Supplementary Table 1. Comorbidities according to Charlson Comorbidity Index

|  |  |
| --- | --- |
| Comorbidities | *n* (%) |
| COPD | 252 (30) |
| Solid tumor other than NSCLC  Non  Localized  Metastatic | 699 (83)  125 (15)  16 (2) |
| CVA or TIA | 73 (9) |
| PVD a | 66 (8) |
| Diabetes mellitus  No medication  Uncomplicated  End-organ damage | 737 (88)  90 (11)  13 (1) |
| Myocardial infarction | 59 (7) |
| Congestive heart failure | 38 (4) |
| Dementia | 5 (1) |
| Connective tissue disease | 35 (4) |
| Peptic ulcer | 34 (4) |
| Hepatitis or cirrhosis | 9 (1) |
| Hemiplegia | <5 |
| Chronic kidney disease | 11 (1) |
| Leukemia | 8 (1) |
| Lymphoma | 14 (2) |

a) Defined as intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or abdominal aneurysm

n, number of patients; COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease;

Supplementary Table 2. Baseline and treatment characteristics according to sex and ECOG performance status

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Baseline characteristics | Male, *n* (%) | Female,  *n* (%) | p-value | PS 0–1  *n* (%) | PS ≥ 2  *n* (%) | p-value |
| All patients | 432 | 408 | - | 661 | 158 | - |
| Sex  Male  Female | - | - | - | 324 (49)  337 (51) | 92 (58)  66 (42) | 0.05 |
| Age, median; range | 69; 22–89 | 67; 34–85 | 0.001 | 68; 22–88 | 69; 25–85 | 0.26 |
| Age  <75 years  ≥75 years | 339 (78)  93 (22) | 338 (83)  70 (17) | 0.13 | 536 (81)  125 (19) | 126 (80)  32 (20) | 0.79 |
| ECOG PS  0  1  ≥2  NA | 92 (22)  232 (56)  92 (22)  16 | 90 (22)  247 (61)  66 (16)  5 | 0.10 | - | - | - |
| CCIS  0 (no)  1 (mild)  2 (moderate)  ≥3 (severe) | 142 (33)  106 (24)  95 (22)  89 (21) | 190 (47)  101 (25)  59 (14)  58 (14) | <0.0001 | 260 (39)  164 (25)  127 (29)  110 (17) | 63 (40)  42 (27)  22 (14)  31 (20) | 0.34 |
| Smoking status  Current  Former  Never  Unknown | 119 (28)  284 (66)  18 (4)  11 (3) | 119 (29)  251 (62)  28 (7)  10 (3) | 0.31 | 180 (27)  425 (64)  36 (5)  20 (3) | 52 (33)  98 (62)  7 (4)  <5 | 0.2 |
| TNM stage  III  IV | 66 (15)  366 (85) | 50 (12)  358 (88) | 0.24 | 95 (14)  566 (86) | 19 (12)  139 (88) | 0.52 |
| Metastatic sitesa  Brain  Bone  Liver  Adrenal  Distant lymph nodes | 30 (7)  104 (24)  70 (16)  66 (15)  111 (26) | 65 (16)  117 (29)  63 (15)  61 (15)  122 (30) | <0.0001  0.15  0.84  0.97  0.2 | 75 (11)  165 (25)  91 (14)  96 (15)  186 (28) | 18 (11)  45 (29)  40 (25)  27 (17)  43 (27) | 1.0  0.42  0.0006  0.49  0.89 |
| NSCLC histopathology  Adenocarcinoma  Squamous cell carcinoma  Otherb | 190 (44)  210 (49)  32 (7) | 295 (72)  93 (23)  20 (5) | <0.0001 | 393 (59)  230 (35)  38 (6) | 80 (51)  64 (40)  14 (9) | 0.09 |
| EGFR mutation  No  Yes  Unknown | 234 (54)  10 (2)  188 (44) | 303 (74)  15 (4)  90 (22) | <0.0001 | 438 (66)  18 (3)  205 (31) | 90 (57)  <5  64 (40) | 0.07 |
| PD-L1 status  Negative  ≥1% and <50%  ≥50%  Unknown | 39 (9)  105 (24)  132 (31)  156 (36) | 33 (8)  128 (31)  158 (39)  89 (22) | <0.0001 | 51 (8)  178 (27)  242 (37)  190 (29) | 18 (11)  50 (32)  40 (25)  50 (32) | 0.04 |
| Treatment line  2  3  4  ≥5 | 298 (69)  98 (23)  30 (7)  6 (1) | 238 (58)  107 (26)  38 (9)  25 (6) | 0.0003 | 421 (64)  159 (24)  54 (8)  27 (4) | 103 (65)  38 (24)  14 (9)  <5 | 0.62 |
| Treatment  Nivolumab  Pembrolizumab | 249 (58)  183 (42) | 195 (48)  213 (52) | 0.005 | 331 (50)  330 (50) | 101 (64)  57 (36) | 0.002 |
| Median cyclesc; range  Nivolumab  Pembrolizumab | 6; 1–61  5; 1–37 | 7; 1–64  6; 1–36 | - | 8; 1–64  7; 1–37 | 3; 1–57  2; 1–34 | - |
| ICI durationc  Median days; range  mTTD months; 95% CI | 87; 1–889  3.0; 2.3–3.6 | 105; 1–961  3.5; 3.0–4.1 | - | 120; 1–961  2.0; 1.5–4.1 | 36; 1–810  1.1; 0.7–1.4 | - |
| Ongoing ICI treatmentd | 5 (1) | 5 (1) | - | 10 (2) | 0 (0) | - |
| ICI discontinuation due toe:  PD  Poor PS  irAEsf  Pneumonitis  Hepatitis  Skin toxicity  Endocrinopathy  Diarrhea/colitis  Other toxicity  irAEs onlyg  Other reasonsh | 247 (58)  62 (15)  90 (21)  27 (6)  5 (1)  18 (4)  6 (1)  16 (4)  31 (7)  75 (18)  72 (17) | 214 (53)  64 (16)  89 (22)  20 (5)  14 (3)  9 (2)  9 (2)  24 (6)  20 (5)  75 (19)  73 (18) | - | 364 (56)  79 (12)  143 (22)  35 (5)  16 (2)  21 (3)  14 (2)  35 (5)  41 (6)  122 (19)  116 (18) | 84 (53)  44 (28)  30 (19)  10 (6)  <5  5 (3)  NS  NS  8 (5)  23 (15)  26 (16) | - |
| Hospitalization due to irAEs | 68 (16) | 67 (17) | - | 102 (15) | 31 (20) | - |
| Death due to irAEs | <5 | <5 | - | <5 | <5 | - |

a) Patients may be registered with more than one metastatic site

b) “Other” includes NSCLC NOS (not otherwise specified) and adenosquamous carcinoma

c) Patients with ongoing ICI treatment (n=10) not included.

d) At date of censoring

e) Each patient could be registered with more than one cause of treatment-discontinuation

f) Each patient could be registered with more than one type of irAE as a cause of treatment-discontinuation

g) Proportion of patients with irAE as the only cause of treatment discontinuation

h) “Other reasons” are not specified irAEs   
n, number of patients; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not available; CCIS, Charlson Comorbidity Index Score; TNM, Tumor-Node-Metastasis classification of malignant tumors; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; ICI, immune checkpoint inhibitor; mTTD, median time to treatment discontinuation; irAEs, immune-related adverse events; PD, progressive disease; PS, performance status

Supplementary Table 3. Univariable Cox regression analysis

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | *n* (%) | HR (95% CI) | p-value |
| All patients | 840 (100) | - | - |
| Sex  Female  Male | 408 (49)  432 (51) | Ref  1.34 (1.14–1.58) | 0.0004 |
| Age  <75 years  ≥75 years | 677 (81)  163 (19) | Ref  1.14 (0.94–1.38) | 0.18 |
| ECOG PS  0  1  ≥2 | 182 (22)  479 (57)  158 (19) | Ref  1.86 (1.51–2.28)  4.48 (3.42–5.86) | <0.00001  <0.00001 |
| CCIS  0–1  ≥ 2 | 539 (64)  301 (36) | Ref  1.07 (0.91–1.27) | 0.41 |
| COPD  No  Yes | 588 (70)  252 (30) | Ref  1.12 (0.95–1.33) | 0.18 |
| Solid tumor other than NSCLC  Non  Localized  Metastatic | 699 (83)  125 (15)  16 (2) | Ref  0.95 (0.76–1.20)  1.22 (0.69–2.14) | 0.69  0.50 |
| CVA or TIA  No  Yes | 767 (91)  73 (9) | Ref  1.26 (0.97–1.65) | 0.086 |
| PVD a  No  Yes | 774 (92)  66 (8) | Ref  0.80 (0.59–1.09) | 0.16 |
| Diabetes mellitus  No medication  Uncomplicated  End-organ damage | 737 (88)  90 (11)  13 (1) | Ref  1.26 (0.99–1.61)  1.23 (0.66–2.31) | 0.06  0.52 |
| Heart disease b  No  Yes | 762 (91)  78 (9) | Ref  1.13 (0.87–1.47) | 0.34 |
| Smoking status  Never  Current/former  Unknown | 46 (5)  773 (92)  21 (2) | Ref  0.83 (0.57–1.21)  0.79 (0.44–1.42) | 0.33  0.43 |
| Brain metastases  No  Yes | 745 (89)  95 (11) | Ref  1.08 (0.83–1.40) | 0.57 |
| Bone metastases  No  Yes | 619 (74)  221 (26) | Ref  1.39 (1.15–1.68) | 0.0006 |
| Liver metastases  No  Yes | 707 (84)  133 (16) | Ref  1.96 (1.56–2.47) | <0.00001 |
| Adrenal metastases  No  Yes | 713 (85)  127 (15) | Ref  1.12 (0.88–1.42) | 0.37 |
| Distant lymph nodes  No  Yes | 607 (72)  233 (28) | Ref  0.95 (0.78–1.15) | 0.59 |
| NSCLC Histopathology  Adenocarcinoma  Squamous cell carcinoma  Other | 485 (58)  303 (36)  52 (6) | Ref  1.14 (0.96–1.35)  1.35 (0.97–1.88) | 0.13  0.078 |
| EGFR mutation  No  Yes  Unknown | 537 (64)  25 (3)  278 (33) | Ref  1.58 (1.04–2.42)  1.04 (0.88–1.22) | 0.033  0.68 |
| PD-L1 status  Negative  ≥ 1% and < 50%  ≥ 50%  Unknown | 72 (9)  233 (28)  290 (35)  245 (29) | Ref  0.76 (0.57–1.01)  0.63 (0.48–0.84)  0.72 (0.55–0.95) | 0.059  0.0013  0.021 |
| Treatment line  2  3  4  ≥ 5 | 536 (64)  205 (25)  68 (8)  31 (4) | Ref  0.93 (0.77–1.13)  1.08 (0.81–1.45)  0.81 (0.46–1.44) | 0.46  0.59  0.47 |

a) Defined as intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or abdominal aneurysm  
b) Myocardial infarction and/or congestive heart failure

HR, hazard ratio; n, number of patients; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CCIS; Charlson Comorbidity Index Score; COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1

Supplementary Table 4. Median OS and mPFS with 95% confidence intervals according to selected baseline characteristics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variables | *n* (%) | mOS, months  (95% CI) | Log rank test | mPFS, months (95% CI) | Log rank test |
| All patients | 840 (100) | 12.2 (10.8–13.8) | - | 5.2 (4.5–5.9) | - |
| Age  < 75 years  ≥ 75 years | 677 (81)  163 (19) | 12.9 (11.3–14.3)  9.9 (8.2–14.0) | 0.08 | 5.3 (4.7–6.2)  4.5 (3.6–6.5) | 0.07 |
| Sex  Female  Male | 408 (49)  432 (51) | 15.1 (13.4–17.2)  10.0 (9.0–11.7) | <0.0001 | 6.4 (5.2–8.1)  4.4 (3.7–5.3) | 0.006 |
| ECOG PS  0  1  ≥ 2 | 182 (22)  479 (57)  158 (19) | 22.1 (18.8–28.5)  12.2 (10.7–13.8)  4.5 (3.2–5.7) | <0.0001 | 8.9 (7.0–11.1)  5.4 (4.7–6.5)  2.0 (1.7–2.6) | <0.0001 |
| CCIS  0–1  ≥ 2 | 539 (64)  301 (36) | 13.1 (11.0–14.4)  11.3 (9.5–14.2) | 0.52 | 5.0 (4.3–5.9)  5.5 (4.3–6.9) | 0.58 |
| Smoking status  Never  Current/former  Unknown | 46 (5)  773 (92)  21 (2) | 8.3 (6.2–13.7)  12.8 (11.0–14.2) | 0.32 | 3.2 (2.5–4.5)  5.3 (4.7–6.1) | 0.03 |
| Brain metastases  No  Yes | 745 (89)  95 (11) | 12.3 (10.8–14.3)  12.0 (7.6–14.2) | 0.53 | 5.3 (4.7–6.2)  4.1 (2.6–5.9) | 0.11 |
| Bone metastases  No  Yes | 619 (74)  221 (26) | 13.7 (12.0–16.0)  9.0 (7.2–11.0) | 0.003 | 5.8 (5.2–6.7)  3.7 (2.7–4.4) | 0.08 |
| Liver metastases  No  Yes | 707 (84)  133 (16) | 13.8 (12.3–16.1)  6.8 (4.3–8.3) | <0.0001 | 5.8 (5.3–6.9)  2.5 (1.9–3.4) | <0.0001 |
| Adrenal metastases  No  Yes | 713 (85)  127 (15) | 12.9 (11.2–14.3)  10.3 (8.1–13.7) | 0.65 | 5.3 (4.4–6.0)  3.9 (3.2–7.3) | 0.95 |
| Distant lymph nodes  No  Yes | 607 (72)  233 (28) | 12.0 (10.6–13.8)  13.1 (9.8–16.7) | 0.18 | 5.3 (4.4–6.0)  5.2 (3.8–6.8) | 0.39 |
| NSCLC histopathology  Adenocarcinoma  Squamous cell carcinoma  Other | 485 (58)  303 (36)  52 (6) | 13.7 (11.5–16.7)  11.0 (9.6–13.2)  10.4 (6.5–16.9) | 0.009 | 5.4 (4.7–6.5)  5.3 (3.9–6.5)  3.7 (2.2–6.4) | 0.1 |
| EGFR mutation  No  Yes  Unknown | 537 (64)  25 (3)  278 (33) | 13.2 (11.0–16.2)  8.2 (6.1–13.5)  11.8 (9.9–14.3) | 0.02 | 5.3 (4.5–6.5)  2.5 (1.8–4.9)  5.3 (3.9–6.5) | 0.004 |
| PD-L1 status  Negative  ≥ 1% and < 50%  ≥ 50%  Unknown | 72 (9)  233 (28)  290 (35)  245 (29) | 9.3 (7.7–12.9)  12.3 (10.0–15.4)  16.7 (12.8–19.9)  11.0 (9.0–13.4) | 0.001 | 2.9 (2.0–4.4)  4.5 (3.5–5.8)  7.4 (5.6–9.5)  4.9 (3.8–6.5) | <0.0001 |
| Treatment line  2  3  4  ≥ 5 | 536 (64)  205 (25)  68 (8)  31 (4) | 12.1 (10.5–14.0)  14.0 (11.0–16.9)  8.8 (7.5–16.3)  10.6 (6.0–NR) | 0.66 | 5.3 (4.3–6.2)  5.4 (4.4–7.3)  4.8 (3.5–6.4)  4.1 (2.2–9.9) | 0.99 |

OS, overall survival; PFS, progression-free survival; n, number of patients; mOS; median overall survival; mPFS, median progression-free survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CCIS, Charlson Comorbidity Index Score; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; NR, not reached

Supplementary Table 5. Estimated hazard ratios for specific contrasts from the interaction analysis between sex and NSCLC histopathology

|  |  |  |
| --- | --- | --- |
| Contrast | HR (95% CI) | p-value |
| Male; squamous vs adeno | 1.0 (0.70–1.44) | 0.99 |
| Female; squamous vs adeno | 1.35 (0.90–2.02) | 0.14 |
| Adeno; male vs female | 1.54 (1.2–1.98) | 0.001 |
| Squamous; male vs female | 1.14 (0.85–1.53) | 0.38 |

NSCLC, non-small cell lung cancer; HR, hazard ratio; Squamous, squamous cell carcinoma; Adeno, adenocarcinoma