**SUPPLEMENTARY MATERIALS**

**Supplementary Table 1. 1L treatments received by treatment class (N=501)**

|  |  |
| --- | --- |
| **1L ICI monotherapy, n (%)** | **n=237** |
| R1: PEMBROLIZUMAB | 204 (86.1) |
| R1: NIVOLUMAB | 14 (5.9) |
| R1: PEMBROLIZUMAB; R2: PEMBROLIZUMAB | 11 (4.6) |
| R1: PEMBROLIZUMAB; R2: CARBOPLATIN, PEMBROLIZUMAB | 2 (<1) |
| R1: DURVALUMAB | 1 (<1) |
| R1: NIVOLUMAB; R2: PEMETREXED; R3: VINORELBINE | 1 (<1) |
| R1: PEMBROLIZUMAB; R2: BEVACIZUMAB, PEMBROLIZUMAB | 1 (<1) |
| R1: PEMBROLIZUMAB; R2: CARBOPLATIN, PACLITAXEL | 1 (<1) |
| R1: PEMBROLIZUMAB; R2: CARBOPLATIN, PACLITAXEL; R3: CARBOPLATIN, CETUXIMAB, PACLITAXEL, PEMBROLIZUMAB | 1 (<1) |
| R1: PEMBROLIZUMAB; R2: NIVOLUMAB | 1 (<1) |
| **1L ICI combination, n (%)** | **n=136** |
| R1: CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED | 100 (73.5) |
| R1: CARBOPLATIN, PACLITAXEL, PEMBROLIZUMAB | 13 (9.6) |
| R1: CARBOPLATIN, PACLITAXEL PROTEIN-BOUND, PEMBROLIZUMAB | 8 (5.9) |
| R1: CARBOPLATIN, PACLITAXEL, PEMBROLIZUMAB; R2: CARBOPLATIN, PACLITAXEL PROTEIN-BOUND, PEMBROLIZUMAB | 2 (1.5) |
| R1: CARBOPLATIN, PEMBROLIZUMAB | 2 (1.5) |
| R1: CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED; R2: PEMBROLIZUMAB | 2 (1.5) |
| R1: CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED; R2: PEMBROLIZUMAB, PEMETREXED | 2 (1.5) |
| R1: ATEZOLIZUMAB, CARBOPLATIN, PACLITAXEL PROTEIN-BOUND | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL, PEMBROLIZUMAB; R2: PEMBROLIZUMAB | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL, PEMBROLIZUMAB; R2: PEMBROLIZUMAB; R3: FLUOROURACIL, OXALIPLATIN, PEMBROLIZUMAB | 1 (<1) |
| R1: CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED; R2: CARBOPLATIN, PACLITAXEL; R3: PEMBROLIZUMAB, PEMETREXED | 1 (<1) |
| R1: CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED; R2: CARBOPLATIN, PEMBROLIZUMAB | 1 (<1) |
| R1: CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED; R2: PEMBROLIZUMAB, PEMETREXED, R3: PEMETREXED | 1 (<1) |
| R1: IPILIMUMAB, NIVOLUMAB | 1 (<1) |
| **1L chemotherapy** | **n=128** |
| R1: CARBOPLATIN, PEMETREXED | 39 (30.5) |
| R1: CARBOPLATIN, PACLITAXEL | 30 (23.4) |
| R1: CARBOPLATIN, GEMCITABINE | 10 (7.8) |
| R1: CARBOPLATIN, PACLITAXEL PROTEIN-BOUND | 8 (6.3) |
| R1: BEVACIZUMAB, CARBOPLATIN, PEMETREXED | 7 (5.5) |
| R1: CARBOPLATIN, PACLITAXEL; R2: PEMBROLIZUMAB | 5 (3.9) |
| R1: CARBOPLATIN, PACLITAXEL; R2: NIVOLUMAB | 4 (3.1) |
| R1: DOCETAXEL | 2 (1.6) |
| R1: PEMETREXED | 2 (1.6) |
| R1: BEVACIZUMAB, CARBOPLATIN, PACLITAXEL | 1 (<1) |
| R1: BEVACIZUMAB, CARBOPLATIN, PEMETREXED; R2: BEVACIZUMAB, PEMETREXED | 1 (<1) |
| R1: BEVACIZUMAB, CARBOPLATIN, PEMETREXED; R2: CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED | 1 (<1) |
| R1: BEVACIZUMAB, CARBOPLATIN, PEMETREXED; R2: PEMETREXED | 1 (<1) |
| R1: CARBOPLATIN, ETOPOSIDE; R2: CARBOPLATIN, PACLITAXEL PROTEIN-BOUND, PEMBROLIZUMAB | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL; R2: ATEZOLIZUMAB | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL; R2: BEVACIZUMAB, CARBOPLATIN, PACLITAXEL | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL; R2: CARBOPLATIN, PACLITAXEL PROTEIN-BOUND | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL; R2: CISPLATIN, GEMCITABINE | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL; R2: DURVALUMAB | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL; R2: PEMBROLIZUMAB, R3: PEMBROLIZUMAB | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL PROTEIN-BOUND; R2: NIVOLUMAB | 1 (<1) |
| R1: CARBOPLATIN, PACLITAXEL PROTEIN-BOUND; R2: PACLITAXEL | 1 (<1) |
| R1: CARBOPLATIN, PEMETREXED; R2: BEVACIZUMAB, CARBOPLATIN, PACLITAXEL; R3: BEVACIZUMAB | 1 (<1) |
| R1: CARBOPLATIN, PEMETREXED; R2: BEVACIZUMAB, CARBOPLATIN, PEMETREXED | 1 (<1) |
| R1: CARBOPLATIN, PEMETREXED; R2: CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED | 1 (<1) |
| R1: CARBOPLATIN, PEMETREXED; R2: CARBOPLATIN, PEMETREXED | 1 (<1) |
| R1: CISPLATIN, DOCETAXEL; R2: CARBOPLATIN, CISPLATIN, DOCETAXEL | 1 (<1) |
| R1: CISPLATIN, ETOPOSIDE; R2: DURVALUMAB | 1 (<1) |
| R1: CISPLATIN, PEMETREXED | 1 (<1) |
| R1: VINORELBINE; R2: CARBOPLATIN, VINORELBINE | 1 (<1) |

R1, Regimen 1; R2, Regimen 2; R3, Regimen 3.

**Supplementary Table 2. Reasons for end of follow-up for patients who did not receive 2L treatment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Overall (n=321)** | **Low-to-moderate PD-L1 tumor expression (n=122)** | **High PD-L1 tumor expression (n=199)** |
| **1L chemotherapy, n (%)** | **n=62** | **n=45** | **n=17** |
| Death | 40 (64.5) | 31 (68.9) | 9 (52.9) |
| Alive but discontinued 1L treatment | 18 (29.0) | 13 (28.9) | 5 (29.4) |
| Alive and still on 1L treatment | 4 (6.5) | 1 (2.2) | 3 (17.6) |
| **1L ICI monotherapy, n (%)** | **n=157** | **n=15** | **n=142** |
| Death | 78 (49.7) | 12 (80.0) | 66 (46.5) |
| Alive but discontinued 1L treatment | 54 (34.4) | 2 (13.3) | 52 (36.6) |
| Alive and still on 1L treatment | 25 (15.9) | 1 (6.7) | 24 (16.9) |
| **1L ICI combination, n (%)** | **n=102** | **n=62** | **n=40** |
| Death | 40 (39.2) | 27 (43.5) | 13 (32.5) |
| Alive but discontinued 1L treatment | 40 (39.2) | 28 (45.2) | 12 (30.0) |
| Alive and still on 1L treatment | 22 (21.6) | 7 (11.3) | 15 (37.5) |

1L, first line; 2L, second line; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1.

**Supplementary Table 3. Subgroup analysis of median OS (N=501)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Subgroup (95% CI)** | **Overall**  **(N=501)** | **Chemotherapy**  **(n=128)** | **IO monotherapy**  **(n=237)** | **IO combination**  **(n=136)** |
| **Age** |  |  |  |  |
| <65 years at metastatic NSCLC diagnosis | 15.7 (10.5-22.4) | 9.8 (6.6-17.9) | 22.1 (10.3-34.3) | 16.2 (11.9-NA) |
| ≥65 years at metastatic NSCLC diagnosis | 16.9 (14.3-19.6) | 13.1 (9.5-19.4) | 16.7 (13.0-19.6) | 22.4 (14.2-NA) |
| **Sex** |  |  |  |  |
| Female | 20.6 (15.7-24.6) | 13.1 (7.9-20.6) | 22.4 (14.9-32.8) | NA (16.2-NA) |
| Male | 14.2 (10.5-17.9) | 9.7 (6.5-16.9) | 14.8 (10.5-18.3) | 18.7 (11.0-29.8) |
| **Histology**\* |  |  |  |  |
| Nonsquamous | 18.5 (15.7-21.0) | 12.8 (8.9-17.9) | 20.6 (15.7-32.8) | 19.8 (14.3-NA) |
| Squamous | 11.2 (7.9-16.4) | 9.7 (5.4-19.5) | 12.0 (7.3-16.7) | NA (6.4-NA) |
| **ECOG PS at 1L initiation** |  |  |  |  |
| 0 | 22.4 (17.0-25.8) | 19.9 (6.0-24.8) | 24.6 (17.0-NA) | 18.7 (9.0-NA) |
| 1 | 15.7 (11.8-19.0) | 9.5 (6.5-12.7) | 18.2 (10.3-23.4) | 19.8 (14.2-NA) |
| ≥2 | 9.4 (5.8-14.3) | 10.4 (5.2-19.4) | 7.4 (4.4-16.7) | 11.0 (2.6-NA) |
| **Smoking status** |  |  |  |  |
| Current | 17.1 (11.9-22.0) | 9.1 (6.1-19.5) | 17.1 (13.0-NA) | 19.8 (18.7-NA) |
| Never | 28.9 (4.4-NA) | 20.0 (0.3-NA) | NA (0.2-NA) | NA (8.1-NA) |
| Past (Not current) | 15.7 (12.8-18.5) | 12.8 (7.9-17.9) | 18.2 (12.8-20.6) | 16.2 (11.9-NA) |
| **Liver metastases** |  |  |  |  |
| No | 18.3 (14.9-19.9) | 12.1 (9.5-19.5) | 18.2 (13.4-21.0) | 29.8 (16.2-NA) |
| Yes | 11.0 (5.5-15.7) | 6.2 (3.7-14.2) | 16.4 (4.3-NA) | 8.7 (4.1-22.4) |
| **Bone metastases** |  |  |  |  |
| No | 20.6 (16.2-23.1) | 15.2 (8.8-21.9) | 19.4 (14.8-25.2) | NA (16.2-NA) |
| Yes | 11.2 (8.7-15.7) | 9.5 (5.9-14.2) | 14.4 (7.4-18.3) | 12.0 (7.9-22.4) |
| **Brain metastases** |  |  |  |  |
| No | 16.4 (13.2-18.5) | 10.5 (7.4-15.7) | 18.2 (14.4-23.4) | 22.4 (12.0-NA) |
| Yes | 19.0 (10.5-21.6) | 14.2 (6.3-24.8) | 14.5 (6.4-22.4) | 19.8 (14.2-NA) |
| **Adrenal metastases** |  |  |  |  |
| No | 16.7 (13.4-19.0) | 11.1 (8.8-16.9) | 16.7 (13.0-20.9) | 22.4 (15.7-NA) |
| Yes | 18.5 (8.1-22.4) | 13.1 (3.1-22.8) | 18.4 (9.4-NA) | 7.9 (2.5-NA) |
| **Pleural metastases** |  |  |  |  |
| No | 16.7 (13.4-19.0) | 12.1 (9.1-17.9) | 18.2 (13.4-22.4) | 19.0 (12.0-NA) |
| Yes | 18.5 (8.1-22.4) | 5.5 (3.4-20.6) | 18.5 (6.2-25.2) | 22.4 (14.3-NA) |

1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immuno-oncology; NA, not applicable; NOS, not otherwise specified; NSCLC, non-small cell lunch cancer; OS, overall survival.

\*These subgroups do not include patients who were not classified as squamous or nonsquamous. Specifically, squamous includes only squamous cell carcinoma and nonsquamous includes only adenocarcinoma, large cell carcinoma, NSCLC NOS. Patients with histology “other” or “adenosquamous carcinoma” are not included.

**Supplementary Table 4. Adjusted cox regression analysis of treatment outcomes for 1L treatment groups**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Adjusted model** | **Overall** | | | **Low-to-moderate PD-L1 subgroup** | | | **High PD-L1 subgroup** | | |
| **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** |
| **Overall survival** |  |  |  |  |  |  |  |  |  |
| ICI combination (vs chemotherapy) | 0.740 | (0.513-1.069) | 0.1083 | 0.747 | (0.466-1.200) | 0.2277 | 0.766 | (0.410-1.431) | 0.4028 |
| ICI monotherapy (vs chemotherapy) | 1.055 | (0.743-1.499) | 0.7640 | 1.108 | (0.634-1.938) | 0.7179 | 1.052 | (0.638-1.736) | 0.8416 |
| ICI combination (vs ICI monotherapy) | 0.702 | (0.490-1.005) | 0.0534 | 0.674 | (0.372-1.222) | 0.1939 | 0.728 | (0.445-1.190) | 0.2051 |
| **Progression-free survival** |  |  |  |  |  |  |  |  |  |
| ICI combination (vs chemotherapy) | 0.522 | (0.382-0.714) | <0.0001 | 0.557 | (0.370-0.839) | 0.0051 | 0.427 | (0.252-0.721) | 0.0015 |
| ICI monotherapy (vs chemotherapy) | 0.745 | (0.537-1.034) | 0.0788 | 1.188 | (0.701-2.012) | 0.5225 | 0.552 | (0.359-0.851) | 0.0071 |
| ICI combination (vs ICI monotherapy) | 0.701 | (0.510-0.963) | 0.0282 | 0.469 | (0.275-0.801) | 0.0055 | 0.772 | (0.506-1.179) | 0.2313 |
| **Time to discontinuation** |  |  |  |  |  |  |  |  |  |
| ICI combination (vs chemotherapy) | 0.554 | (0.424-0.724) | <0.0001 | 0.589 | (0.412-0.843) | 0.0038 | 0.469 | (0.297-0.739) | 0.0011 |
| ICI monotherapy (vs chemotherapy) | 0.604 | (0.450-0.810) | 0.0008 | 0.859 | (0.528-1.396) | 0.5386 | 0.475 | (0.318-0.711) | 0.0003 |
| ICI combination (vs ICI monotherapy) | 0.918 | (0.709-1.188) | 0.5144 | 0.686 | (0.423-1.113) | 0.1269 | 0.986 | (0.713-1.363) | 0.9311 |
| **Duration of response\*** |  |  |  |  |  |  |  |  |  |
| ICI combination (vs chemotherapy) | 0.282 | (0.160-0.496) | <0.0001 | 0.270 | (0.110-0.663) | 0.0043 | 0.224 | (0.094-0.533) | 0.0007 |
| ICI monotherapy (vs chemotherapy) | 0.155 | (0.077-0.313) | <0.0001 | 0.202 | (0.033-1.215) | 0.0806 | 0.110 | (0.045-0.272) | <0.0001 |
| ICI combination (vs ICI monotherapy) | 1.819 | (0.979-3.379) | 0.0584 | 1.340 | (0.252-7.116) | 0.7314 | 2.034 | (0.977-4.238) | 0.0578 |

Notes: This table includes multiple adjusted Cox models—1 per outcome, with ICI combination vs ICI monotherapy comparisons added. Patients with an initial chemotherapy-based regimen followed by ICI in the second regimen within 1L were excluded from adjusted models (n=17).

Each model controlled for the following patient characteristics: age, sex, insurance type, histology, ECOG performance status, weighted comorbidity index, bone metastasis, liver metastasis, and brain metastasis. The overall models also controlled for PD-L1 expression group.

1L, first line; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; PR, partial response.

\*Analysis only includes patients who achieved CR or PR by the end of 1L.