**Supplementary Table 1.** Clinical and pathologic characteristics (N = 231)

|  |  |
| --- | --- |
| Characteristics | Data |
| Age (y) | 64.2 (29-92) |
| Sex |  |
| Men | 173 (74.9) |
| Women | 58 (25.1) |
| ECOG Performance status |  |
| 0 | 162 (70.1) |
| 1 | 63 (27.3) |
| 2 | 6 (2.6) |
| Smoking history |  |
| Never smoker | 69 (29.9) |
| Current smoker | 57 (24.7) |
| Ex-smoker | 105 (45.5) |
| Smoking (pack\*year) | 162 |
| <20 | 18 (11.1) |
| ≥20 (heavy smoker) | 144 (88.9) |
| Clinical stage at diagnosis |  |
| ≤Stage IIIc | 76 (33.6) |
| Stage IVa | 93 (36.4) |
| Stage IVb | 62 (31.8) |
| Histology |  |
| Adenocarcinoma | 162 (70.1) |
| Squamous cell carcinoma | 62 (26.8) |
| Others (Adenosquamous cell carcinoma, etc.) | 7 (3.1) |
| Metastatic site |  |
| Lymph node (SCN or extrathoracic) | 89 (38.5) |
| Pleural metastasis | 80 (34.6) |
| Malignant pleural/pericardial effusion | 60 (26.0) |
| Lung to lung metastasis | 57 (24.7) |
| Bone metastasis | 76 (32.9) |
| Brain or CNS | 47 (20.3) |
| Liver | 28 (12.1) |
| Miscellaneous† | 18 (7.8) |
| Number of metastatic sites |  |
| 0 | 13 (5.6) |
| 1 | 89 (38.5) |
| 2 | 63 (27.3) |
| 3 | 37 (16.0) |
| ≥4 | 29 (12.6) |
| Oncogenic driver mutation (n=43) |  |
| EGFR | 31 (13.4) |
| ALK / ROS-1 | 4 (1.7) |
| Others (K-Ras, B-RAF, BRCA…) | 8 (3.4) |
| Immune checkpoint blockade |  |
| Pembrolizumab | 98 (42.4) |
| Nivolumab | 108 (46.8) |
| Durvalumab | 10 (4.3) |
| Avelumab | 6 (2.6) |
| Atezolizumab | 2 (0.9) |
| Switch to other ICB or combination | 7 (3.0) |
| Number of prior systemic treatment |  |
| ≤1 | 141 (61.0) |
| 2 | 53 (22.9) |
| 3 | 17 (7.4) |
| ≥4 | 20 (8.7) |
| Tumor response to ICBs |  |
| CR/PR | 50 (21.6) |
| SD | 79 (34.2) |
| PD | 82 (35.5) |
| UnKnown | 20 (8.7) |

Values are presented as mean (range) or number (%).

†Miscellany includes lymphagitic metastasis and metastasis to the adrenal glands, skin, kidney, bowel.

**Supplementary Table 2.** Serologic inflammatory markers associated with HPD by univariate and multivariate analyses (n = 155)†

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Univariate** | | **Multivariate** | |
|  | **HR (95% CI)** | ***P*-value** | **HR (95% CI)** | ***P*-value** |
| NLR (base‡), ≥5 vs <5 | 2.20 (0.88-5.52) | 0.092 | 1.53 (0.55-4.26) | 0.4117 |
| PLR (base), ≥150 vs <150 | 1.67 (0.68-4.13) | 0.2644 | 1.24 (0.47-3.31) | 0.6638 |
| CAR (base), ≥0.5 vs <0.5 | 2.62 (1.09-6.33) | **0.0318** | 2.18 (0.85-5.55) | 0.1031 |
| LDH (base), ≥400 vs <400 | 0.35 (0.09-1.36) | 0.1290 | 0.77 (0.32-1.85) | 0.553 |

† Non evaluable group and Non-HPD PD group were excluded.

‡ Base implies at the beginning of immunotherapy

*HPD* hyperprogressive disease, HR hazard ratio, CAR, C-reactive protein-albumin ratio; ICB, immune checkpoint blockades; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

**Supplementary figure legends**

**Supplementary Fig. 1** CONSORT flow diagram for the present study.

*HPD* hyperprogressive disease, *ICBs* Immune checkpoint blockades, *Non-HPD PD* non-HPD progressive disease, *NE* Not evaluable, *PR/CR* partial/complete response, *SD* stable disease.

**Supplementary Fig. 2** Spider plot depicting percentage change in the sum of the largest diameters of target lesions over time according to hyperprogressive disease status.

*ICBs* Immune checkpoint blockades.

**Supplementary Fig. 3** Scatterplot of tumor response pattern and PD-L1 expression levels.

Symbols (dots) in the scatterplot represent the tumoral PD-L1 (22C3) expressions. The mean level of PD-L1 expression in HPD group was significantly lower compared to that of SD/PR/CR group (*P* = 0.003).

*HPD* hyperprogressive disease, *SD stable disease, PR/CR partial/complete response*

**Supplementary Fig. 4** Kaplan-Meier survival curve in each patient group according to the tumor response pattern (n = 211) †.

† Non evaluable group was excluded.

*HPD* hyperprogressive disease, *Non-HPD PD* non-HPD progressive disease, *PR/CR* partial/complete response, *SD* stable disease.