**Supplementary Tables**

**Table S1 Treatment response in LT and NLT groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No. (%)** | | | |
| **Characteristic** | **All**  **(n=676)** | **LT group**  **(n =114)** | **NLT group**  **(n=562)** | ***p*-value** |
| Response |  |  |  | <0.0001 |
| CR | 21 (3.1) | 14 (12.3) | 7 (1.2) |  |
| PR | 157 (23.2) | 79 (69.3) | 78 (13.9) |  |
| SD | 203 (30.0) | 21 (18.4) | 182 (32.4) |  |
| PD | 255 (37.7) | 0 (0) | 255 (45.4) |  |
| NE | 40 (5.9) | 0 (0) | 40 (7.1) |  |

Abbreviations: CR, complete response; LT group, patients receiving initial immune checkpoint inhibitor for >1 year without progression disease; NE, not evaluable NLT group, patients other than LT group; PD, progressive disease; PR, partial response; SD, stable disease.

**Table S2 Univariate and multivariate analyses of PFS in all patients**

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model. Without considering the results of the univariate analysis, the factors considered important from the results of the previous report and the medical point of view were selected for inclusion in multivariate analysis.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Univariate** | | | **Multivariate** | | |
| **Parameter** | **Category** | **HR** | **95% CI** | ***p*-value** | **HR** | **95% CI** | ***p*-value** |
| Age (years) | ≥75 (vs.<75) | 0.86 | 0.70–1.06 | 0.1546 | 0.89 | 0.72–1.10 | 0.2759 |
| Sex | Female (vs. male) | 1.55 | 1.29–1.85 | <0.0001 | 1.25 | 1.01–1.54 | 0.0433 |
| Smoking status | Smoker (vs. never) | 0.61 | 0.49–0.77 | <0.0001 | 0.74 | 0.57–0.97 | 0.0291 |
| Pack-years | ≥30 (vs.<30) | 0.71 | 0.60–0.84 | 0.0001 |  |  |  |
| Histology | Ad (vs. others) | 1.12 | 0.94–1.32 | 0.2056 |  |  |  |
| Stage at diagnosis | Stage IV (vs. others) | 1.34 | 1.13–1.58 | 0.0006 | 1.12 | 0.94–1.33 | 0.1924 |
| Tumor burden | <45 mm (vs.≥45 mm) | 0.77 | 0.65–0.91 | 0.0020 | 0.83 | 0.70–0.98 | 0.0325 |
| No. of prior therapy | ≥2 (vs. 0 or 1) | 1.32 | 1.18–1.55 | 0.0011 | 1.13 | 0.95–1.33 | 0.1684 |
| Performance Status | ≥2 (vs. 0 or 1) | 2.32 | 1.88–2.85 | <0.0001 | 2.09 | 1.68–2.59 | <0.0001 |
| PD-L1 status | 1-49 % (vs. <1%) | 0.65 | 0.43–1.00 | 0.0498 |  |  |  |
|  | ≥50% (vs. <1%) | 0.52 | 0.36–0.76 | 0.0010 |  |  |  |
| Response | CR (vs. others) | 0.07 | 0.02–0.18 | <0.0001 | 0.08 | 0.02–0.22 | <0.0001 |
|  | CR + PR (vs. SD) | 0.15 | 0.12–0.19 | <0.0001 |  |  |  |
| WBC fraction | Group A (vs. others) | 0.74 | 0.61–0.90 | 0.0020 | 0.93 | 0.76–1.13 | 0.4872 |
| Radiation therapy | With (vs. without) | 1.12 | 0.87–1.43 | 0.3546 | 0.97 | 0.75–1.24 | 0.8020 |
| AE | With (vs. without) | 0.53 | 0.42–0.66 | <0.0001 | 0.59 | 0.47–0.73 | <0.0001 |

Abbreviations: Ad, adenocarcinoma; AE, adverse event; CR, complete response; No, number; PD-L1, programmed death-ligand-1; PR, partial response; PFS, progression-free survival; SD, stable disease; WBC, white blood cell.

**Table S3 Univariate and multivariate analyses of OS in all patients**

The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model. Without considering the results of the univariate analysis, the factors considered important from the results of the previous report and the medical point of view were selected for inclusion in multivariate analysis.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Univariate** | | | **Multivariate** | | |
| **Parameter** | **Category** | **HR** | **95% CI** | ***P*-value** | **HR** | **95% CI** | ***p*-value** |
| Age (years) | ≥75 (vs. <75) | 0.94 | 0.75–1.16 | 0.5564 | 1.04 | 0.82–1.30 | 0.768 |
| Sex | Female (vs. male) | 1.15 | 0.94–1.39 | 0.173 | 0.97 | 0.77–1.22 | 0.7868 |
| Smoking status | Smoker (vs. never) | 0.84 | 0.67–1.08 | 0.172 | 0.93 | 0.70–1.25 | 0.6217 |
| Pack-years | ≥30 (vs. <30) | 0.89 | 0.74–1.07 | 0.1988 |  |  |  |
| Histology | Ad (vs. others) | 1.07 | 0.90–1.29 | 0.4404 |  |  |  |
| Stage at diagnosis | Stage IV (vs. others) | 1.46 | 1.22–1.75 | <0.0001 | 1.26 | 1.05–1.52 | 0.0143 |
| Tumor burden | <45 mm (vs. ≥45 mm) | 0.71 | 0.59–0.85 | 0.0002 | 0.77 | 0.63–0.92 | 0.0047 |
| No. of prior therapy | ≥2 (vs. 0 or 1) | 1.39 | 1.17–1.66 | 0.0003 | 1.29 | 1.08–1.55 | 0.0057 |
| Performance Status | ≥2 (vs. 0 or 1) | 3.18 | 2.56–3.91 | <0.0001 | 2.89 | 2.30–3.59 | <0.0001 |
| PD-L1 status | 1-49% (vs. <1%) | 0.73 | 0.46–1.16 | 0.1743 |  |  |  |
|  | ≥50% (vs. <1%) | 0.66 | 0.44–1.00 | 0.052 |  |  |  |
| Response | CR (vs. others) | 0.07 | 0.01–0.22 | <0.0001 | 0.096 | 0.02–0.30 | <0.0001 |
|  | CR + PR (vs. SD) | 0.20 | 0.15–0.26 | <0.0001 |  |  |  |
| WBC fraction | Group A (vs. others) | 0.68 | 0.54–0.84 | 0.0003 | 0.85 | 0.68–1.06 | 0.1483 |
| Radiation therapy | With (vs. without) | 1.24 | 0.95–1.60 | 0.1117 | 1.01 | 0.77–1.31 | 0.9357 |
| AE | With (vs. without) | 0.64 | 0.50–0.80 | <0.0001 | 0.71 | 0.56–0.90 | 0.0035 |

Abbreviations: Ad, adenocarcinoma; AE, adverse event; CR, complete response; No, number; OS, overall survival; PD-L1, programmed death-ligand-1; PR, partial response; SD, stable disease; WBC, white blood cell.

**Table S4 Univariate and multivariate analyses of OS in the LT group**

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model. Without considering the results of the univariate analysis, the factors considered important from the results of the previous report and the medical point of view were selected for inclusion in multivariate analysis.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Univariate** | | | **Multivariate** | | |
| **Parameter** | **Category** | **HR** | **95% CI** | ***p*-value** | **HR** | **95% CI** | ***p*-value** |
| Age (years) | ≥75 (vs. <75) | 0.80 | 0.19–2.38 | 0.7103 | 0.89 | 0.20–2.72 | 0.8515 |
| Sex | Female (vs. male) | 1.11 | 0.32–3.02 | 0.8579 |  |  |  |
| Smoking Status | Smoker (vs. never) | 0.65 | 0.19–4.10 | 0.5872 |  |  |  |
| Pack-years | ≥30 (vs. <30) | 0.65 | 0.27–1.70 | 0.3559 |  |  |  |
| Histology | Ad (vs. others) | 0.51 | 0.21–1.18 | 0.1159 |  |  |  |
| Stage at diagnosis | Stage IV (vs. others) | 1.26 | 0.54–3.16 | 0.6002 |  |  |  |
| Tumor burden | <45 mm (vs. ≥45 mm) | 0.75 | 0.28–1.80 | 0.5246 |  |  |  |
| No. of prior therapy | ≥2 (vs. 0 or 1) | 2.62 | 1.11–6.62 | 0.0278 | 2.43 | 1.02–6.21 | 0.0449 |
| Performance status | ≥2 (vs. 0 or 1) | 0.61 | 0.03–2.95 | 0.6064 |  |  |  |
| PD-L1 status | 1-49% (vs. <1%) | NAa | 0–0.67 | 0.033 |  |  |  |
|  | ≥50% (vs. <1%) | 0.36 | 0.07–6.77 | 0.402 |  |  |  |
| Response category | CR (vs. others) | NAa | 0.95–0.95 | 0.0455 | NAa | 0.92–1.11 | 0.062 |
|  | CR + PR (vs.SD) | 0.47 | 0.20–1.24 | 0.1219 |  |  |  |
| WBC fraction | Group A (vs. others) | 1.20 | 0.45–2.85 | 0.7059 |  |  |  |
| Radiation therapy | With (vs. without) | 0.94 | 0.15–3.24 | 0.9308 |  |  |  |
| AE | With (vs. without) | 0.64 | 0.50–0.80 | <0.0001 |  |  |  |

Abbreviations: Ad, adenocarcinoma; AE, adverse event. CR, complete response; LT group, patients receiving initial immune checkpoint inhibitor for >1 year without progression disease; No, number; OS, overall survival; PD-L1, programmed death-ligand-1; PR, partial response; SD, stable disease; WBC, white blood cell.

a Number of patients who achieved complete response or had PS ≥2 at the start of ICI administration showed disease progression. Therefore, hazard ratios could not be calculated.

**Table S5** **Univariate analysis of PFSR**

The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model. Without considering the results of the univariate analysis, the factors considered important from the results of the previous report and the medical point of view were selected for inclusion in multivariate analysis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Univariate** | | |
| **Parameter** | **Category** | **HR** | **95% CI** | ***p*-value** |
| Age (years) | ≥75 (vs. <75) | 0.91 | 0.27–2.36 | 0.8555 |
| Sex | Female (vs. male) | 1.47 | 0.58–3.34 | 0.3939 |
| Smoking status | Smoker (vs. never) | 1.52 | 0.53–6.40 | 0.4735 |
| Pack-years | ≥30 (vs. <30) | 0.94 | 0.44–2.13 | 0.8857 |
| Histology | Ad (vs. others) | 0.92 | 0.43–1.95 | 0.8354 |
| PD-L1 status | 1-49% (vs. <1%) | 3.37 | 0.48–66.8 | 0.2366 |
|  | ≥50% (vs. <1%) | 4.09 | 0.80–74.8 | 0.1004 |
| Duration of prior ICI therapy | LT group (vs. NLT group) | 1.13 | 0.46–2.51 | 0.7817 |
| Response category of prior ICI therapy | CR +PR (vs. others) | 0.44 | 0.20–0.96 | 0.0381 |
| Reason of discontinuation of prior ICI therapy | PD (vs. others) | 2.81 | 1.25–6.93 | 0.0122 |
| PFS from discontinuation of prior ICI therapy | ≥3 months (vs. <3 months) | 0.36 | 0.14–0.80 | 0.0122 |

Abbreviations: Ad, adenocarcinoma; CR, complete response; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand-1; PFSR, progression-free survival of rechallenge; PD, progression disease; PR, partial response; RFS, recurrence-free survival.

**Table S6** **Frequency and time to AEs in the LT group**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No. (%)** | | |
|  | **All**  **(n=24)** | **Grade 3 to 5 AEs**  **(n=8)** | **Median months (range) to onset of serious AEa** |
| **Category** |
| Pulmonary | 12 (50) | 1 (13) | 23.3 (12.2–39.6) |
| GI | 2 (8) | 2 (25) | 14.2 (13.2–15.2) |
| Skin | 3 (13) | 2 (25) | 13.6 (13.4–33.8) |
| Endocrine | 4 (17) | 1 (13) | 22.0 (14.0–38.7) |
| Brain | 1 (4) | 1 (13) | 15.2 |
| Musculoskeletal | 2 (8) | 1 (13) | 20.0 (15.7–24.2) |

Abbreviations: AE, adverse event; GI, gastrointestinal; LT group, patients receiving initial immune checkpoint inhibitor for >1 year without progression disease; No., number.

a serious AE refers to Grade 3 to 5 AE