**The Effectiveness and Safety of Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer Patients with Stage III/IV**

Supplementary Appendix

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# **Table S1**. Studies related to efficacy and safety of cancer immunotherapies (Clinical Trials)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Name of Trial** | **Drug name** | **Author** | **PD L1, %** | **With chemo** | **Line** | **N\_E** | **N\_C** | **Study Time** | **RR, %** | **Median OS, (month)** | **Median PFS, (month)** | **≥Grade 3 AE, %** |
| KEYNOTE-021 | Pembrolizumab | Langer (2016) | All | V | 1st | 60 | 63 | 2014.11-2016.01 | 55 vs. 29 | - | 13 vs. 8.9 | 39 vs. 26 |
| IMpower150 | Atezolizumab | Socinski (2018) | - | V | 1st | 400 | 400 | 2015.03-2016.12 | 63.5 vs. 48 | 19.2 vs. 17.4 | 8.3 vs. 6.8 | 55.7 vs. 47.7 |
| KEYNOTE-407 | Pembrolizumab | Paz-Ares (2018) | All | V | 1st | 278 | 281 | 2016.08-2017.12 | 57.9 vs. 38.4 | 15.9 vs. 11.3 | 6.4 vs. 4.8 | 69.2 vs. 68.2 |
| KEYNOTE-189 | Pembrolizumab | Gandhi (2018) | All | V | 1st | 410 | 206 | 2016.02-2017.03 | 47.6 vs. 18.9 | NR vs. 11.3 | 8.8 vs. 4.9 | 67.2 vs. 65.8 |
| KEYNOTE-024 | Pembrolizumab | Reck (2016) | ≥50% | X | 1st | 154 | 151 | 2014.09-2015.10 | 44.8 vs. 27.8 | - | 10.3 vs. 6 | 26.6 vs. 53.3 |
| KEYNOTE-042 | Pembrolizumab | Mok (2019) | ≥50%, ≥20%, ≥1% | V | 1st | 637 | 637 | 2014.12-2017.03 | - | 20.0 vs. 12.2;17.7 vs. 13.016.7 vs. 12.1 | 7.1 vs. 6.46.2 vs. 6.65.4 vs. 6.5 | 17.8 vs. 41.0 |
| CheckMate-026 | Nivolumab | Carbone (2017) | ≥1% | X | 1st | 271 | 270 | 2014.03-2015.04 | 26 vs. 33 | 14.4 vs. 13.2 | 4.2 vs. 5.9 | 18 vs. 51 |
| OAK | Atezolizumab | Rittmeyer (2017) | All | X | 2nd | 425 | 425 | 2014.03-2015.04 | 14 vs. 13 | 13.8 vs. 9.6 | 2.8 vs. 4 | 15 vs. 43 |
| CheckMate-017 | Nivolumab | Brahmer (2015) | All | X | 2nd | 135 | 137 | 2012.10-2013.12 | 20 vs. 9 | 9.2 vs. 6 | 3.5 vs. 2.8 | 7 vs. 55 |
| CheckMate -057 | Nivolumab | Borghaei (2015) | All | X | 2nd | 292 | 290 | 2012.11-2013.12 | 19 vs. 12 | 12.2 vs. 9.4 | 2.3 vs. 4.2 | 10 vs. 54 |
| KEYNOTE-010 | Pembrolizumab | Herbst (2016) | >1% | X | 2nd | 344(2mg/kg); 346(10mg/kg) | 343 | 2013.08-2015.02 | - | 10.42(2mg/kg); 12.7(10mg/kg) vs. 8.5 | 3.9(2mg/kg); 4(10mg/kg) vs. 4 | 13(2mg/kg); 16(10mg/kg) vs. 35 |

**Note**: N\_E, number of experimental group; N\_C, number of control group; RR, response rate; OS, overall survival; PFS, progress-free survival; AE, adverse events;

# **Table S2.** Demographic characteristic of ICIs patients before matching

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Immune checkpoint inhibitors, n = 91, N (%)** | **Variables** | **Immune checkpoint inhibitors, n = 91, N (%)** |
| **Age** |  | **Smoking status** |  |
| Mean (SD) | 62.87 (11.54) | Current | 17 (18.7) |
| 30-39 | 2 (2.2) | Never | 74 (81.3) |
| 40-49 | 11 (12.1) | **HBsAg** |  |
| 50-59 | 22 (24.2) | Positive | 12 (13.2) |
| 60-69 | 29 (31.9) | Negative | 74 (81.3) |
| 70-79 | 21 (23.1) | Missing | 5 (5.5) |
| 80-89 | 6 (6.6) | **HCVAb** |  |
| **Sex** |  | Positive | 2 (2.2) |
| Male | 58 (63.7) | Negative | 82 (90.1) |
| Female | 33 (36.3) | Missing | 7 (7.7) |
| **Performance status** |  | **Lung cancer surgery history** |  |
| 0-1 | 79 (86.8) | Yes | 16 (17.6) |
| 2-4 | 12 (13.2) | No | 75 (82.4) |
| **EGFR/ALK mutation** |  | **Steroid usec** |  |
| Positive | 22 (24.2) | Yes | 19 (20.9) |
| Negative | 68 (74.7) | No | 72 (79.1) |
| **Treatment linesa** |  | **ICIs types** |  |
| First-line | 30 (33) | Pembrolizumab | 37 (40.7) |
| Second-line | 17 (18.7) | Nivolumab | 42 (46.2) |
| Third-line and over | 44 (48.4) | Atezolizumab | 12 (13.2) |
| **Histology** |  | **Median treatment duration, month** |  |
| Squamous | 15 (16.5) | Pembrolizumab | 2.07 |
| Non-squamous | 76 (83.5) | Nivolumab | 3.44 |
| **Tumor stageb** |  | Atezolizumab | 3.45 |
| III | 7 (7.7) | **Combined with chemotherapy** |  |
| IV | 84 (92.3) | Yes | 41 (45.1) |
| **Brain metastasis** |  | No | 50 (54.9) |
| Yes | 27 (29.7) | **Combined with radiotherapy**  |  |
| No | 64 (70.3) | Yes | 10 (11) |
| **PD-L1 expression** |  | No | 81 (89) |
| Positive | 46 (50.5) | **Grade 3 and over of AE** |  |
| Negative | 8 (8.8) | Yes | 11 (12.1) |
| Missing | 37 (40.7) | No | 80 (87.9) |

**Note**: aTreatment lines, represents the line of treatment with medications.

bTumor stage, represents the stage of patients at the time of cancer diagnosis.

cSteroid used, represents the patients who used steroid drugs more than a week (7 days) at the time of cancer treatment.

# **Table S3.** Basic characteristics of both ICIs and Chemo groups by treatment lines before matching

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **First-linea** | **Second-linea** | **Third-line and overa** |
| **Immune checkpoint inhibitors****n = 30, N (%)** | **Chemotherapy****n = 130, N (%)** | **p-valueb** | **Immune checkpoint inhibitors****n = 17, N (%)** | **Chemotherapy****n = 92, N (%)** | **p-valueb** | **Immune checkpoint inhibitors****n = 44, N (%)** | **Chemotherapy****n = 78, N (%)** | **p-valueb** |
| **Age** |  |  | 0.155 |  |  | 0.127 |  |  | 0.339 |
| Mean (SD) | 66.6 (12.2) | 62.02 (11.1) | **0.047** | 62 (9.5) | 67.4 (11.1) | 0.063 | 60.05 (11.3) | 63.79 (11.0) | 0.075 |
| 30-39 | 1 (3.3) | 5 (3.8) |  | 0 (0) | 1 (1.1) |  | 2 (4.5) | 1 (1.3) |  |
| 40-49 | 1 (3.3) | 10 (7.7) |  | 2 (11.8) | 5 (5.4) |  | 7 (15.9) | 5 (6.4) |  |
| 50-59 | 8 (26.7) | 33 (25.4) |  | 3 (17.6) | 17 (15.8) |  | 12 (27.3) | 25 (32.1) |  |
| 60-69 | 6 (20) | 51 (39.2) |  | 10 (58.8) | 28 (30.4) |  | 12 (27.3) | 20 (25.6) |  |
| 70-79 | 10 (33.3) | 24 (18.5) |  | 2 (11.8) | 29 (31.5) |  | 10 (22.7) | 21 (26.9) |  |
| 80-89 | 4 (13.3) | 7 (5.4) |  | 0 (0) | 12 (13) |  | 1 (2.3) | 6 (7.7) |  |
| **Sex** |  |  | 0.815 |  |  | 0.552 |  |  | 0.751 |
| Male | 23 (76.7) | 97 (74.6) |  | 10 (58.8) | 61 (66.3) |  | 25 (56.8) | 42 (53.8) |  |
| Female | 7 (23.3) | 33 (25.4) |  | 7 (41.2) | 31 (33.7) |  | 19 (43.2) | 36 (46.2) |  |
| **Histology** |  |  | 0.517 |  |  | 0.897 |  |  | 0.983 |
| Squamous | 7 (23.3) | 38 (29.2) |  | 4 (23.5) | 23 (25) |  | 4 (9.1) | 7 (9) |  |
| Non-squamous | 23 (76.7) | 92 (70.8) |  | 13 (76.5) | 69 (75) |  | 40 (90.9) | 71 (91) |  |
| **Stage** |  |  | **0.004** |  |  | 0.374 |  |  | 0.185 |
| III | 1 (3.3) | 37 (28.5) |  | 2 (11.8) | 20 (21.7) |  | 4 (9.1) | 14 (17.9) |  |
| IV | 29 (96.7) | 93 (71.5) |  | 15 (88.2) | 72 (78.3) |  | 40 (90.9) | 64 (82.1) |  |
| **Performance status** |  |  | 0.324 |  |  | 0.430 |  |  | 0.062 |
| 0-1 | 26 (86.7) | 120 (92.3) |  | 14 (82.4) | 63 (68.5) |  | 39 (88.6) | 55 (70.5) |  |
| 2-4 | 4 (13.3) | 10 (7.7) |  | 3 (17.7) | 23 (25) |  | 5 (11.4) | 19 (24.4) |  |
| **EGFR/ALK mutation** |  |  | 0.630 |  |  | 0.825 |  |  | 0.125 |
| Positive | 0 (0) | 1 (0.8) |  | 4 (23.5) | 24 (26.1) |  | 18 (40.9) | 44 (56.4) |  |
| Negative | 30 (100) | 129 (99.2) |  | 13 (76.5) | 68 (73.9) |  | 25 (56.8) | 34 (43.6) |  |
| **PD-L1 expression** |  |  | **<0.001** |  |  | **0.027** |  |  | **0.012** |
| Positive | 23 (76.7) | 35 (26.9) |  | 9 (52.9) | 20 (21.7) |  | 11 (25) | 16 (20.5) |  |
| Negative | 1 (3.3) | 10 (7.7) |  | 1 (5.9) | 7 (7.6) |  | 6 (13.6) | 1 (1.3) |  |
| Missing | 6 (20) | 85 (65.4) |  | 7 (41.2) | 65 (70.7) |  | 27 (61.4) | 61 (78.2) |  |

**Note**: aTreatment lines, represents the initial line of treatment with medications.

bp-value was calculated using Student t test with continuous variables and chi-square or Fisher exact test with category variables.

# **Table S4.** Overall survival analysis between ICIs and Chemo group by treatment lines after matching

|  |  |  |
| --- | --- | --- |
|  | **Unadjusted** | **Adjusted** |
| **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| All line | 0.96 (0.64-1.44) | 0.838 | 0.93 (0.64-1.44) | 0.838 |
|  First-line | 1.1 (0.51-2.35) | 0.812 | 1.11 (0.51-2.43) | 0.796 |
|  Second-line | 1.04 (0.35-3.12) | 0.947 | 0.95 (0.28-3.19) | 0.931 |
|  Third-line and over | 0.75 (0.43-1.32) | 0.319 | 0.81 (0.45-1.45) | 0.477 |

**Note**: The adjusted hazard ratio was adjusted for histological types, Tumor stage, Brain metastasis, and PD-L1 expression variables

# **Table S5.** Treatment-related adverse events in both ICIs and Chemo groups

|  |  |  |
| --- | --- | --- |
| **Adverse event types** | **Immune checkpoint inhibitors****n = 79, N (%)** | **Chemotherapy****n = 79, N (%)** |
| **Overall** | 10 (12.7) | 17 (21.5) |
| Pneumonitis | 5 (6.3) | 0 |
| Hepatitis | 1 (1.3) | 0 |
| Hyperthyroidism | 1 (1.3) | 0 |
| Multiple arthralgia | 1 (1.3) | 0 |
| Pruritus | 1 (1.3) | 0 |
| Encephalitis  | 1 (1.3) | 0 |
| Chronic inflammatory  | 1 (1.3) | 0 |
| Demyelinating polyneuropathy |  |  |
| Fatigue | 2 (2.5) | 2 (2.5) |
| Skin rash | 3 (3.8) | 0 |
| Neutropenia  | 0 | 10 (12.7) |
| Alopecia | 0 | 3 (3.8) |
| Anemia  | 0 | 2 (2.5) |
| Diarrhea | 0 | 1 (1.3) |
| Nausea   | 0 | 1 (1.3) |
| Vomiting | 0 | 1 (1.3) |
| Numbness  | 0 | 1 (1.3) |
| Septic cardiomyopathy | 0 | 1 (1.3) |
| Septic shock | 0 | 1 (1.3) |
| Anorexia | 0 | 1 (1.3) |

|  |
| --- |
| A. |
| B. |

# **Figure S1.** Treatment-related adverse events by time

**Note**: A, ICIs drugs group; B, Chemotherapy drugs group