Supplementary Table 1. Comorbidities according to Charlson Comorbidity Index

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| --- | --- |
| Comorbidities | *n* (%) |
| COPD | 252 (30) |
| Solid tumor other than NSCLCNonLocalizedMetastatic | 699 (83)125 (15)16 (2) |
| CVA or TIA | 73 (9) |
| PVD a | 66 (8) |
| Diabetes mellitusNo medicationUncomplicatedEnd-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

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| --- | --- | --- | --- | --- | --- | --- |
| 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 PS01≥2NA | 92 (22)232 (56)92 (22)16 | 90 (22)247 (61)66 (16)5 | 0.10 | - | - | - |
| CCIS0 (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 statusCurrentFormerNever 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 stageIIIIV | 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) | <0.00010.150.840.970.2 | 75 (11)165 (25)91 (14)96 (15)186 (28) | 18 (11)45 (29)40 (25)27 (17)43 (27) | 1.00.420.00060.490.89 |
| NSCLC histopathologyAdenocarcinomaSquamous cell carcinomaOtherb | 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 mutationNoYesUnknown | 234 (54)10 (2)188 (44) | 303 (74)15 (4)90 (22) | <0.0001 | 438 (66)18 (3)205 (31) | 90 (57)<564 (40) | 0.07 |
| PD-L1 statusNegative≥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 line234≥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 |
| TreatmentNivolumabPembrolizumab | 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; 1–615; 1–37 | 7; 1–646; 1–36 | - | 8; 1–647; 1–37 | 3; 1–572; 1–34 | - |
| ICI durationc  Median days; rangemTTD months; 95% CI | 87; 1–889 3.0; 2.3–3.6 | 105; 1–9613.5; 3.0–4.1 | - | 120; 1–9612.0; 1.5–4.1 | 36; 1–8101.1; 0.7–1.4 | - |
| Ongoing ICI treatmentd | 5 (1) | 5 (1) | - | 10 (2) | 0 (0) | - |
| ICI discontinuation due toe:PDPoor PSirAEsfPneumonitisHepatitisSkin toxicityEndocrinopathyDiarrhea/colitisOther toxicityirAEs onlygOther 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)<55 (3)NSNS8 (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

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| --- | --- | --- | --- |
| Variables | *n* (%) | HR (95% CI)  | p-value |
| All patients | 840 (100) | - | - |
| SexFemaleMale | 408 (49)432 (51) | Ref1.34 (1.14–1.58) | 0.0004 |
| Age<75 years≥75 years | 677 (81)163 (19) | Ref1.14 (0.94–1.38) | 0.18 |
| ECOG PS 0 1 ≥2 | 182 (22)479 (57)158 (19) | Ref1.86 (1.51–2.28)4.48 (3.42–5.86) | <0.00001<0.00001 |
| CCIS 0–1 ≥ 2 | 539 (64)301 (36) | Ref1.07 (0.91–1.27) | 0.41 |
| COPDNoYes | 588 (70)252 (30) | Ref1.12 (0.95–1.33) | 0.18 |
| Solid tumor other than NSCLCNonLocalizedMetastatic | 699 (83)125 (15)16 (2) | Ref0.95 (0.76–1.20)1.22 (0.69–2.14) | 0.690.50 |
| CVA or TIANoYes | 767 (91)73 (9) | Ref1.26 (0.97–1.65) | 0.086 |
| PVD aNoYes | 774 (92)66 (8) | Ref0.80 (0.59–1.09) | 0.16 |
| Diabetes mellitusNo medicationUncomplicatedEnd-organ damage | 737 (88)90 (11)13 (1) | Ref1.26 (0.99–1.61)1.23 (0.66–2.31) | 0.060.52 |
| Heart disease bNoYes | 762 (91)78 (9) | Ref1.13 (0.87–1.47) | 0.34 |
| Smoking statusNeverCurrent/formerUnknown | 46 (5)773 (92)21 (2) | Ref0.83 (0.57–1.21)0.79 (0.44–1.42) | 0.330.43 |
| Brain metastasesNoYes | 745 (89)95 (11) | Ref1.08 (0.83–1.40) | 0.57 |
| Bone metastasesNo Yes | 619 (74)221 (26) | Ref1.39 (1.15–1.68) | 0.0006 |
| Liver metastasesNoYes | 707 (84)133 (16) | Ref1.96 (1.56–2.47) | <0.00001 |
| Adrenal metastasesNoYes | 713 (85)127 (15) | Ref1.12 (0.88–1.42) | 0.37 |
| Distant lymph nodesNoYes | 607 (72)233 (28) | Ref0.95 (0.78–1.15) | 0.59 |
| NSCLC HistopathologyAdenocarcinomaSquamous cell carcinomaOther | 485 (58)303 (36)52 (6) | Ref1.14 (0.96–1.35)1.35 (0.97–1.88) | 0.130.078 |
| EGFR mutationNoYes Unknown | 537 (64)25 (3)278 (33) | Ref1.58 (1.04–2.42)1.04 (0.88–1.22) | 0.0330.68 |
| PD-L1 statusNegative≥ 1% and < 50%≥ 50%Unknown | 72 (9)233 (28)290 (35)245 (29) | Ref0.76 (0.57–1.01)0.63 (0.48–0.84)0.72 (0.55–0.95) | 0.0590.00130.021 |
| Treatment line234≥ 5 | 536 (64)205 (25)68 (8)31 (4) | Ref0.93 (0.77–1.13)1.08 (0.81–1.45)0.81 (0.46–1.44) | 0.460.590.47 |

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

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| --- | --- | --- | --- | --- | --- |
| 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 |
| SexFemaleMale | 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 statusNeverCurrent/formerUnknown | 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 metastasesNoYes | 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 metastasesNo 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 metastasesNoYes | 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 metastasesNoYes | 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 nodesNoYes | 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 histopathologyAdenocarcinomaSquamous cell carcinomaOther | 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 mutationNoYesUnknown | 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 statusNegative≥ 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 line234≥ 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

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| --- | --- | --- |
| 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