

Supplementary Table 1. Baseline characteristics of patients with available *HER2* variant

| Variables | All (%) (N = 22) | <i>HER2</i> variant | | <i>P</i> |
|--|---------------------|---------------------|---------------------|----------|
| | | Group a (N = 9) | Group b (N = 13) | |
| Median age, years (range) | 55 (38-69) | 58 (38-68) | 53 (40-69) | |
| Gender | | | | 1.000 |
| Male | 12 (54.5) | 5 (55.6) | 7 (53.8) | |
| Female | 10 (45.5) | 4 (44.4) | 6 (46.2) | |
| Smoking history | | | | 0.965 |
| Never smokers | 16 (72.7) | 6 (66.7) | 10 (76.9) | |
| Former or current smokers | 6 (27.3) | 3 (33.3) | 3 (23.1) | |
| ECOG PS | | | | 0.304 |
| 0-1 | 20 (90.9) | 7 (77.8) | 13 (100) | |
| ≥ 2 | 2 (9.1) | 2 (22.2) | 0 (0) | |
| PD-L1 status | | | | 0.731 |
| 1-49% | 6 (27.3) | 2 (22.2) | 4 (30.8) | |
| Negative | 6 (27.3) | 2 (22.2) | 4 (30.8) | |
| Unknown | 10 (45.5) | 5 (55.6) | 5 (38.5) | |
| History of pulmonary resection for lung cancer | | | | 0.730 |
| Yes | 3 (13.6) | 2 (22.2) | 1 (7.7) | |
| No | 19 (86.4) | 7 (77.8) | 12 (92.3) | |
| Line of ICIs therapy | | | | 1.000 |
| First-line | 5 (22.7) | 2 (22.2) | 3 (23.1) | |
| > Second-line | 17 (77.3) | 7 (77.8) | 10 (76.9) | |
| Treatment data | | | | 0.997 |
| Monotherapy | 5 (22.7) | 2 (22.2) | 3 (23.1) | |
| Combination with chemotherapy | 12 (54.5) | 5 (55.6) | 7 (53.8) | |
| Others ^a | 5 (22.7) | 2 (22.2) | 3 (23.1) | |
| Best response to ICIs therapy | | | | 0.715 |
| PR | 7 (31.8) | 2 (22.2) | 5 (38.5) | |
| SD | 11 (50) | 5 (55.6) | 6 (46.2) | |
| PD | 4 (18.2) | 2 (22.2) | 2 (15.4) | |
| Objective response rate, % | 31.8 | 22.2 | 38.5 | 0.735 |
| Disease control rate, % | 81.8 | 77.8 | 84.6 | 1.000 |

a, including combination with anti-angiogenesis (n=3), combination with chemotherapy plus anti-angiogenesis (n=1), or combination with chemotherapy plus *HER2*-targeting drugs (n=1).

Group a, A775_G776insYVMA; Group b: other *HER2* variant, including Y772_A775dup, G776 mutation, G778_P780dup and L755P mutation.

ICIs, immune checkpoint inhibitors; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response; SD, stable disease; PD, progression disease.

SupplementaryTable2. Baseline characteristics of the entire cohort

| Variables | All (%) (N = 26) | Group 1 (N = 5) | Group 2 (N = 6) | Group 3 (N = 15) | <i>P</i> |
|--|---------------------|--------------------|--------------------|---------------------|----------|
| Median age, years (range) | 55 (38-69) | 57 (46-65) | 55 (45-68) | 53 (38-69) | |
| Gender | | | | | 0.672 |
| Male | 14 (53.8) | 2 (40) | 4 (66.7) | 8 (53.3) | |
| Female | 12 (46.2) | 3 (60) | 2 (33.3) | 7 (46.70) | |
| Smoking history | | | | | 0.051 |
| Never smokers | 18 (69.2) | 5 (100) | 2 (33.3) | 11 (73.3) | |
| Former or current smokers | 8 (30.8) | 0 | 4 (66.7) | 4 (26.7) | |
| ECOG PS | | | | | 0.027 |
| 0-1 | 24 (92.3) | 5 (100) | 4 (66.7) | 15 (100) | |
| ≥ 2 | 2 (7.7) | 0 | 2 (33.3) | 0 | |
| PD-L1 status | | | | | 0.623 |
| ≥50% | 1 (3.8) | 0 | 0 | 1 (6.7) | |
| 1-49% | 6 (23.1) | 0 | 2 (33.3) | 4 (26.7) | |
| Negative | 8 (30.8) | 3 (60) | 2 (33.3) | 3 (20) | |
| Unknown | 11 (42.3) | 2 (40) | 2 (33.3) | 7 (46.7) | |
| History of pulmonary resection for lung cancer | | | | | 0.652 |
| Yes | 3 (11.5) | 1 (20) | 1 (16.7) | 1 (6.7) | |
| No | 23 (88.5) | 4 (80) | 5 (83.3) | 14 (93.3) | |
| Line of ICIs therapy | | | | | 0.122 |
| First-line | 9 (34.6) | 2 (40) | 0 | 7 (46.7) | |
| > Second-line | 17 (65.4) | 4 (60) | 6 (100) | 8 (53.3) | |
| Treatment data | | | | | 0.731 |
| Monotherapy | 5 (19.2) | 1 (20) | 1 (16.7) | 3 (20) | |
| Combination with chemotherapy | 16 (61.5) | 4 (80) | 3 (50) | 9 (60) | |
| Others ^a | 5 (19.2) | 0 | 2 (33.3) | 3 (20) | |
| Best response to ICIs therapy | | | | | 0.519 |
| PR | 10 (38.5) | 3 (60) | 2 (33.3) | 5 (33.3) | |
| SD | 12 (46.2) | 1 (20) | 4 (66.7) | 7 (46.7) | |
| PD | 4 (15.4) | 1 (20) | 0 | 3 (20) | |
| Objective response rate, % | 38.5 | 60 | 33.3 | 33.3 | 0.545 |
| Disease control rate, % | 84.6 | 80 | 100 | 80 | 0.492 |

a, including combination with anti-angiogenesis (n=3), combination with chemotherapy plus anti-angiogenesis (n=1), or combination with chemotherapy plus *HER2*-targeting drugs (n=1). Group 1, patients received ICIs before *EGFR/HER2*-targeting drugs; Group 2, patients received ICIs after *EGFR/HER2*-targeting drugs; Group 3, patients never treated with *EGFR/HER2*-targeting drugs until their last follow-up.

ICIs, immune checkpoint inhibitors; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response; SD, stable disease; PD, progression disease.