**Supplementary Material**

**Table S1:** Demographics and clinical characteristics of patients with NSCLC treated with nivolumab in 2L+ in ESME-AMLC and CRISP cohort over time (i.e., by year of nivolumab start)

| | | ESME-AMLC | | | | | CRISP | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 2015 | 2016 | 2017 | 2018 | 2019 | 2016 | 2017 | 2018 | 2019 |
| Cohort size | N | 186 | 695 | 856 | 460 | 65 | 42 | 167 | 214 | 93 |
| Age (years) | Median | 61.3 | 63.5 | 63.4 | 64.2 | 67.1 | 64.5 | 65.0 | 65.0 | 67.0 |
| | Q1–Q3 | 54.9–67.4 | 56.7–69.3 | 57.0–69.8 | 58.0–71.3 | 59.0–72.0 | 61.0–74.0 | 59.0–74.0 | 59.0–72.0 | 62.0–74.0 |
| | Range | 27.8–83.9 | 33.3–91.8 | 32.1–89.5 | 36.1–89.3 | 44.7–85.4 | 42.0–82.0 | 41.0–86.0 | 45.0–86.0 | 46.0–88.0 |
| Sex | Male | 134 (72.0) | 503 (72.4) | 571 (66.7) | 304 (66.1) | 48 (73.8) | 23 (54.8) | 107 (64.1) | 135 (63.1) | 60 (64.5) |
| ECOG PS | 0–1 | 84 (45.2) | 313 (45.0) | 372 (43.4) | 211 (45.9) | 34 (52.3) | 22 (52.4) | 91 (54.5) | 122 (57.0) | 56 (60.2) |
| | 2 | 20 (10.7) | 61 (8.8) | 106 (12.4) | 52 (11.3) | 8 (17.4) | 9 (21.4) | 37 (22.2) | 33 (15.4) | 12 (12.9) |
| | 3–4 | 8 (4.3) | 19 (2.7) | 33 (3.8) | 17 (3.7) | <5 | <5 | <5 | <5 | 0 |
| | Missing | 74 (39.8) | 302 (43.4) | 345 (40.3) | 180 (39.1) | 19 (29.2) | 9 (21.4) | 35 (21.0) | 55 (25.7) | 25 (26.9) |
| Histology | Adenocarcinoma | 99 (53.2) | 432 (62.2) | 549 (64.1) | 324 (70.4) | 50 (76.9) | 25 (59.5) | 114 (68.3) | 155 (72.4) | 58 (62.4) |
| | Large cell carcinoma | <5 | 19 (2.7) | 13 (1.5) | 11 (2.4) | <5 | <5 | 5 (3.0) | <5 | <5 |
| | Undifferentiated carcinoma | 7 (3.8) | 15 (2.2) | 22 (2.6) | 5 (1.1) | 0 | NR | NR | NR | NR |
| | Squamous | 63 (33.9) | 184 (26.5) | 213 (24.9) | 95 (20.7) | 12 (18.5) | 14 (33.3) | 40 (24.0) | 48 (22.4) | 30 (32.3) |
| | Others | 14 (7.5) | 45 (6.5) | 59 (6.9) | 25 (5.4) | <5 | <5 | 8 (4.8) | 10 (4.7) | <5 |
| At least one metastasis | | 169 (90.9) | 638 (91.8) | 775 (90.5) | 412 (89.6) | 58 (89.2) | 42 (100.0) | 163 (97.6) | 204 (95.3) | 92 (98.9) |
| Metastases locations | Bone metastases | 91 (48.9) | 305 (43.9) | 366 (42.8) | 198 (43.0) | 32 (49.2) | 16 (38.1) | 77 (46.1) | 100 (46.7) | 41 (44.1) |
| | Brain metastases | | | | | | 11 (26.2) | 40 (24.0) | 54 (25.2) | 20 (21.5) |
| | - Symptomatic brain met | 10 (5.4) | 57 (8.2) | 80 (9.3) | 41 (8.9) | <5 | NR | NR | NR | NR |

| Cohort size | N | ESME-AMLC | | | | | CRISP | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **2015** **186** | **2016** **695** | **2017** **856** | **2018** **460** | **2019** **65** | **2016** **42** | **2017** **167** | **2018** **214** | **2019** **93** |
| | - **Asymptomatic brain met** | 35 (18.8) | 168 (24.2) | 237 (27.7) | 133 (28.9) | 20 (30.8) | NR | NR | NR | NR |
| | **Liver metastases** | 46 (24.7) | 170 (24.5) | 193 (22.5) | 90 (19.6) | 16 (24.6) | 6 (14.3) | 44 (26.3) | 57 (26.6) | 19 (20.4) |
| **PD-L1 testing done** | **Testing done** | 18 (9.7) | 110 (15.8) | 234 (27.3) | 266 (57.8) | 50 (76.9) | 12 (28.6) | 72 (43.1) | 149 (69.6) | 74 (79.6) |
| | **Positive** | 12 (6.5) | 48 (6.9) | 114 (13.3) | 82 (17.8) | 20 (30.8) | 8 (19.0) | 34 (20.4) | 70 (32.7) | 23 (24.7) |
| | **1–49%** | 6 (3.2) | 25 (3.6) | 54 (6.3) | 57 (12.4) | 12 (18.5) | <5 | 19 (11.4) | 55 (25.7) | 16 (17.2) |
| | **≥50%** | <5 | 27 (3.9) | 55 (6.4) | 24 (5.2) | 6 (9.2) | <5 | 12 (7.2) | 11 (5.1) | <5 |
| | **Unknown expression level** | <5 | 10 (1.4) | 25 (2.9) | 15 (15.6) | 4 (18.2) | <5 | <5 | <5 | <5 |
| | **Negative** | 6 (3.2) | 48 (6.9) | 100 (11.7) | 170 (37.0) | 28 (43.1) | <5 | 38 (22.8) | 76 (35.5) | 51 (58.4) |
| | **Not done** | 168 (90.3) | 585 (84.2) | 622 (72.7) | 194 (42.2) | 15 (23.1) | 30 (71.4) | 95 (56.9) | 65 (30.4) | 19 (20.4) |
| *EGFR* | **Positive** | <5 | 16 (2.3) | 35 (4.1) | 17 (3.7) | 7 (10.8) | <5 | 6 (3.6) | 8 (3.7) | 7 (7.5) |
| *ALK* | **Positive** | <5 | 6 (0.9) | 8 (0.9) | <5 | <5 | <5 | <5 | 5 (2.3) | <5 |
| *ROS* | **Positive** | 0 (0.0) | 7 (1.0) | 5 (0.6) | <5 | 0 | 0 | <5 | <5 | <5 |
| **Time from initial diag. to starting nivolumab (months)** | **Median** | 6.3 | 9.3 | 9.8 | 12.0 | 12.2 | 6.1 | 7.1 | 7.2 | 11.3 |
| | **Q1–Q3** | 4.8–8.4 | 6.4–13.3 | 6.0–16.7 | 7.5–21.5 | 8.3–22.3 | 3.8–9.0 | 4.8–10.5 | 5.0–11.3 | 7.6–15.9 |
| **Line of nivolumab treatment** | **2L** | 140 (75.3) | 460 (66.2) | 568 (66.4) | 308 (67.0) | 40 (61.5) | 35 (83.3) | 145 (86.8) | 178 (83.2) | 73 (78.5) |
| | **3L** | 42 (22.6) | 167 (24.0) | 218 (25.5) | 111 (24.1) | 16 (24.6) | 7 (16.7) | 22 (13.2) | 28 (13.1) | 16 (17.2) |
| | **4L** | <5 | 49 (7.1) | 54 (6.3) | 28 (6.1) | 7 (10.8) | 0 | 0 | 5 (2.3) | <5 |
| | **5L+** | <5 | 19 (2.7) | 16 (1.9) | 13 (2.8) | <5 | 0 | 0 | <5 | 0 |
| **Previous regimens** | **Platinum (PT)-based chemotherapy (CT)** | 159 (85.5) | 616 (88.6) | 784 (91.6) | 430 (93.5) | 63 (96.9) | 37 (88.1) | 161 (96.4) | 205 (95.8) | 84 (90.3) |

| | | ESME-AMLC | | | | | CRISP | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **2015** | **2016** | **2017** | **2018** | **2019** | **2016** | **2017** | **2018** | **2019** |
| **Cohort size** | **N** | **186** | **695** | **856** | **460** | **65** | **42** | **167** | **214** | **93** |
| received (all) | **Non-PT based CT** | 33 (17.7) | 165 (23.7) | 195 (22.8) | 101 (22.0) | 12 (18.5) | 5 (11.9) | 10 (6.0) | 16 (7.5) | 10 (10.8) |
| | **EGFR/ALK targeted therapy** | 7 (3.8) | 33 (4.7) | 51 (6.0) | 19 (4.1) | 10 (15.4) | <5 | <5 | 9 (4.2) | <5 |
| | **Immunotherapy** | 0 | 0 | <5 | <5 | <5 | <5 | <5 | 5 (2.3) | 5 (5.4) |
| | **Investigational agents** | 16 (8.6) | 74 (10.6) | 58 (6.8) | 21 (4.6) | 2 (3.1) | 0 | 0 | <5 | <5 |
| | **Other combinations** | <5 | 7 (1.0) | 6 (0.7) | 6 (1.3) | 0 | <5 | 10 (6.0) | 12 (5.6) | 6 (6.5) |
| Last LoT regimen received prior to nivolumab | **PT-based CT** | 132 (71.0) | 467 (67.2) | 599 (70.0) | 341 (74.1) | 51 (78.5) | 35 (83.3) | 144 (86.2) | 184 (86.0) | 73 (78.5) |
| | **Non-PT based CT** | 30 (16.1) | 146 (21.0) | 183 (21.4) | 92 (20.0) | 10 (15.4) | 5 (11.9) | 10 (6.0) | 14 (6.5) | 9 (9.7) |
| | **EGFR/ALK targeted therapy** | 7 (3.8) | 18 (2.6) | 31 (3.6) | 7 (1.5) | <5 | 0 | <5 | <5 | <5 |
| | **Immunotherapy** | 0 | 0 | <5 | <5 | 0 | <5 | <5 | <5 | <5 |
| | **Investigational agents** | 16 (8.6) | 60 (8.6) | 39 (4.6) | 14 (3.0) | <5 | 0 | 0 | <5 | <5 |
| | **Other combinations** | <5 | <5 | <5 | 5 (1.1) | 0 | <5 | 9 (5.4) | 12 (5.6) | 6 (6.5) |
| Time from start of previous LoT until start of nivolumab (months) | **Median** | 3.7 | 5.1 | 5.6 | 6.9 | 6.5 | 3.3 | 5.1 | 5.2 | 7.7 |
| | **Q1–Q3** | 2.3–5.7 | 2.8–8.0 | 2.9–8.9 | 3.7–11.0 | 4.5–9.2 | 2.1–5.8 | 3.0–7.7 | 3.1–7.4 | 5.2–11.8 |
| | **<3** | 70 (37.6) | 204 (29.4) | 232 (27.1) | 87 (18.9) | 13 (20.0) | 18 (42.9) | 43 (25.7) | 51 (23.8) | 8 (8.6) |
| | **≥3–<6** | 78 (41.9) | 214 (30.8) | 227 (26.5) | 116 (25.2) | 14 (21.5) | 14 (33.3) | 57 (34.1) | 78 (36.4) | 22 (23.7) |
| | **≥6–<12** | 38 (20.4) | 229 (32.9) | 274 (32.0) | 163 (35.4) | 26 (40.0) | 10 (23.8) | 56 (33.5) | 74 (34.6) | 42 (45.2) |
| | **≥12** | 0 | 48 (6.9) | 123 (14.4) | 94 (20.4) | 12 (18.5) | 0 | 11 (6.6) | 10 (4.7) | 21 (22.6) |

2L, second-line; 2L+, second-line or later; 3L, third-line; 4L, fourth-line; 5L+, fifth-line or later; *ALK*, anaplastic lymphoma kinase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; LoT, line of therapy; NR, not reported; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PT, platinum; *ROS*, c-ros oncogene.

**Table S2:** Factors associated with overall survival in patients treated with nivolumab in ESME-AMLC

| Risk factor* | | Cohort size | OS | | Univariate Cox regression | | Multivariate Cox regression | |
|---|---|---|---|---|---|---|---|---|
| | | | Median | 95% CI | HR (95% CI) | p-value | HR (95% CI) | p-value |
| **Age (years)** | | | | | | 0.16 | | 0.39 |
| | <70 | 1,709 | 12.2 | 10.7–13.9 | | | | |
| | 70−74 | 291 | 12.6 | 9.2–14.8 | 1.05 (0.88–1.25) | | 1.08 (0.90–1.29) | |
| | ≥75 | 262 | 9.7 | 7.5–12.6 | 1.18 (0.99–1.41) | | 1.12 (0.93–1.34) | |
| **Sex** | | | | | | 0.04 | | 0.04 |
| | Female | 702 | 13.9 | 11.0–16.0 | | | | |
| | Male | 1,560 | 11.2 | 10.0–12.8 | 1.14 (1.01–1.29) | | 1.15 (1.01–1.31) | |
| **ECOG PS** | | | | | | <0.01 | | <0.01 |
| | 0 | 228 | 19.8 | 17.0–27.1 | | | | |
| | 1 | 786 | 10.7 | 9.4–12.5 | 1.78 (1.43–2.22) | | 1.73 (1.38–2.15) | |
| | 2+ | 328 | 3.7 | 2.9–4.3 | 3.48 (2.74–4.42) | | 3.24 (2.55–4.12) | |
| | Missing | 920 | 15.4 | 13.2–18.0 | 1.41 (1.13–1.76) | | 1.42 (1.13–1.77) | |
| **Smoking status** | | | | | | 0.06 | | 0.07 |
| | Non-smokers | 138 | 10.7 | 8.0–17.3 | | | | |
| | Former smokers | 1,259 | 10.7 | 9.9–12.4 | 0.95 (0.75–1.20) | | 0.96 (0.76–1.22) | |
| | Current smokers | 804 | 14.7 | 11.6–16.6 | 0.82 (0.64–1.04) | | 0.82 (0.64–1.06) | |
| | Missing | 61 | 14.6 | 7.6–23.8 | 0.77 (0.50–1.19) | | 0.75 (0.48–1.15) | |
| **Number of comorbidities at inclusion** | | | | | | 0.26 | | |
| | 0 | 1,283 | 10.7 | 9.6–13.0 | | | | |
| | 1 | 691 | 13.2 | 11.6–15.4 | 0.90 (0.79–1.02) | | | |
| | 2+ | 288 | 12.1 | 9.2–14.8 | 0.99 (0.83–1.18) | | | |
| **Stage at diagnosis** | | | | | | 0.53 | | |
| | I−II | 176 | 10.9 | 8.7–15.2 | | | | |
| | III | 507 | 13.4 | 11.2–16.0 | 0.95 (0.74–1.22) | | | |
| | IV | 1,550 | 11.1 | 10.0–13.0 | 1.04 (0.83–1.31) | | | |
| | Missing | 29 | 16.6 | 3.2– NE | 0.86 (0.50–1.49) | | | |
| **PD-L1 expression** | | | | | | 0.49 | | |
| | Positive | 276 | 13.0 | 9.4–18.4 | | | | |
| | Negative | 352 | 10.8 | 8.4–15.8 | 1.14 (0.91–1.43) | | | |
| | Unknown | 1,634 | 12.0 | 10.6–13.3 | 1.06 (0.88–1.27) | | | |
| **Year of nivolumab start** | | | | | | 0.68 | | |
| | 2015 | 186 | 9.9 | 7.0–14.9 | | | | |
| | 2016 | 856 | 12.1 | 10.4–14.3 | 0.93 (0.76–1.14) | | | |
| | 2017 | 460 | 11.6 | 9.7– NE | 0.94 (0.74–1.19) | | | |
| | 2018 | 695 | 12.5 | 10.0–13.9 | 0.96 (0.79–1.18) | | | |
| | 2019 | 65 | NR | NE – NE | 0.60 (0.29–1.23) | | | |
| **Histology** | | | | | | 0.32 | | |
| | Squamous | 567 | 10.5 | 9.6–12.5 | | | | |
| | All others | 1,695 | 12.6 | 10.8–14.2 | 0.94 (0.82–1.07) | | | |
| **Metastases** | | | | | | 0.04 | | 0.05 |
| | Brain metastases | 785 | 13.0 | 11.0–15.1 | | | | |
| | Other metastases only | 1,267 | 10.5 | 9.2–12.5 | 1.12 (0.99–1.27) | | 1.07 (0.94–1.22) | |
| | No metastases | 210 | 14.5 | 12.0–17.3 | 0.89 (0.72–1.11) | | 0.84 (0.67–1.04) | |
| **Treatment line** | | | | | | 0.11 | | 0.49 |
| | 2 | 1,516 | 13.2 | 11.2–14.5 | | | | |
| | 3+ | 746 | 10.4 | 9.0–12.2 | 1.10 (0.98–1.24) | | 0.96 (0.84–1.09) | |
| **Time from start of previous LoT until start of nivolumab** | | | | | | <0.01 | | <0.01 |
| | <3 months | 606 | 7.0 | 6.0–8.3 | | | | |
| | ≥3–<6 months | 649 | 9.8 | 8.4–11.6 | 0.85 (0.74–0.98) | | 0.86 (0.75–1.00) | |
| | ≥6–<12 months | 730 | 15.4 | 14.0–18.5 | 0.60 (0.52–0.70) | | 0.61 (0.53–0.71) | |
| | ≥12 months | 277 | 23.8 | 18.0–28.0 | 0.41 (0.33–0.52) | | 0.44 (0.35–0.55) | |
| **Autoimmune disease** | | | | | | 0.58 | | |
| | No (Ref) | 2,209 | 12.1 | 10.7–13.3 | | | | |
| | Yes | 53 | 9.2 | 5.5–16.2 | 1.11 (0.77–1.60) | | | |
| ***EGFR*, *ALK* or *ROS* mutations** | | | | | | 0.56 | | |
| | No (Ref) | 2,154 | 12.2 | 10.7–13.3 | | | | |
| | Yes | 108 | 10.7 | 7.6–16.0 | 1.08 (0.83–1.40) | | | |

*Characteristics at time of nivolumab start if not specified.

*ALK*, anaplastic lymphoma kinase; BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; LoT, line of therapy; OS, overall survival; PD-L1, programmed death-ligand 1; *ROS*, c-ros oncogene.

**Table S3:** Factors associated with overall survival in patients treated with nivolumab in CRISP

| Variable* | | Cohort size | OS Median | OS 95% CI | Univariate Cox regression HR (95% CI) | p-value | Multivariate Cox regression HR (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | 0.16 | | 0.08 |
| | <70 | 328 | 7.3 | 5.4–8.5 | Reference | | Reference | |
| | 70–74 | 68 | 8.0 | 5.3–18.9 | 0.72 (0.51–1.01) | | 0.71 (0.51–1.01) | |
| | ≥75 | 126 | 7.8 | 6.1–11.4 | 0.98 (0.76–1.25) | | 1.11 (0.86–1.44) | |
| **Sex** | | | | | | 0.68 | | 0.58 |
| | Female | 195 | 8.0 | 5.8–9.9 | Reference | | Reference | |
| | Male | 327 | 7.4 | 5.8–8.9 | 0.96 (0.77–1.18) | | 0.94 (0.75–1.17) | |
| **ECOG PS** | | | | | | <0.01 | | <0.01 |
| | 0 | 68 | 11.8 | 7.9–15.3 | Reference | | Reference | |
| | 1 | 225 | 7.8 | 6.2–9.3 | 1.21 (0.86–1.71) | | 1.22 (0.86–1.73) | |
| | 2+ | 102 | 3.9 | 2.5–5.5 | 1.88 (1.29–2.75) | | 2.00 (1.36–2.94) | |
| | Missing | 127 | 7.6 | 5.3–13.2 | 1.15 (0.79–1.68) | | 1.07 (0.73–1.57) | |
| **BMI** | | | | | | 0.72 | | |
| | Underweight | 30 | 7.7 | 2.0–19.4 | Reference | | | |
| | Normal weight | 281 | 7.6 | 5.6–11.3 | 0.90 (0.57–1.42) | | | |
| | Overweight | 145 | 6.2 | 5.0–8.1 | 1.05 (0.65–1.69) | | | |
| | Obesity | 57 | 8.7 | 6.1–12.4 | 0.86 (0.51–1.47) | | | |
| | Missing | 9 | 8.8 | 1.0–NA | 0.81 (0.31–2.17) | | | |
| **Number of comorbidities at inclusion** | | | | | | 0.61 | | |
| | 0 | 192 | 7.0 | 4.9–8.7 | Reference | | | |
| | 1 | 197 | 8.1 | 6.2–10.9 | 0.89 (0.70–1.13) | | | |
| | 2+ | 133 | 7.4 | 5.4–12.0 | 0.96 (0.74–1.26) | | | |
| **Smoking status** | | | | | | 0.99 | | |
| | Non-smoker | 46 | 6.8 | 3.9–17.0 | Reference | | | |
| | Former smoker | 261 | 8.1 | 5.8–11.3 | 0.97 (0.67–1.42) | | | |
| | Current smoker | 160 | 7.2 | 5.0–8.1 | 1.01 (0.68–1.51) | | | |
| | Missing | 55 | 8.9 | 5.2–12.7 | 0.99 (0.61–1.59) | | | |
| **Stage at diagnosis** | | | | | | 0.02 | | 0.14 |
| | I–II | 18 | 27.3 | 6.9–NA | Reference | | Reference | |
| | III | 53 | 12.1 | 6.2–18.0 | 1.81 (0.80–4.07) | | 2.02 (0.88–4.62) | |
| | IV | 428 | 7.2 | 5.5–8.0 | 2.56 (1.21–5.42) | | 2.38 (1.12–5.07) | |
| | Missing | 23 | 7.2 | 4.8–11.4 | 2.78 (1.13–6.84) | | 2.19 (0.88–5.48) | |
| **PD-L1 expression** | | | | | | 0.1 | | <0.01 |
| | Positive | 136 | 10.8 | 5.8–13.3 | Reference | | Reference | |
| | Negative | 170 | 6.1 | 4.6–7.7 | 1.34 (1.01–1.78) | | 1.66 (1.24–2.23) | |
| | Unknown | 216 | 7.8 | 6.1–8.9 | 1.27 (0.98–1.66) | | 1.39 (1.06–1.82) | |
| **Year of nivolumab start** | | | | | | 0.27 | | |
| | 2016 | 42 | 10.4 | 3.4–16.1 | Reference | | | |
| | 2017 | 167 | 8.7 | 6.1–12.6 | 0.98 (0.66–1.46) | | | |
| | 2018 | 214 | 6.1 | 5.1–8.0 | 1.24 (0.84–1.83) | | | |
| | 2019/2020 | 99 | 7.6 | 6.2–11.3 | 1.05 (0.67–1.64) | | | |
| **Histology** | | | | | | 0.61 | | |
| | Squamous | 133 | 7.9 | 6.1–11.6 | Reference | | | |
| | All others | 389 | 7.4 | 5.8–8.7 | 1.06 (0.84–1.35) | | | |
| **Metastases** | | | | | | 0.06 | | 0.17 |
| | Brain metastases | 128 | 7.1 | 4.1–8.5 | Reference | | Reference | |
| | Other metastases only | 379 | 7.6 | 6.2–9.6 | 0.92 (0.72–1.18) | | 0.90 (0.70–1.17) | |
| | No metastases | 15 | 23.7 | 5.3–NA | 0.40 (0.18–0.86) | | 0.44 (0.19–1.05) | |
| **Treatment line** | | | | | | 0.64 | | |
| | 2 | 433 | 7.7 | 6.3–8.9 | Reference | | | |
| | 3+ | 89 | 6.1 | 4.1–11.3 | 1.07 (0.80–1.43) | | | |
| **Time from start of previous LoT until start of nivolumab** | | | | | | <0.01 | | <0.01 |
| | <3 months | 121 | 4.0 | 2.8–6.1 | Reference | | Reference | |
| | ≥3–<6 months | 173 | 6.7 | 5.0–7.9 | 0.79 (0.60–1.03) | | 0.75 (0.57–1.00) | |
| | ≥6–<12 months | 183 | 10.9 | 7.7–13.4 | 0.60 (0.45–0.78) | | 0.57 (0.43–0.75) | |
| | ≥12 months | 44 | 12.8 | 6.2–19.7 | 0.48 (0.30–0.75) | | 0.48 (0.30–0.77) | |

*Characteristics at time of nivolumab start if not specified.
BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; LoT, line of therapy; OS, overall survival; PD-L1, programmed death-ligand 1.

**Table S4:** Factors associated with treatment duration in patients treated with nivolumab in ESME-AMLC

| Risk factor* | Cohort size | Treatment duration | | Univariable Cox regression | | Multivariable Cox regression | |
|---|---|---|---|---|---|---|---|
| | | Median | 95% CI | HR (95% CI) | p-value | HR (95% CI) | p-value |
| **Age (years)** | | | | | 0.54 | | 0.67 |
| <70 | 1,709 | 2.6 | 2.3–2.8 | | | | |
| 70–74 | 291 | 2.9 | 2.4–3.4 | 1.07 (0.94–1.23) | | 1.06 (0.92–1.21) | |
| ≥75 | 262 | 2.4 | 2.1–3.1 | 1.05 (0.91–1.21) | | 0.98 (0.84–1.14) | |
| **Sex** | | | | | 0.76 | | 0.55 |
| Female | 702 | 2.5 | 2.3–2.8 | | | | |
| Male | 1560 | 2.7 | 2.4–2.9 | 1.02 (0.92–1.12) | | 1.03 (0.93–1.14) | |
| **ECOG PS** | | | | | <0.01 | | <0.01 |
| 0 | 228 | 3.7 | 2.8–4.7 | | | | |
| 1 | 786 | 2.6 | 2.3–2.9 | 1.21 (1.03–1.42) | | 1.18 (1.00–1.39) | |
| 2+ | 328 | 1.4 | 1.3–1.8 | 1.94 (1.61–2.33) | | 1.87 (1.55–2.25) | |
| Missing | 920 | 3.0 | 2.8–3.3 | 1.11 (0.95–1.30) | | 1.12 (0.95–1.31) | |
| **Smoking status** | | | | | 0.06 | | 0.16 |
| Non-smokers | 138 | 2.0 | 1.6–2.4 | | | | |
| Former smokers | 1,259 | 2.6 | 2.3–2.8 | 0.86 (0.71–1.04) | | 0.98 (0.80–1.20) | |
| Smokers | 804 | 2.8 | 2.5–3.2 | 0.78 (0.64–0.95) | | 0.88 (0.71–1.09) | |
| Missing | 61 | 2.6 | 1.9–4.0 | 0.78 (0.55–1.10) | | 0.84 (0.60–1.19) | |
| **Number of comorbidities at inclusion** | | | | | 0.67 | | |
| 0 | 1,283 | 2.4 | 2.3–2.8 | | | | |
| 1 | 691 | 2.9 | 2.5–3.2 | 0.96 (0.87–1.06) | | | |
| 2+ | 288 | 2.6 | 2.3–3.2 | 1.01 (0.88–1.16) | | | |
| **Stage at diagnosis** | | | | | 0.62 | | |
| I–II | 176 | 2.8 | 2.3–3.3 | | | | |
| III | 507 | 2.8 | 2.4–3.2 | 0.96 (0.79–1.16) | | | |
| IV | 1,550 | 2.5 | 2.3–2.8 | 0.99 (0.83–1.17) | | | |
| Missing | 29 | 2.8 | 1.8–6.0 | 0.75 (0.48–1.18) | | | |
| **PD-L1 expression** | | | | | 0.04 | | 0.03 |
| Positive | 276 | 2.8 | 2.3–3.4 | | | | |
| Negative | 352 | 2.3 | 1.8–2.7 | 1.19 (1.00–1.42) | | 1.24 (1.03–1.48) | |
| Unknown | 1,634 | 2.8 | 2.5–2.9 | 1.01 (0.87–1.16) | | 1.04 (0.90–1.20) | |
| **Year of nivolumab start** | | | | | 0.10 | | 0.17 |
| 2015 | 186 | 2.2 | 1.9–2.8 | | | | |
| 2016 | 695 | 2.6 | 2.3–3.0 | 0.92 (0.78–1.09) | | 0.99 (0.83–1.17) | |
| 2017 | 856 | 2.5 | 2.3–2.8 | 0.91 (0.77–1.08) | | 1.00 (0.84–1.18) | |
| 2018 | 460 | 3.1 | 2.4–3.5 | 0.83 (0.69–1.00) | | 0.91 (0.75–1.11) | |
| 2019 | 65 | 6.2 | 2.3–NE | 0.60 (0.39–0.94) | | 0.60 (0.38–0.94) | |
| **Histology** | | | | | 0.32 | | |
| Squamous | 567 | 2.8 | 2.5–3.2 | | | | |
| All others | 1,695 | 2.5 | 2.3–2.8 | 0.95 (0.86–1.05) | | | |
| **Metastases** | | | | | 0.01 | | 0.03 |
| Brain metastases | 785 | 2.5 | 2.3–2.9 | | | | |
| Other metastases only | 1,267 | 2.5 | 2.3–2.8 | 1.10 (0.99–1.21) | | 1.07 (0.96–1.18) | |
| No metastases | 210 | 3.5 | 3.0–4.7 | 0.88 (0.74–1.05) | | 0.87 (0.73–1.03) | |
| **Treatment line** | | | | | 0.01 | | 0.43 |
| 2 | 1,516 | 2.9 | 2.6–3.1 | | | | |
| 3+ | 746 | 2.3 | 2.0–2.5 | 1.13 (1.03–1.25) | | 1.04 (0.94–1.15) | |
| **Time from start of previous LoT until start of nivolumab** | | | | | <0.01 | | <0.01 |
| <3 months | 606 | 1.9 | 1.8–2.3 | | | | |
| ≥3–<6 months | 649 | 2.3 | 1.9–2.4 | 0.95 (0.84–1.07) | | 0.99 (0.87–1.11) | |
| ≥6–<12 months | 730 | 3.1 | 2.8–3.5 | 0.77 (0.68–0.86) | | 0.80 (0.71–0.91) | |
| ≥12 months | 277 | 4.4 | 3.5–5.5 | 0.59 (0.50–0.69) | | 0.63 (0.53–0.75) | |
| **Autoimmune disease** | | | | | 0.38 | | |
| No (Ref) | 2,209 | 2.6 | 2.4–2.8 | | | | |
| Yes | 53 | 2.6 | 1.8–3.9 | 1.14 (0.85–1.53) | | | |
| ***EGFR*, *ALK* or *ROS* mutations** | | | | | <0.01 | | <0.01 |
| No (Ref) | 2154 | 2.7 | 2.5–2.9 | | | | |
| Yes | 108 | 2.0 | 1.5–2.3 | 1.48 (1.20–1.82) | | 1.50 (1.20–1.87) | |

\* Characteristics at time of nivolumab start if not specified

*ALK*, anaplastic lymphoma kinase; BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; LoT, line of therapy; PD-L1, programmed death-ligand 1; ROS, c-ros oncogene.

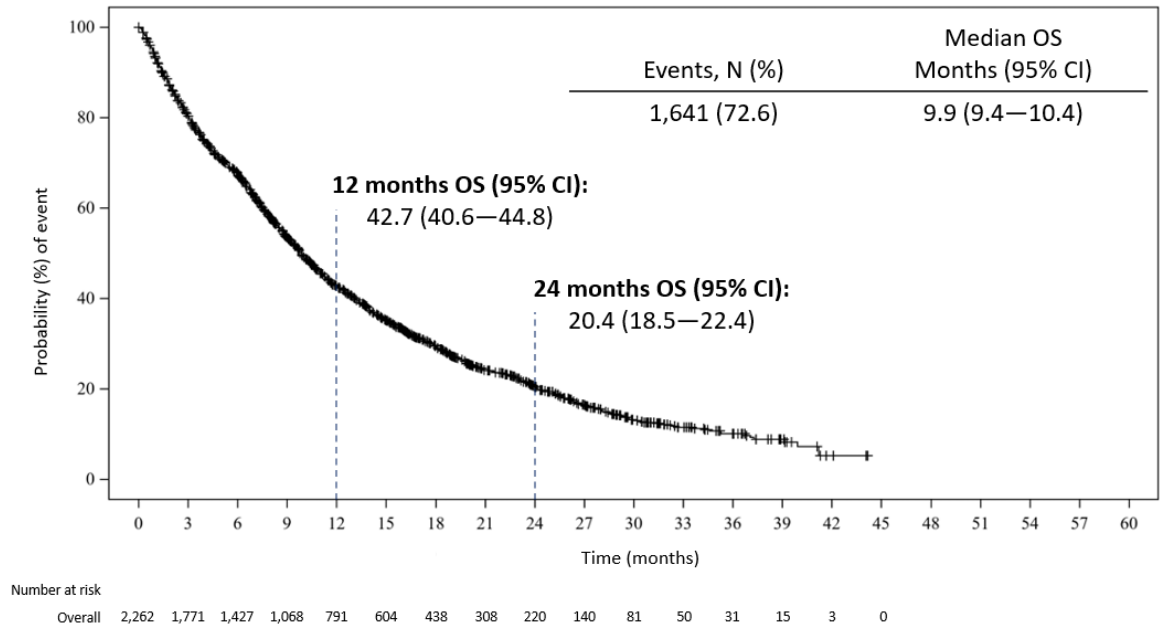**Table S5:** Factors associated with treatment duration in patients treated with nivolumab in CRISP

| Variable* | Cohort size | Treatment duration | | Univariable Cox regression | | Multivariable Cox regression | |
|---|---|---|---|---|---|---|---|
| | | Median | 95% CI | HR (95% CI) | p-value | HR (95% CI) | p-value |
| **Age (years)** | | | | | 0.63 | | 0.67 |
| <70 | 328 | 2.2 | 1.8–2.5 | Reference | | Reference | |
| 70–74 | 68 | 2.8 | 2.1–3.7 | 0.87 (0.67–1.15) | | 0.89 (0.67–1.17) | |
| ≥75 | 126 | 2.6 | 2.0–3.2 | 0.97 (0.78–1.20) | | 1.01 (0.81–1.27) | |
| **Sex** | | | | | 0.5 | | 0.29 |
| Female | 195 | 2.3 | 1.8–2.8 | Reference | | Reference | |
| Male | 327 | 2.3 | 1.9–2.8 | 0.94 (0.78–1.13) | | 0.90 (0.74–1.09) | |
| **ECOG PS** | | | | | 0.13 | | 0.03 |
| 0 | 68 | 2.8 | 2.1–3.4 | Reference | | Reference | |
| 1 | 225 | 2.3 | 2.0–2.8 | 1.04 (0.78–1.38) | | 1.02 (0.76–1.36) | |
| 2+ | 102 | 1.4 | 1.0–2.3 | 1.25 (0.91–1.72) | | 1.29 (0.93–1.79) | |
| Missing | 127 | 2.5 | 1.7–3.6 | 0.90 (0.66–1.23) | | 0.82 (0.59–1.13) | |
| **BMI** | | | | | 0.15 | | 0.29 |
| Underweight | 30 | 1.5 | 1.0–3.7 | Reference | | Reference | |
| Normal weight | 281 | 2.3 | 1.7–2.8 | 1.03 (0.69–1.53) | | 1.16 (0.77–1.76) | |
| Overweight | 145 | 2.3 | 1.9–2.8 | 1.18 (0.78–1.78) | | 1.36 (0.88–2.10) | |
| Obesity | 57 | 3.5 | 2.1–4.6 | 0.85 (0.53–1.36) | | 1.07 (0.65–1.74) | |
| Missing | 9 | 6.0 | 0.6–NA | 0.51 (0.19–1.31) | | 0.72 (0.27–1.93) | |
| **Number of comorbidities at inclusion** | | | | | 0.93 | | |
| 0 | 192 | 2.1 | 1.8–2.6 | Reference | | | |
| 1 | 197 | 2.7 | 2.3–3.1 | 0.96 (0.78–1.19) | | | |
| 2+ | 133 | 2.3 | 1.4–2.8 | 0.99 (0.79–1.26) | | | |
| **Stage at diagnosis** | | | | | 0.34 | | |
| I–II | 18 | 4.6 | 2.3–10.2 | Reference | | | |
| III | 53 | 2.6 | 1.5–3.7 | 1.55 (0.87–2.76) | | | |
| IV | 428 | 2.3 | 1.9–2.6 | 1.59 (0.95–2.66) | | | |
| Missing | 23 | 1.8 | 1.0–3.9 | 1.75 (0.90–3.40) | | | |
| **PD-L1 expression** | | | | | 0.14 | | 0.06 |
| Positive | 136 | 1.9 | 1.5–2.8 | Reference | | Reference | |
| Negative | 170 | 2.3 | 1.7–2.8 | 1.27 (1.00–1.61) | | 1.31 (1.01–1.68) | |
| Unknown | 216 | 2.4 | 2.2–3.2 | 1.20 (0.95–1.51) | | 1.29 (1.02–1.64) | |
| **Year of nivolumab start** | | | | | 0.18 | | 0.08 |
| 2016 | 42 | 2.3 | 1.0–5.2 | Reference | | Reference | |
| 2017 | 167 | 2.6 | 1.9–3.5 | 1.03 (0.73–1.47) | | 1.11 (0.77–1.59) | |
| 2018 | 214 | 1.9 | 1.4–2.3 | 1.26 (0.89–1.77) | | 1.42 (1.00–2.04) | |
| 2019/2020 | 99 | 3.1 | 2.4–3.7 | 1.02 (0.69–1.50) | | 1.30 (0.86–1.98) | |
| **Histology** | | | | | 0.98 | | |
| Squamous | 133 | 2.3 | 1.4–3.1 | Reference | | | |
| All others | 389 | 2.3 | 2.0–2.8 | 1.00 (0.82–1.23) | | | |
| **Metastases** | | | | | 0.82 | | |
| Brain metastases | 128 | 2.1 | 1.4–2.6 | Reference | | | |
| Other metastases only | 379 | 2.3 | 2.0–2.8 | 1.01 (0.81–1.25) | | | |
| No metastases | 15 | 3.3 | 1.4–7.0 | 0.85 (0.49–1.48) | | | |
| **Treatment line** | | | | | 0.05 | | 0.34 |
| 2 | 433 | 2.4 | 2.1–2.8 | Reference | | Reference | |
| 3+ | 89 | 1.9 | 1.4–2.6 | 1.27 (1.00–1.61) | | 1.13 (0.88-1.46) | |
| **Time from start of previous LoT until start of nivolumab** | | | | | 0.01 | | <0.01 |
| <3 months | 121 | 1.4 | 1.1–2.1 | Reference | | Reference | |
| ≥3–<6 months | 173 | 2.1 | 1.4–2.4 | 0.85 (0.67–1.08) | | 0.78 (0.61–1.01) | |
| ≥6–<12 months | 183 | 2.8 | 2.3–3.5 | 0.70 (0.55–0.89) | | 0.65 (0.50–0.84) | |
| ≥12 months | 44 | 4.6 | 3.2–7.9 | 0.61 (0.42–0.88) | | 0.55 (0.37–0.82) | |

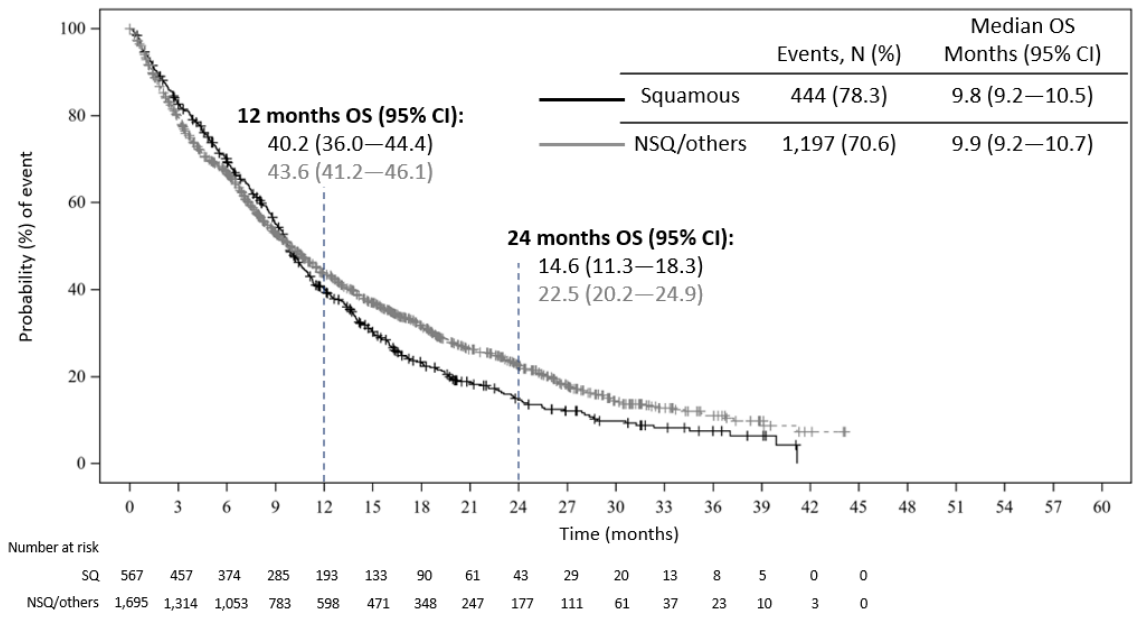*Characteristics at time of nivolumab start if not specified
BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; LoT, line of therapy; PD-L1, programmed death-ligand 1.

**Figure S1:** Sensitivity analysis for OS by histology in ESME-AMLC

**Overall**



**By histology**



CI, confidence interval; NSQ, non-squamous; OS, overall survival; SQ, squamous.