|---|---|---|---|---|
| 70 / F / Caucasian | 5 | Not able to evaluate | Cardiac Arrest | Cardiac risk factors, including baseline pleural effusion and pericardial effusion |
| 79 / M / Caucasian | 7 | Not able to evaluate | Myocardial Infarction | Cardiac risk factors<br>Died at home with limited data |
| 59 / M / Caucasian | 46 | Not able to evaluate | Respiratory Failure | Pneumonia (ongoing at time of death), shortness of breath, hypoxemia, respiratory deterioration. Fatal outcome 6 days after Selpercatinib discontinuation |
| 74 / F / Caucasian | 60 | Not able to evaluate | Respiratory Failure | Bilateral pleural effusion and suspected carcinomatous lymphangitis. Worsening clinical condition due to PD reported by investigator. Fatal outcome 26 days after last dose of selpercatinib |
| 55 / M / Caucasian | 71 | Progressive disease | Myocardial Infarction | Metastases in the left hilar and aortopulmonary regions<br>CT showed obstruction to main pulmonary artery |

| | | | | |
|---|---|---|---|---|
| 74 / M / Asian | 238 | Stable disease | Sudden Death* | Chest pain, shortness of breath, asthenia, productive cough at baseline. Died at home with limited data |
| 77 / M / Asian | 579 | Stable disease | Malnutrition* | Sore throat, poor breathing, and loss of appetite. Family members had similar respiratory symptoms, but COVID-19 could not be tested. Died at home with limited data |

*Related to selpercatinib as assessed by the investigator. For the patient with malnutrition the investigator attribution was noted to be related as drug effect could not be ruled out

Table S7. Time to Confirmed Deterioration on Pulmonary Symptoms, Measured by the NSCLC-SAQ Total Score

| | ITT-pembrolizumab population | ITT population |
|---|---|---|

| | Selpercatinib (n=129) | Control (n=83) | Selpercatinib (n=159) | Control (n=102) |
|---|---|---|---|---|
| Patients with event, n (%) | 30 (23.3%) | 36 (43.4%) | 38 (23.9%) | 44 (43.1%) |
| Censored due to missing PRO data, n (%) | 39 (30.2%) | 27 (32.5%) | 50 (31.4%) | 34 (33.3%) |
| 25-percentile of time to event, months (95% CI) | 4.4 (1.7, 13.9) | 0.4 (0.3, 0.7) | 3.5 (1.2, 8.1) | 0.4 (0.3, 0.6) |
| Median Time to event, months (95% CI) ‡ | NE | 1.9 (0.7, 6.6) | NE | 1.6 (0.7, 4.9) |
| Proportion Not Deteriorated (%) | | | | |
| 6 weeks | 84.3% | 55.4% | 82.5% | 52.8% |
| 12 weeks | 80.9% | 48.2% | 76.8% | 45.3% |
| 24 weeks | 74.8% | 39.3% | 71.8% | 37.7% |

| | | | | |
|---|---|---|---|---|
| 48 weeks | 65.8% | 31.1% | 64.5% | 30.3% |

Note that confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. NE denotes could not be evaluated.

*Includes patients with no PRO data, baseline PRO missing, or baseline only.

Abbreviations: NE, not able to be evaluated