cancers

# Supplementary Materials: Is There an Interplay between Immune Checkpoint Inhibitors, Thromboprophylactic Treatments and Thromboembolic Events? Mechanisms and Impact in Non-Small Cell Lung Cancer Patients

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**Table S1.** Baseline laboratory values in the whole case series and according to the presence or absence of TE events.

| Characteristic | Overall *n* = 217 | Without TE *n* = 187 | With TE *n* = 30 |
|---|---|---|---|
| LDH | | | |
| Normal | 163 (75.1) | 140 (74.9) | 23 (76.7) |
| > 480 U/L § | 42 (19.4) | 35 (18.7) | 7 (23.3) |
| Leucocytes | | | |
| ≥11 × $10^9$/L | 45 (20.7) | 39 (20.9) | 6 (20.0) |
| <11 × $10^9$/L | 170 (78.3) | 146 (78.1) | 24 (80) |
| Neutrophils, median (range) | 5400 (1100–51600) | 5500 (1100–51600) | 5350 (2600–15600) |
| >8 × $10^9$/L § | 171 (79.5) | 147 (78.6) | 24 (80.0) |
| ≤8 × $10^9$/L | 44 (20.5) | 38 (20.3) | 6 (20.0) |
| Lymphocytes, median (range) | 1400 (100–7600) | 1300 (100–3800) | 1600 (200–7600) |
| Hemoglobin | | | |
| ≥10 g/dl | 200 (92.2) | 171 (91.4) | 29 (96.7) |
| <10 g/dl | 15 (6.9) | 14 (7.5) | 1 (3.3) |
| Platelets | | | |
| ≥ 350 × $10^9$/L | 62 (28.6) | 53 (28.3) | 9 (30.0) |
| < 350 × $10^9$/L | 153 (70.5) | 132 (70.6) | 21 (70.0) |
| PLR, median (range) | 201 (27–1390) | 262 (53–1390) | 219 (27–760) |
| >181 | 126 (58.1) | 117 (62.6) | 9 (30.0) |
| ≤181 | 89 (41.0) | 68 (36.4) | 21 (70.0) |
| NLR, median (range) | 3.9 (0.6–38.7) | 4.1 (0.6–38.7) | 3.2 (1.0–33.0) |
| >3.2 | 141 (65.0) | 127 (67.9) | 14 (46.7) |
| ≤3.2 | 74 (34.1) | 58 (31.0) | 16 (53.3) |
| Khorana Score¶ | | | |
| 1 | 122 (56.2) | 105 (56.1) | 17 (56.7) |
| 2 | 57 (26.3) | 49 (26.2) | 8 (26.7) |
| ≥3 | 35 (16.1) | 30 (16.0) | 5 (16.7) |
| LIPI | | | |
| Low | 60 (27.6) | 47 (25.1) | 13 (43.3) |
| Intermediate | 12 (51.6) | 99 (52.9) | 13 (43.3) |
| High | 33 (15.2) | 29 (15.5) | 4 (13.3) |

All blood tests were performed at INT. Data for blood cell count was not available for 2 pts. Cut-offs for hemoglobin and platelets counts were chosen according to the Khorana Score. The following parameters were calculated as follows: (a) NLR by dividing neutrophil by lymphocyte counts; (b) PLR by dividing platelet by lymphocyte counts; (c) LIPI based on NLR greater than 3 and LDH greater than institutional laboratory ULN;.(d) Khorana Score based on: lung cancer (1 point); baseline leukocyte count ≥11 × 109/L (1 point), platelet count ≥ 350 × 109/L (1 point), hemoglobin < 10 g/dL (1 point), and BMI ≥ 35kg/$m^2$ (1 point). Receiver operating characteristic (ROC) curves were used to set

the optimal threshold for NLR and PLR according to the occurrence of a TE. § reference ULN for internal laboratory. Data for LDH was not available for 12 pts. data was missing for 3 patients. Abbreviations: LDH: Lactate Dehydrogenase; LIPI: Lung Immune Prognostic Index; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; TE: thromboembolic events; ULN: upper limit of normal.

**Table S2.** Characteristics of Thromboembolic Events occurred during treatment with Immune-Checkpoint Inhibitors.

| Patient | TE Event-Free Time (Months) | N° of Administered Cycles | Type of TE Event |
|---|---|---|---|
| 1 | 1.4 | 2 | PE |
| 2 | 1.3 | 2 | Portal vein thrombosis |
| 3 | 1.2 | 3 | Upper limb DVT |
| 4 | 1.3 | 3 | Cerebrovascular accident |
| 5 | 1.4 | 3 | Cerebrovascular accident |
| 6 | 1.9 | 4 | PE |
| 7 | 2.6 | 4 | Thrombosis of the abdominal aorta |
| 8 | 2.5 | 5 | Acute coronary syndrome |
| 9 | 2.0 | 5 | Thrombosis of the abdominal aorta |
| 10 | 10.4 | 6 | Jugular vein thrombosis |
| 11 | 2.1 | 6 | Lower limb DVT + PE + iliac vein thrombosis |
| 12 | 7.8 | 9 | Lower limb DVT + PE |
| 13 | 6.3 | 9 | Cerebrovascular accident |
| 14 | 7.5 | 10 | Thrombosis of the abdominal aorta |
| 15 | 7.6 | 12 | PE |
| 16 | 5.8 | 12 | Lower limb DVT + PE + Upper limb DVT |
| 17 | 5.3 | 12 | Lower limb DVT |
| 18 | 10.1 | 13 | Upper limb DVT |
| 19 | 9.7 | 19 | Cerebrovascular accident |
| 20 | 18.5 | 20 | Cerebrovascular accident |
| 21 | 10.2 | 20 | PE |
| 22 | 13.6 | 21 | PE |
| 23 | 18.3 | 26 | Lower limb DVT |
| 24 | 14.0 | 27 | Portal vein thrombosis |
| 25 | 6.5 | 30 | Cerebrovascular accident |
| 26 | 20.8 | 39 | Acute coronary syndrome |
| 27 | 23.8 | 43 | PE |
| 28 | 31.4 | 66 | Cerebrovascular accident |
| 29 | 31.2 | 67 | Cerebrovascular accident |
| 30 | 33.7 | 71 | Cerebrovascular accident |
| TE-EFT | 7.5 | 1.2–33.6 | |
| Arterial | 7.0 | 1.3–33.6 | |
| Venous | 7.7 | 1.2–23.7 | Log-Rank $p = 0.59$ |

Abbreviations: PE: pulmonary embolism; DVT: deep vein thrombosis; TE-EFT: thromboembolic event-free time.

**Table S3.** Use of anticoagulant treatment according to patients' baseline ECOG PS.

| Anticoagulant Treatment | ECOG PS 0–1 | ECOG PS ≥ 2 | *p* |
|---|---|---|---|
| No | 159 (80.3) | 11 (57.9) | **0.05** |
| Yes | 39 (19.7) | 8 (42.1) | |

Data are presented as n (%). The *p* value of the $\chi^2$ test is indicated in the right column of the table. Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance status.

**Table S4.** Baseline patients' characteristics in the whole case series and according to antiplatelet use.

| Characteristic | Overall n = 217 | Antiplatelet Non-Users n = 148 | Antiplatelet Users n = 69 | *p* |
|---|---|---|---|---|
| Sex | | | | |
| Male | 136 (62.7) | 84 (56.8) | 52 (75.4) | **0.012** |
| Age, median (range), y | 70 (32–90) | 67 (32–88) | 74 (58–90) | **<0.001** |
| ≤65 | 77 (35.5) | 69 (46.6) | 8 (11.6) | |
| >65 | 140 (64.5) | 79 (53.4) | 61 (88.4) | **<0.001** |
| Comorbidities | | | | |
| Arterial hypertension | 44 (20.3) | 26 (17.6) | 18 (26.1) | 0.20 |
| COPD | 25 (11.5) | 13 (8.8) | 12 (17.4) | 0.11 |
| Diabetes Mellitus | 21 (9.7) | 7 (4.7) | 14 (20.3) | **0.001** |
| Previous ACS | 18 (8.3) | 2 (1.4) | 16 (23.2 | **<0.001** |
| Previous Stroke | 9 (4.1) | 3 (2.0) | 6 (8.7) | **0.05** |
| Atrial Fibrillation | 10 (4.6) | 6 (4.1) | 4 (5.8) | 0.68 |
| Previous venous TE events | 37 (17.7) | 19 (12.8) | 18 (26.1) | **0.03** |
| Use of LMWH | 47 (21.7) | 40 (27) | 7 (10.1) | **0.001** |

The *p* value is indicated in bold numbers when statistically significant. Data are presented as *n* (%) except where otherwise noted. The *p* value of the $\chi^2$ and MWW test assessing the association between each characteristic and ASA use is indicated in the right column of the table. The *p* value of the test is indicated in bold numbers when statistically significant. Abbreviations: ACS: acute coronary syndrome; LMWH: Low Molecular Weight Heparin; TE events: thromboembolic events

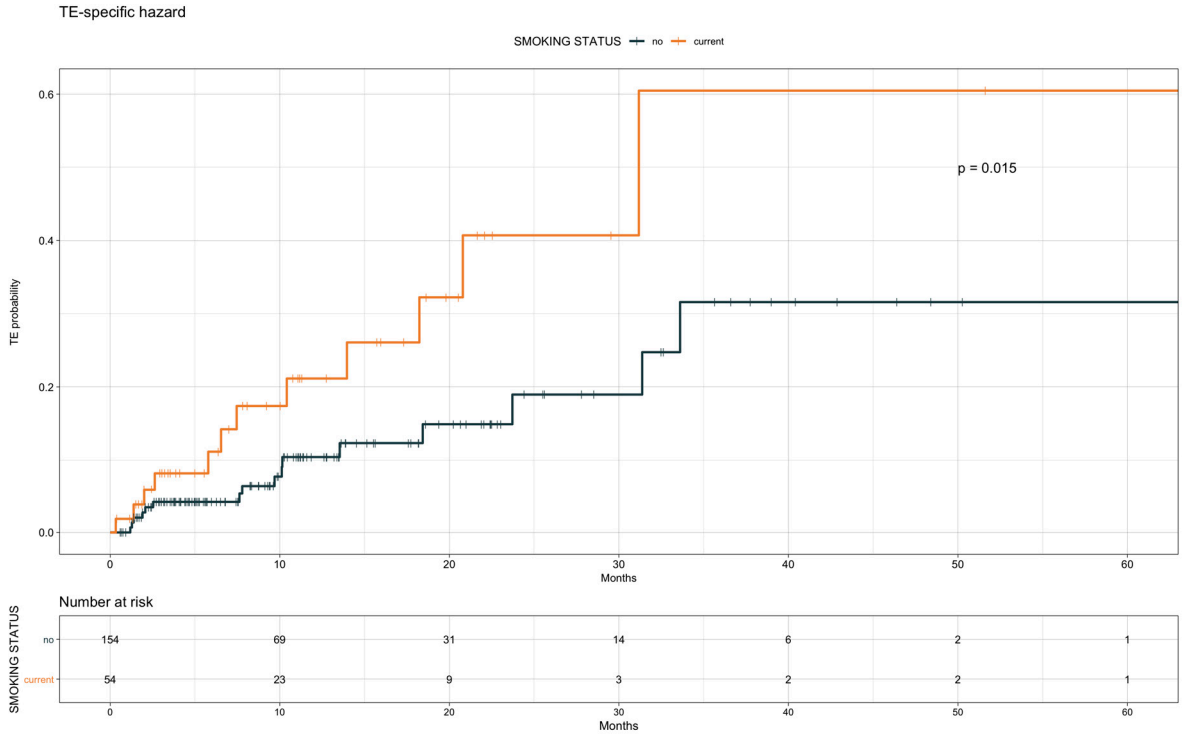


**Figure S1.** TE-specific hazard according to smoking status.

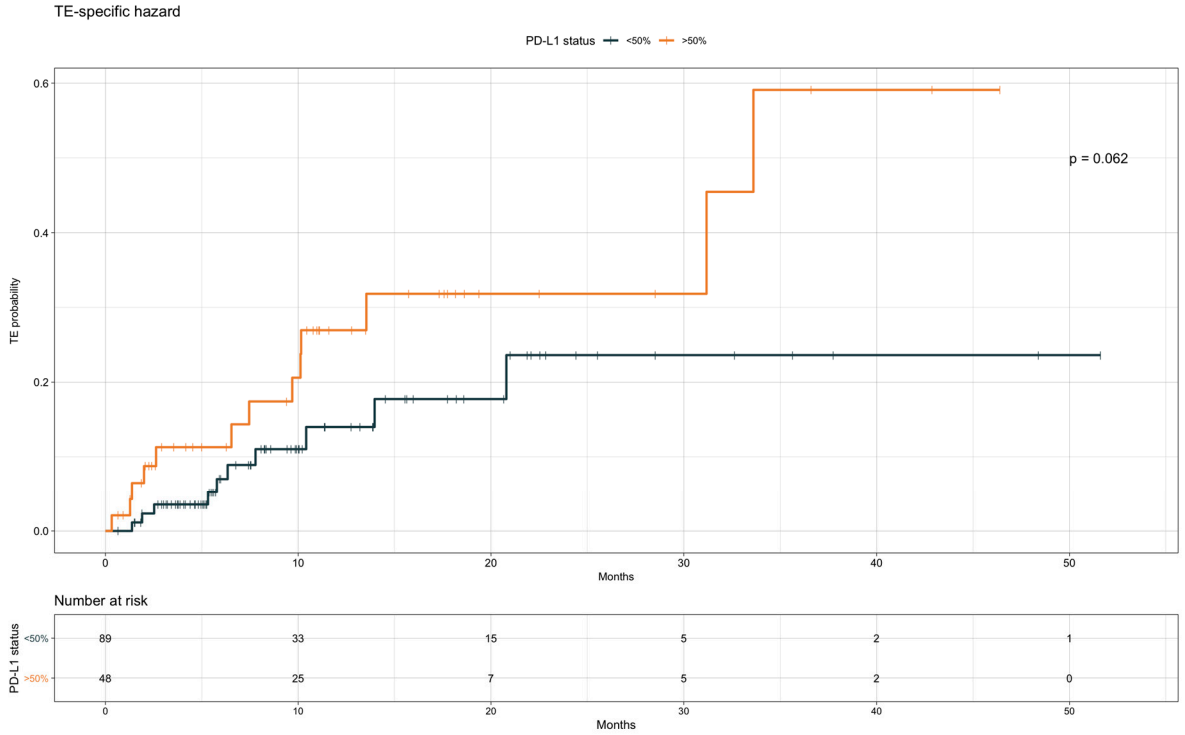


**Figure S2.** TE-specific hazard according to PD-L1 status.

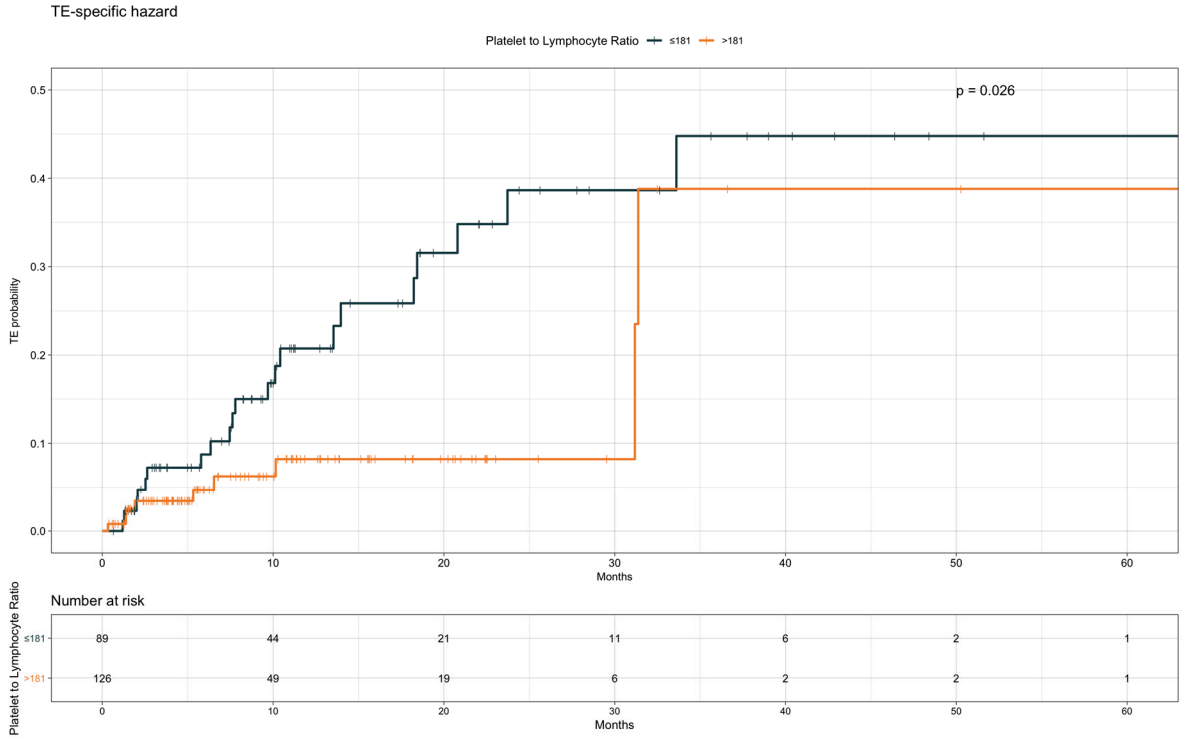


**Figure S3.** TE-specific hazard according to Platelet to Lymphocyte Ratio (PLR).

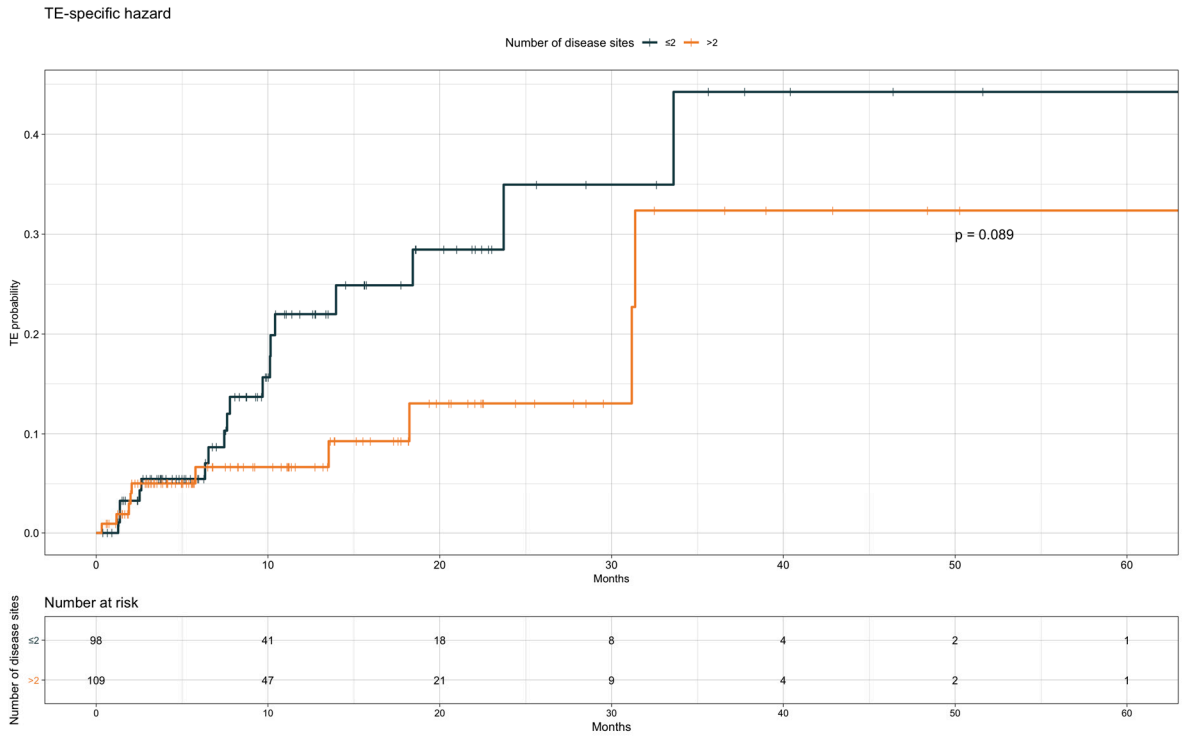


**Figure S4.** TE-specific hazard according to number of disease sites.

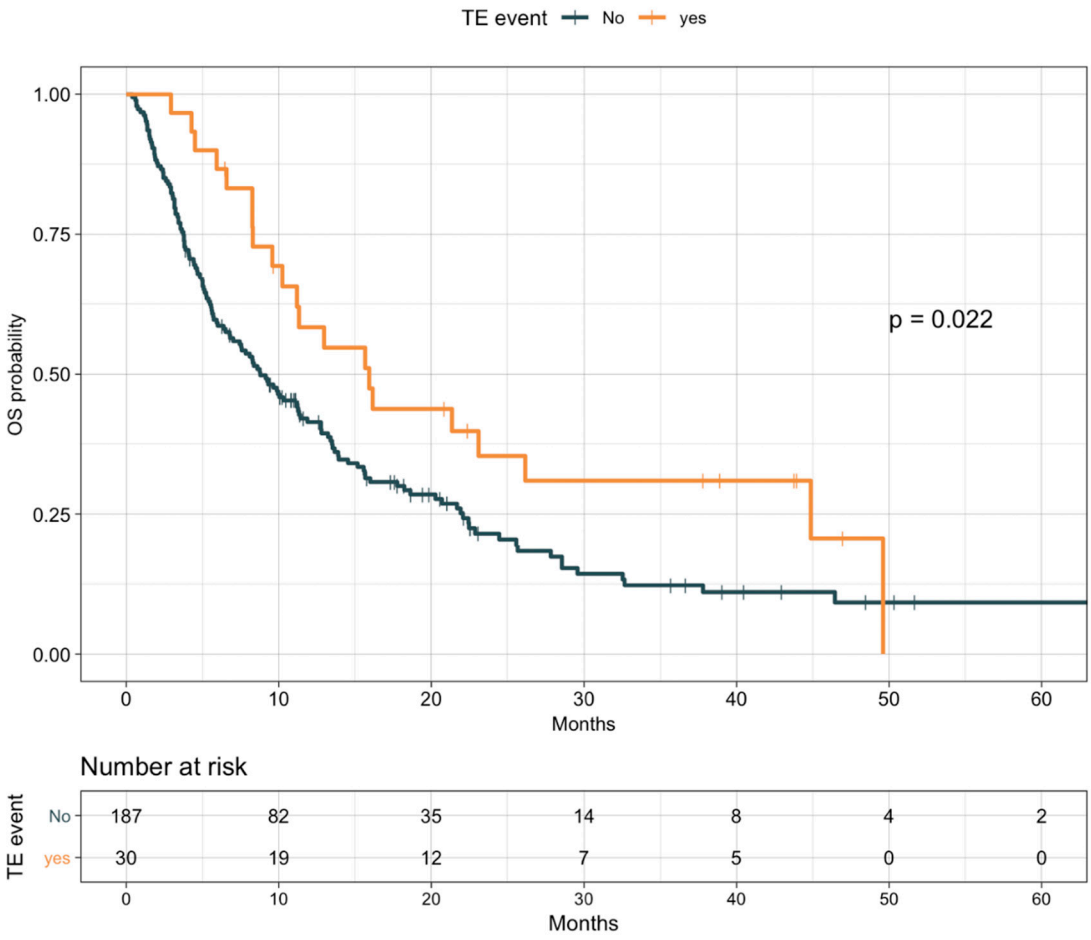


**Figure S5.** Overall Survival Among Patients with or without TE Events considered as a time-independent variable.

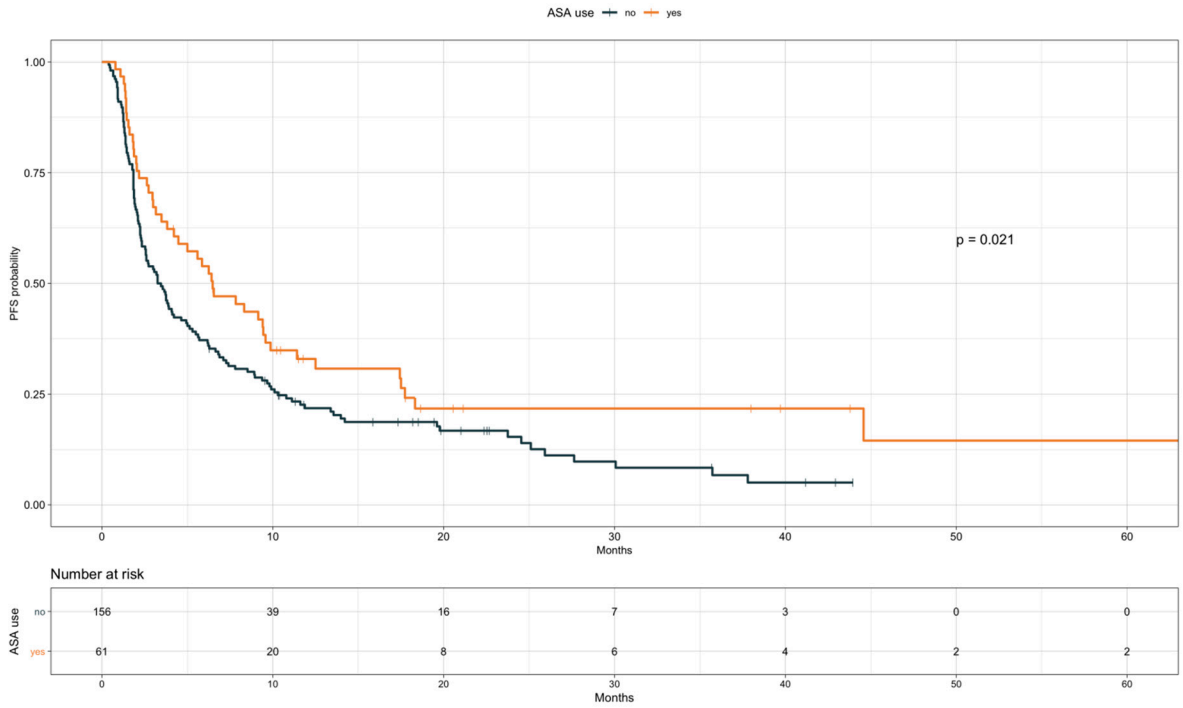


**Figure S6.** Progression Free Survival according to Aspirin (ASA) treatment.