

# Real-World Treatments and Clinical Outcomes in Advanced NSCLC without Actionable Mutations after Introduction of Immunotherapy in Japan

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## Supplemental Methods

The full definition and censoring rules for rwPFS2 were as follows:

- Real-world progression-free survival on next line therapy (rwPFS2) was defined as the time from first dose of first-line (1L) treatment to documented (earliest of clinical or radiological) disease progression while on next-line treatment, i.e., second-line (2L) therapy, or death due to any cause, whichever occurred first. Patients without documented disease progression or death were censored for rwPFS2 on the last day of follow-up or last assessment date. The last day of follow-up or last assessment date was operationalized as last known activity. Patients who did not receive 2L therapy or who stopped 2L therapy without progressive disease and did not start third-line (3L) therapy were (a) counted as an event at the time of death if the patient died, or (b) censored at the time of last known survival if the patient was alive. Patients who stopped 2L therapy with progressive disease were counted as an event at the time of progression, and patients who stopped 2L therapy without progression and started 3L therapy were counted as an event at the start of 3L therapy."

**Table S1.** First-line therapy regimens by PD-L1 expression and tumor histology.

| PD-L1 TPS     | Platinum Doublet              |                            | ICI Monotherapy               |                            | Nonplatinum Cytotoxic        |                           |
|---------------|-------------------------------|----------------------------|-------------------------------|----------------------------|------------------------------|---------------------------|
|               | Nonsquamous<br><i>n</i> = 391 | Squamous<br><i>n</i> = 191 | Nonsquamous<br><i>n</i> = 275 | Squamous<br><i>n</i> = 132 | Nonsquamous<br><i>n</i> = 46 | Squamous<br><i>n</i> = 44 |
| ≥50%          | 33 (8.4)                      | 29 (15.2)                  | 272 (98.9)                    | 127 (96.2)                 | 3 (6.5)                      | 1 (2.3)                   |
| 1–49%         | 172 (44.0)                    | 99 (51.8)                  | 3 (1.1)                       | 5 (3.8)                    | 24 (52.2)                    | 31 (70.5)                 |
| <1%           | 181 (46.3)                    | 63 (33.0)                  | 0                             | 0                          | 19 (41.3)                    | 12 (27.3)                 |
| Not evaluable | 5 (1.3)                       | 0                          | 0                             | 0                          | 0                            | 0                         |

1L, first-line; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

**Table S2.** Baseline characteristics of patients included in outcome analyses.

| Characteristic                               | All Patients<br><i>n</i> = 1182 | First-Line Regimen         |                                   |                              |
|--|---------------------------------|----------------------------|-----------------------------------|------------------------------|
|  |                                 | Platinum<br><i>n</i> = 635 | ICI Monotherapy<br><i>n</i> = 452 | Nonplatinum<br><i>n</i> = 95 |
| <b>Men</b>                                   | 954 (80.7)                      | 522 (82.2)                 | 353 (78.1)                        | 79 (83.2)                    |
| <b>Age</b>                                   |                                 |                            |                                   |                              |
| Median (range)                               | 70 (27–92)                      | 69 (27–83)                 | 70 (30–89)                        | 80 (45–92)                   |
| <75 years old                                | 834 (70.6)                      | 504 (79.4)                 | 311 (68.8)                        | 19 (20.0)                    |
| ≥75 years old                                | 348 (29.4)                      | 131 (20.6)                 | 141 (31.2)                        | 76 (80.0)                    |
| <b>Smoking status, <i>n</i> <sup>a</sup></b> | 1158                            | 618                        | 446                               | 94                           |
| Current smoker                               | 178 (15.4)                      | 106 (17.2)                 | 66 (14.8)                         | 6 (6.4)                      |
| Former smoker                                | 866 (74.8)                      | 461 (74.6)                 | 332 (74.4)                        | 73 (77.7)                    |
| Never smoker                                 | 114 (9.8)                       | 51 (8.3)                   | 48 (10.8)                         | 15 (16.0)                    |
| <b>ECOG PS</b>                               |                                 |                            |                                   |                              |
| PS 0–1                                       | 648 (54.8)                      | 366 (57.6)                 | 242 (53.5)                        | 40 (42.1)                    |
| PS 2   | 93 (7.9)                        | 38 (6.0)                   | 38 (8.4)                          | 17 (17.9)                    |
| PS unknown                                   | 441 (37.3)                      | 231 (36.4)                 | 172 (38.1)                        | 38 (40.0)                    |

|  |            |            |            |           |
|--|------------|------------|------------|-----------|
| <b>Advanced NSCLC at diagnosis</b>           | 945 (79.9) | 506 (79.7) | 362 (80.1) | 77 (81.1) |
| <b>NSCLC histology, <i>n</i><sup>a</sup></b> | 1130       | 609        | 430        | 91        |
| Nonsquamous                                  | 698 (61.8) | 383 (62.9) | 270 (62.8) | 45 (49.5) |
| Squamous                                     | 360 (31.9) | 188 (30.9) | 129 (30.0) | 43 (47.3) |
| Other  | 72 (6.4)   | 38 (6.2)   | 31 (7.2)   | 3 (3.3)   |
| <b>Brain metastasis</b>                      | 194 (16.4) | 96 (15.1)  | 92 (20.4)  | 6 (6.3)   |
| Pretreated <sup>b</sup>                      | 126 (64.9) | 56 (58.3)  | 66 (71.7)  | 4 (66.7)  |
| <b>Liver metastasis</b>                      | 96 (8.1)   | 50 (7.9)   | 36 (8.0)   | 10 (10.5) |
| <b>Bone metastasis</b>                       | 296 (25.0) | 162 (25.5) | 120 (26.5) | 14 (14.7) |
| <b>History of lung surgery</b>               | 203 (17.2) | 121 (19.1) | 67 (14.8)  | 15 (15.8) |
| <b>Prior radiation therapy</b>               | 94 (8.0)   | 45 (7.1)   | 41 (9.1)   | 8 (8.4)   |
| <b>Prior chemoradiation</b>                  | 38 (3.2)   | 18 (2.8)   | 18 (4.0)   | 2 (2.1)   |

Data are *n* (%) unless otherwise indicated. Percentages may not add up to 100% because of rounding. <sup>a</sup> Percentages are of known totals. <sup>b</sup> Brain metastases treated before initiation of first-line therapy. ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor.

**Table S3.** Real-world treatment outcomes for first-line regimens.

|  | <b>Platinum</b><br><i>n</i> = 635 | <b>ICI Monotherapy</b><br><i>n</i> = 452 | <b>Nonplatinum</b><br><i>n</i> = 95 |
|--|-----------------------------------|--|-------------------------------------|
| <b>First-line rwToT, <i>n</i></b>                | 635                               | 452                                      | 95                                  |
| Events, <i>n</i> (%)                             | 599 (94.3)                        | 428 (94.7)                               | 87 (91.6)                           |
| Censored, <i>n</i> (%)                           | 36 (5.7)                          | 24 (5.3)                                 | 8 (8.4)                             |
| Median rwToT (95% CI), mo                        | 3.0 (2.8–3.3)                     | 5.5 (4.4–6.7)                            | 2.2 (1.2–3.2)                       |
| <b>On-treatment rate, % (95% CI)<sup>a</sup></b> |                                   |  |                                     |
| At 6 months                                      | 18.6 (15.6–21.9)                  | 48.8 (44.0–53.5)                         | 17.7 (10.5–26.4)                    |
| At 12 months                                     | 5.9 (4.2–8.0)                     | 25.6 (21.5–29.8)                         | 3.5 (0.9–9.1)                       |
| At 18 months                                     | 1.2 (0.5–2.3)                     | 12.1 (9.2–15.4)                          | 2.4 (0.5–7.4)                       |
| <b>rwTTNT, <i>n</i></b>                          | 634                               | 452                                      | 95                                  |
| Events, <i>n</i> (%)                             | 404 (63.7)                        | 167 (36.9)                               | 44 (46.3)                           |
| Censored, <i>n</i> (%)                           | 230 (36.3)                        | 285 (63.1)                               | 51 (53.7)                           |
| Median rwTTNT (95% CI), mo                       | 6.3 (5.9–6.9)                     | 18.3 (14.0–NR)                           | 6.7 (4.3–9.4)                       |
| <b>rwTTNT rate, % (95% CI)<sup>a</sup></b>       |                                   |  |                                     |
| At 6 months                                      | 53.6 (49.3–57.7)                  | 77.2 (72.6–81.1)                         | 53.2 (40.9–64.0)                    |
| At 12 months                                     | 25.1 (21.2–29.3)                  | 58.9 (53.4–63.9)                         | 33.7 (21.5–46.4)                    |
| At 24 months                                     | 13.8 (9.1–19.4)                   | 46.9 (39.3–54.2)                         | n/a                                 |

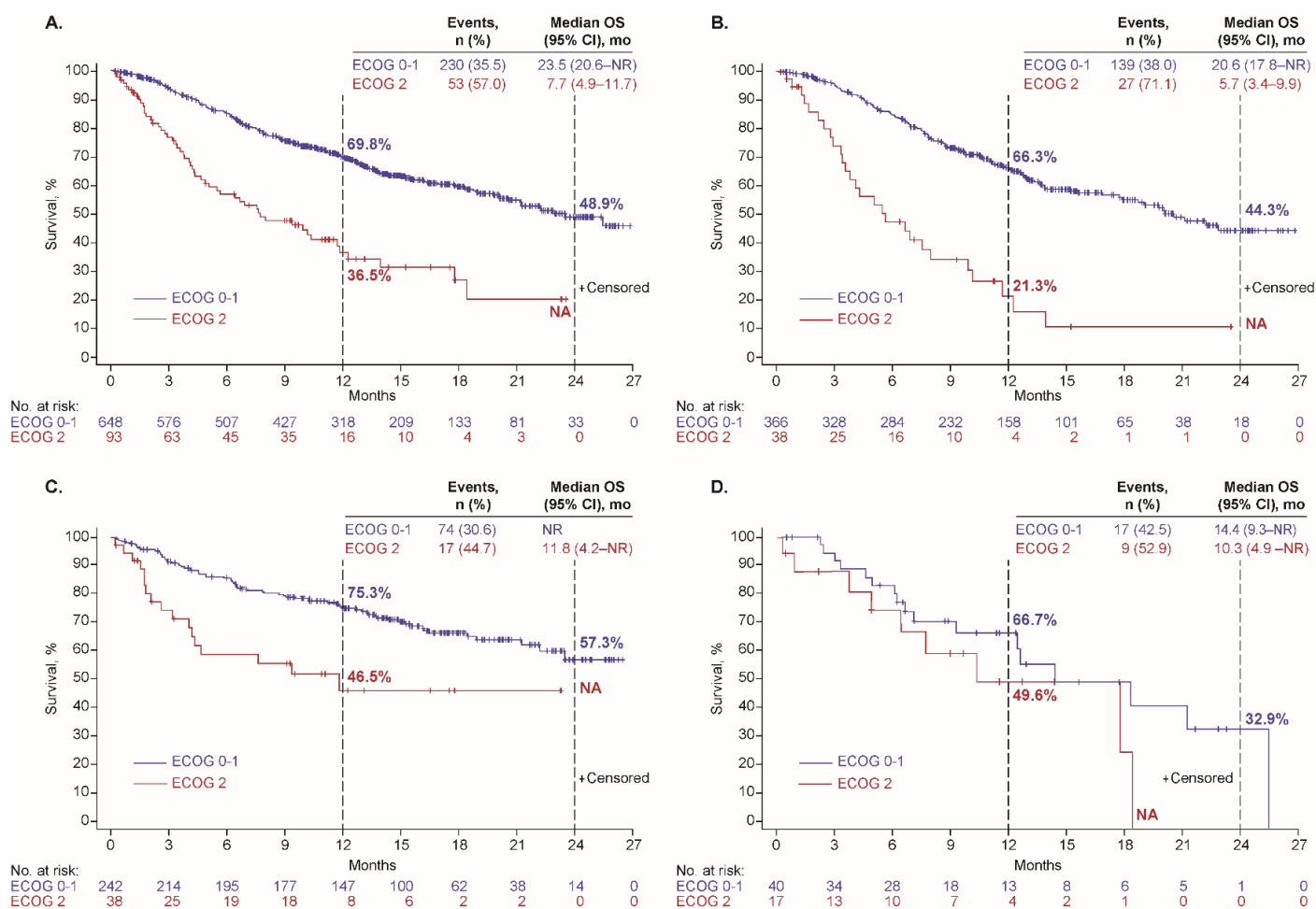
<sup>a</sup> rwTTNT was determined only by first-line regimen. The rwTTNT rate represents the percentage of patients who had not initiated a second-line regimen at 6, 12, and 24 months. n/a, not assessed; NR, not reached; rw, real-world; ToT, time on treatment; TTNT, time to next treatment.

**Table S4.** Treatment sequence overall and by tumor histology.

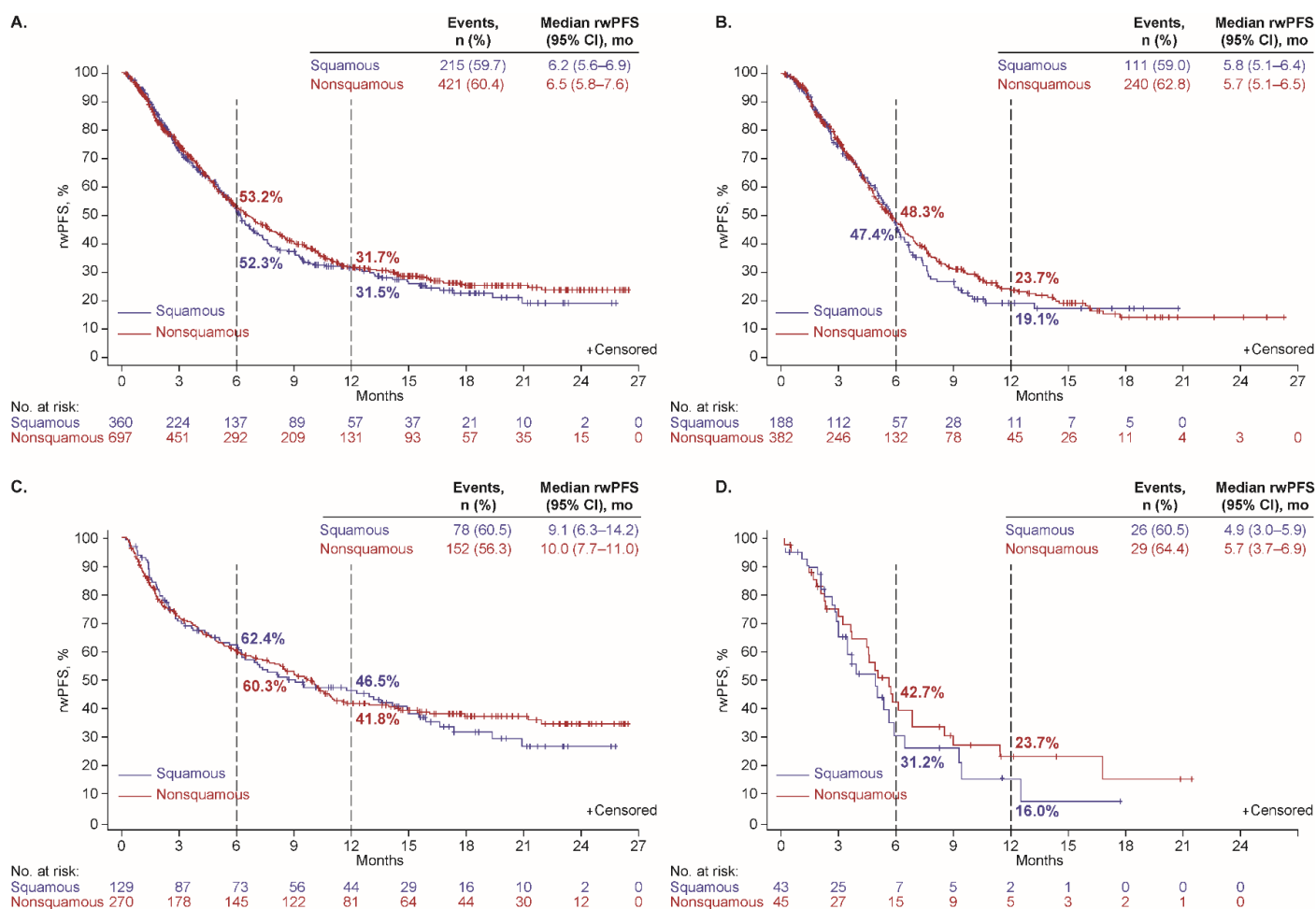
| <b>Real-World Treatment Sequence, n (%)</b>  |                   |
|--|-------------------|
| <b>All patients</b>  | <b>(n = 1182)</b> |
| 1L Platinum doublet; 2L none; 3L none  | 230 (19.5)        |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L ICI - Monotherapy                                | 6 (0.5)           |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L Nonplatinum cytotoxic agent                      | 94 (8.0)          |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L Platinum doublet                                 | 10 (0.8)          |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L none   | 149 (12.6)        |
| 1L Platinum doublet; 2L Platinum doublet; 3L ICI - Monotherapy                                 | 15 (1.3)          |
| 1L Platinum doublet; 2L Platinum doublet; 3L Nonplatinum cytotoxic agent                       | 9 (0.8)           |
| 1L Platinum doublet; 2L Platinum doublet; 3L Other   | 1 (0.1)           |
| 1L Platinum doublet; 2L Platinum doublet; 3L none  | 12 (1.0)          |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L ICI - Monotherapy                      | 38 (3.2)          |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L Nonplatinum cytotoxic agent            | 16 (1.4)          |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L Platinum doublet                       | 1 (0.1)           |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L none                                   | 53 (4.5)          |
| 1L Platinum doublet; 2L Tyrosine Kinase Inhibitors; 3L none                                    | 1 (0.1)           |
| 1L ICI - Monotherapy; 2L none; 3L none   | 285 (24.1)        |
| 1L ICI - Monotherapy; 2L ICI - Monotherapy; 3L Nonplatinum cytotoxic agent                     | 1 (0.1)           |
| 1L ICI - Monotherapy; 2L ICI - Monotherapy; 3L none  | 2 (0.2)           |
| 1L ICI - Monotherapy; 2L ICI - Combination with chemotherapy; 3L none                          | 1 (0.1)           |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L ICI - Monotherapy                                | 10 (0.8)          |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Nonplatinum cytotoxic agent                      | 42 (3.6)          |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Other  | 1 (0.1)           |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Platinum doublet                                 | 6 (0.5)           |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Tyrosine Kinase Inhibitors                       | 2 (0.2)           |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L none   | 65 (5.5)          |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L ICI - Monotherapy                     | 4 (0.3)           |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L Nonplatinum cytotoxic agent           | 10 (0.8)          |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L Platinum doublet                      | 1 (0.1)           |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L none                                  | 21 (1.8)          |
| 1L ICI - Monotherapy; 2L Other; 3L none  | 1 (0.1)           |
| 1L Nonplatinum cytotoxic agent; 2L none; 3L none   | 51 (4.3)          |
| 1L Nonplatinum cytotoxic agent; 2L ICI - Monotherapy; 3L ICI - Monotherapy                     | 1 (0.1)           |
| 1L Nonplatinum cytotoxic agent; 2L ICI - Monotherapy; 3L Nonplatinum cytotoxic agent           | 6 (0.5)           |
| 1L Nonplatinum cytotoxic agent; 2L ICI - Monotherapy; 3L none                                  | 23 (1.9)          |
| 1L Nonplatinum cytotoxic agent; 2L Nonplatinum cytotoxic agent; 3L ICI - Monotherapy           | 1 (0.1)           |
| 1L Nonplatinum cytotoxic agent; 2L Nonplatinum cytotoxic agent; 3L Nonplatinum cytotoxic agent | 3 (0.3)           |
| 1L Nonplatinum cytotoxic agent; 2L Nonplatinum cytotoxic agent; 3L none                        | 10 (0.8)          |
| <b>Nonsquamous histology</b>   | <b>(n = 698)</b>  |
| 1L Platinum doublet; 2L none; 3L none  | 146 (20.9)        |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L ICI - Monotherapy                                | 2 (0.3)           |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L Nonplatinum cytotoxic agent                      | 55 (7.9)          |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L Platinum doublet                                 | 4 (0.6)           |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L none   | 81 (11.6)         |
| 1L Platinum doublet; 2L Platinum doublet; 3L ICI - Monotherapy                                 | 7 (1.0)           |
| 1L Platinum doublet; 2L Platinum doublet; 3L Nonplatinum cytotoxic agent                       | 8 (1.1)           |
| 1L Platinum doublet; 2L Platinum doublet; 3L Other   | 1 (0.1)           |
| 1L Platinum doublet; 2L Platinum doublet; 3L none  | 6 (0.9)           |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L ICI - Monotherapy                      | 30 (4.3)          |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L Nonplatinum cytotoxic agent            | 9 (1.3)           |

|  |            |
|--|------------|
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L none                                   | 33 (4.7)   |
| 1L Platinum doublet; 2L Tyrosine Kinase Inhibitors; 3L none                                    | 1 (0.1)    |
| 1L ICI - Monotherapy; 2L none; 3L none   | 167 (23.9) |
| 1L ICI - Monotherapy; 2L ICI - Monotherapy; 3L Nonplatinum cytotoxic agent                     | 1 (0.1)    |
| 1L ICI - Monotherapy; 2L ICI - Monotherapy; 3L none  | 1 (0.1)    |
| 1L ICI - Monotherapy; 2L ICI - Combination with chemotherapy; 3L none                          | 1 (0.1)    |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L ICI - Monotherapy                                | 7 (1.0)    |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Nonplatinum cytotoxic agent                      | 28 (4.0)   |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Other  | 1 (0.1)    |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Platinum doublet                                 | 5 (0.7)    |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Tyrosine Kinase Inhibitors                       | 2 (0.3)    |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L none   | 39 (5.6)   |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L ICI - Monotherapy                     | 3 (0.4)    |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L Nonplatinum cytotoxic agent           | 6 (0.9)    |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L Platinum doublet                      | 1 (0.1)    |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L none                                  | 7 (1.0)    |
| 1L ICI - Monotherapy; 2L Other; 3L none  | 1 (0.1)    |
| 1L Nonplatinum cytotoxic agent; 2L none; 3L none   | 26 (3.7)   |
| 1L Nonplatinum cytotoxic agent; 2L ICI - Monotherapy; 3L Nonplatinum cytotoxic agent           | 4 (0.6)    |
| 1L Nonplatinum cytotoxic agent; 2L ICI - Monotherapy; 3L none                                  | 9 (1.3)    |
| 1L Nonplatinum cytotoxic agent; 2L Nonplatinum cytotoxic agent; 3L ICI - Monotherapy           | 1 (0.1)    |
| 1L Nonplatinum cytotoxic agent; 2L Nonplatinum cytotoxic agent; 3L none                        | 5 (0.7)    |
| <b>Squamous histology (n = 360)</b>  |            |
| 1L Platinum doublet; 2L none; 3L none  | 66 (18.3)  |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L ICI - Monotherapy                                | 4 (1.1)    |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L Nonplatinum cytotoxic agent                      | 29 (8.1)   |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L Platinum doublet                                 | 5 (1.4)    |
| 1L Platinum doublet; 2L ICI - Monotherapy; 3L none   | 50 (13.9)  |
| 1L Platinum doublet; 2L Platinum doublet; 3L ICI - Monotherapy                                 | 7 (1.9)    |
| 1L Platinum doublet; 2L Platinum doublet; 3L none  | 3 (0.8)    |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L ICI - Monotherapy                      | 6 (1.7)    |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L Nonplatinum cytotoxic agent            | 4 (1.1)    |
| 1L Platinum doublet; 2L Nonplatinum cytotoxic agent; 3L none                                   | 14 (3.9)   |
| 1L ICI - Monotherapy; 2L none; 3L none   | 80 (22.2)  |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L ICI - Monotherapy                                | 2 (0.6)    |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L Nonplatinum cytotoxic agent                      | 11 (3.1)   |
| 1L ICI - Monotherapy; 2L Platinum doublet; 3L none   | 20 (5.6)   |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L ICI - Monotherapy                     | 1 (0.3)    |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L Nonplatinum cytotoxic agent           | 3 (0.8)    |
| 1L ICI - Monotherapy; 2L Nonplatinum cytotoxic agent; 3L none                                  | 12 (3.3)   |
| 1L Nonplatinum cytotoxic agent; 2L none; 3L none   | 21 (5.8)   |
| 1L Nonplatinum cytotoxic agent; 2L ICI - Monotherapy; 3L ICI - Monotherapy                     | 1 (0.3)    |
| 1L Nonplatinum cytotoxic agent; 2L ICI - Monotherapy; 3L Nonplatinum cytotoxic agent           | 2 (0.6)    |
| 1L Nonplatinum cytotoxic agent; 2L ICI - Monotherapy; 3L none                                  | 12 (3.3)   |
| 1L Nonplatinum cytotoxic agent; 2L Nonplatinum cytotoxic agent; 3L Nonplatinum cytotoxic agent | 2 (0.6)    |
| 1L Nonplatinum cytotoxic agent; 2L Nonplatinum cytotoxic agent; 3L none                        | 5 (1.4)    |

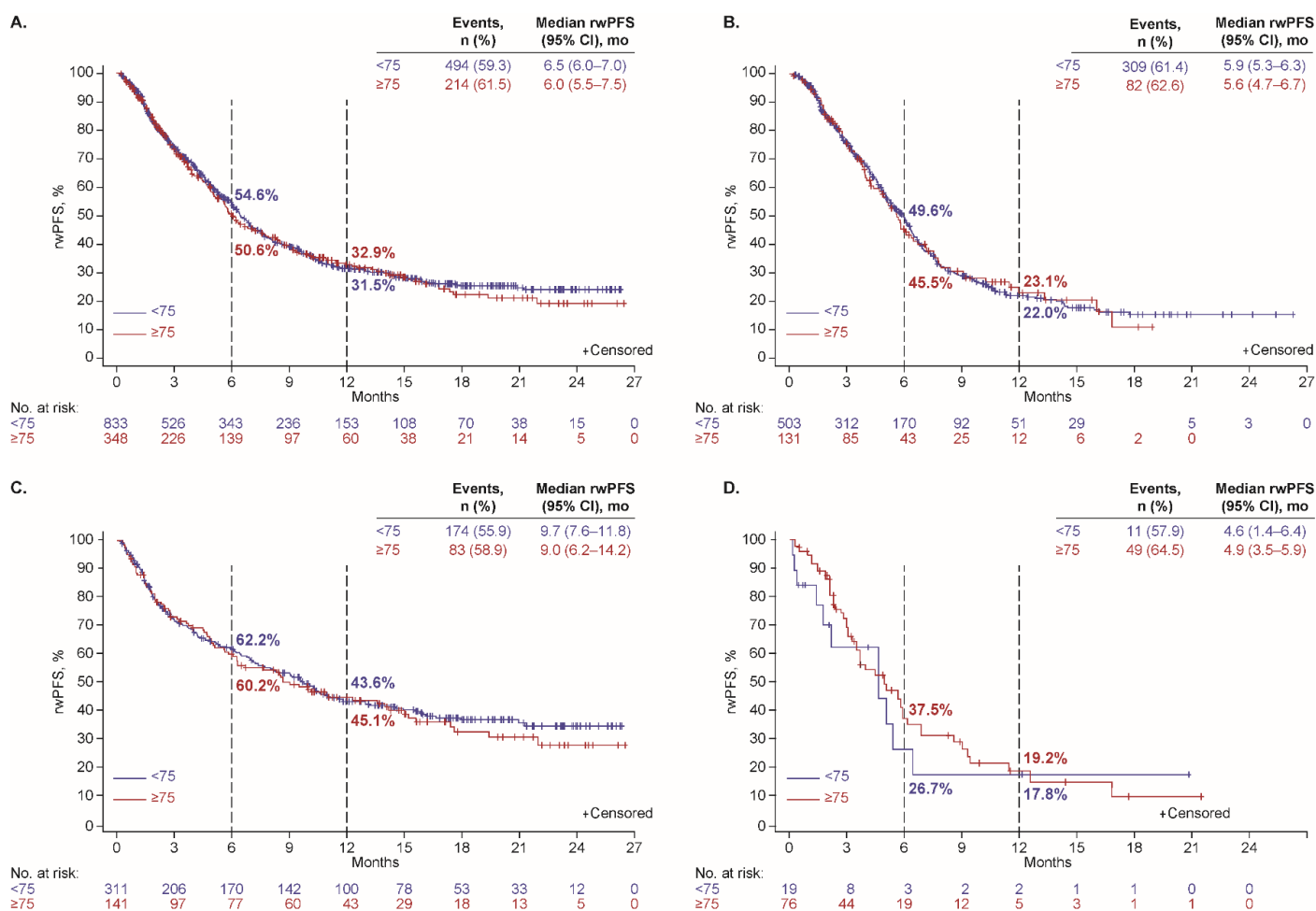
1L, 2L, 3L, first-, second-, third-line therapy; ICI, immune checkpoint inhibitor.



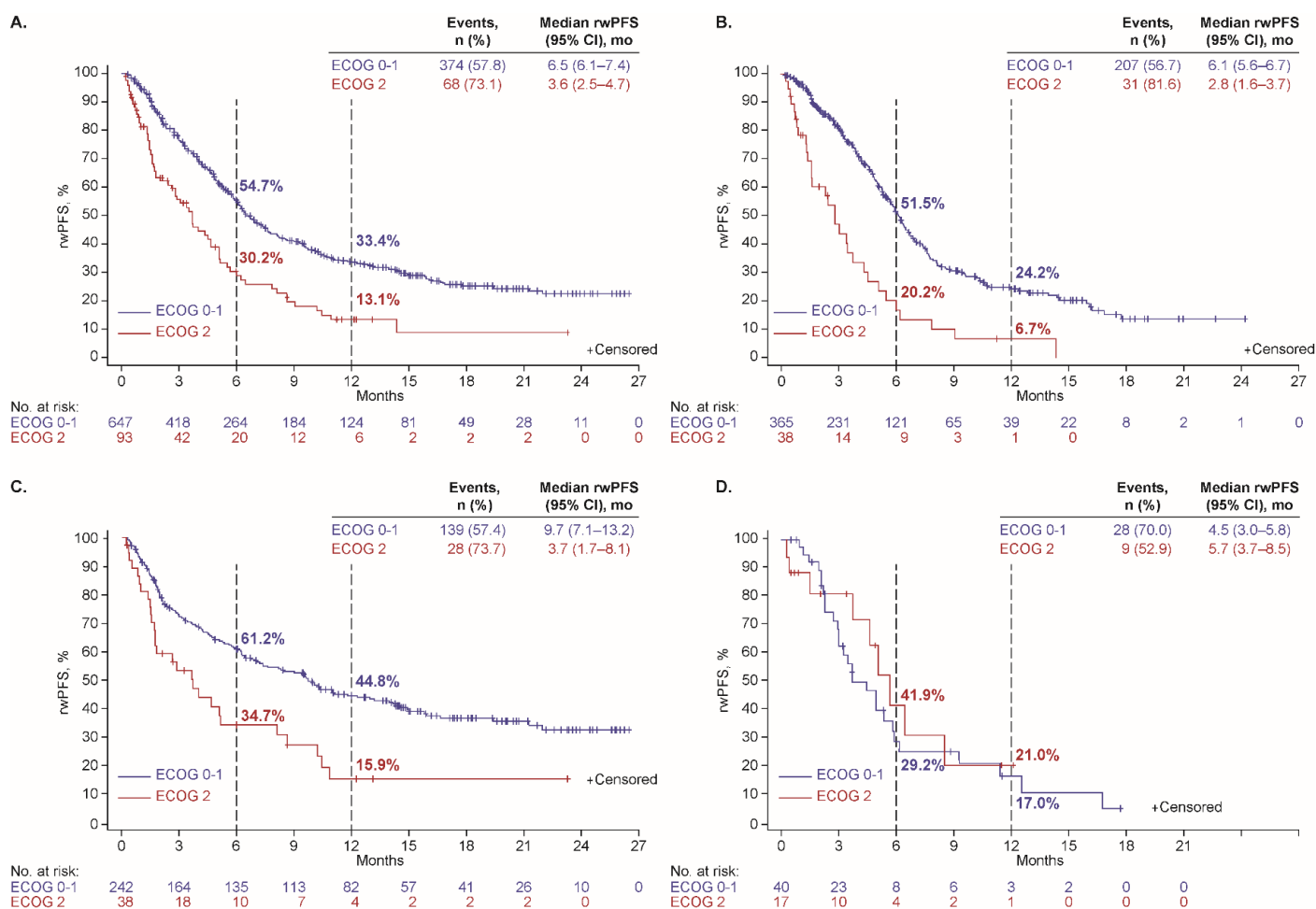
**Figure S1.** Overall survival by ECOG performance status among patients who received first-line therapy (A) overall and with (B) platinum doublet, (C) ICI monotherapy, and (D) nonplatinum cytotoxic regimen.



**Figure S2.** Real-world progression-free survival (rwPFS) by tumor histology among patients who received first-line therapy (A) overall and with (B) platinum doublet, (C) ICI monotherapy, and (D) nonplatinum cytotoxic regimen.

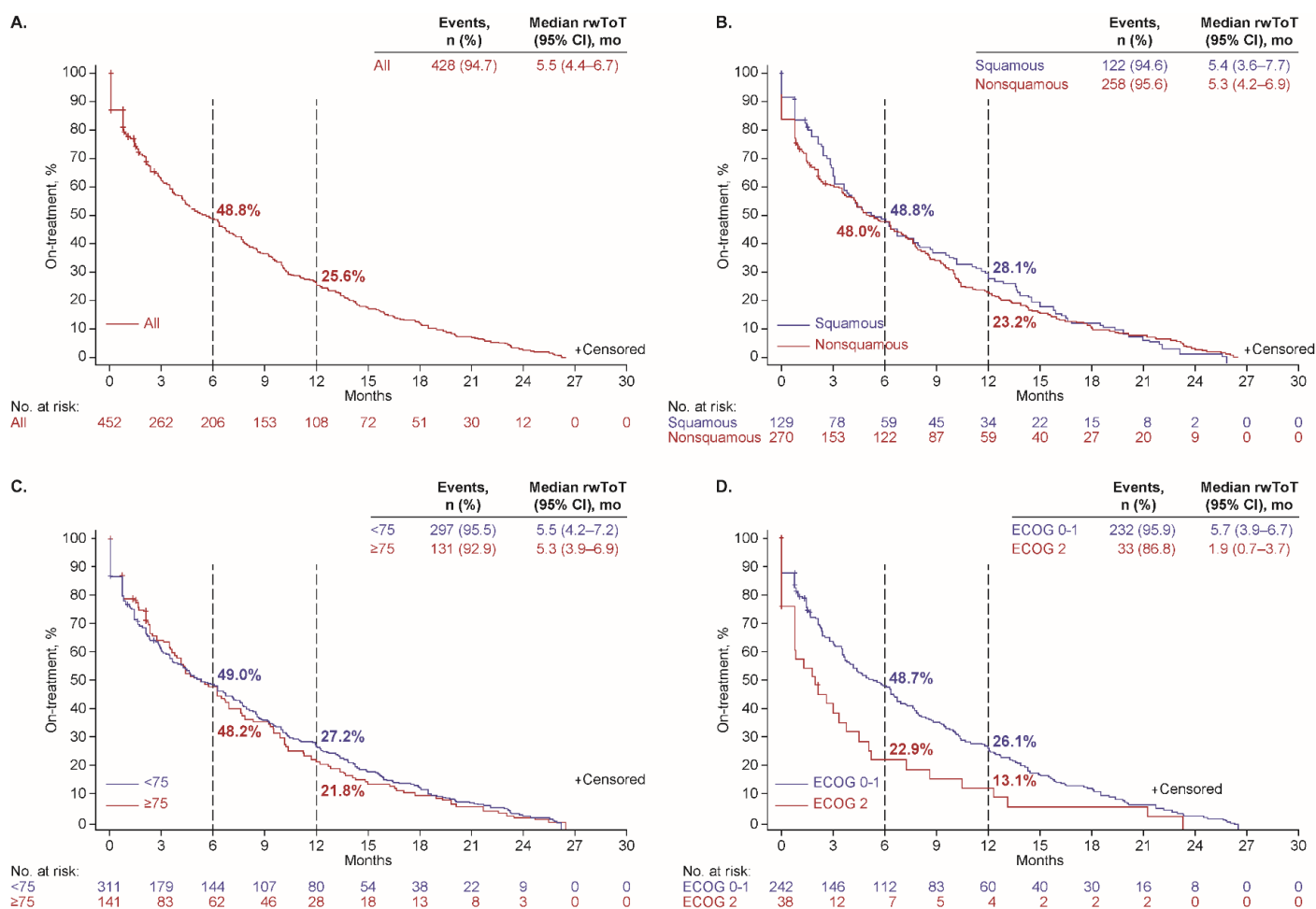


**Figure S3.** Real-world progression-free survival (rwPFS) by age group among patients who received first-line therapy (A) overall and with (B) platinum doublet, (C) ICI monotherapy, and (D) nonplatinum cytotoxic regimen.



**Figure S4.** Real-world progression-free survival (rwPFS) by ECOG PS among patients who received first-line therapy (A) overall and with (B) platinum doublet, (C) ICI monotherapy, and (D) nonplatinum cytotoxic regimen.





**Figure S5.** Real-world time on treatment for patients who received first-line ICI monotherapy (A) overall; (B) by histology, (C) by age group, and (D) by ECOG PS.