|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **ALL NSCLC** | | | ***RET+EGFR-* Distribution by Histologic subtypes** | | | | | | | | | | | |
| **N (%)** | ***RET+EGFR-*** | ***RET-*** | **Odds Ratio (OR)/ P value** | **High grade** | **Non-High grade** | **OR/ P value** | **Subtype undetermined/ Adenocarcinoma, NOS** | **Non-Subtype undetermined** | **OR/ P value** | **Papillary** | **Non-Papillary** | **OR/ P value** | **Acinar** | **Non-Acinar** | **OR/ P value** |
| **Total N** | **503** | **72003** |  | 161 | 342 |  | 112 | 391 |  | 102 | 401 |  | 50 | 453 |  |
| **Male sex** | 243 (48.31) | 35971 (49.96) | 0.94/ p=0.65 | 91 (56.52) | 152 (44.44) | 1.63/ p=0.07 | 48 (42.86) | 195 (49.87) | 0.75/ p=1.00 | 44 (43.14) | 199 (49.63) | 0.77/ p=0.84 | 26 (52.00) | 217 (47.90) | 1.18/ p=1.00 |
| **Median age range in years** | 66 (28-89) (57-74) | 69 (4-89) (62-76) |  | 66 (30-89) (57.75-73) | 66 (28-89) (56.5-74) |  | 67.5 (28-89) (55.25-75) | 66 (30-89) (58-73) |  | 68 (36-89) (59-74.5) | 66 (28-89) (56-74) |  | 65 (37-88) (57.75-73) | 66 (28-89) (57-74) |  |
| **GA/tumor** | 4.7 | 6.1 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Genomic alterations** | | | | | | | | | | | | | | | |
| **Total N** | **503** | **71876** |  | 161 | 342 |  | 112 | 391 |  | 102 | 401 |  | 50 | 453 |  |
| ***APC*** | 9 (1.79) | 2137 (2.97) | 0.60/ p=0.31 | 3 (1.86) | 6 (1.75) | 1.06/ p=1.00 | 2 (1.79) | 7 (1.79) | 1.00/ p=1.00 | 0 (0.00) | 9 (2.24) | 0.00/ p=1.00 | 1 (2.00) | 8 (1.77) | 1.14/ p=1.00 |
| ***ARFRP1*** | 14 (2.78) | 1105 (1.54) | 1.84/ p=0.13 | 4 (2.48) | 10 (2.92) | 0.85/ p=1.00 | 1 (0.89) | 13 (3.32) | 0.26/ p=1.00 | 5 (4.90) | 9 (2.24) | 2.25/ p=1.00 | 3 (6.00) | 11 (2.43) | 2.56/ p=1.00 |
| ***ATM*** | 22 (4.37) | 3474 (4.83) | 0.90/ p=0.81 | 9 (5.59) | 13 (3.80) | 1.14/ p=1.00 | 4 (3.57) | 18 (4.60) | 0.73/ p=1.00 | 4 (3.92) | 18 (4.49) | 0.36/ p=1.00 | 2 (4.00) | 20 (4.42) | 1.38/ p=1.00 |
| ***BRAF*** | 5 (0.99) | 3864 (5.38) | 0.18/ p<0.05 | 2 (1.24) | 3 (0.88) | 1.50/ p=1.00 | 1 (0.89) | 4 (1.02) | 0.77/ p=1.00 | 2 (1.96) | 3 (0.75) | 0.87/ p=1.00 | 0 (0.00) | 5 (1.10) | 0.90/ p=1.00 |
| ***BRCA1*** | 1 (0.20) | 1066 (1.48) | 0.13/ p<0.05 | 1 (0.62) | 0 (0.00) | 1.42/ p=1.00 | 0 (0.00) | 1 (0.26) | 0.87/ p=1.00 | 0 (0.00) | 1 (0.25) | 2.65/ p=1.00 | 0 (0.00) | 1 (0.22) | 0.00/ p=1.00 |
| ***BRCA2*** | 7 (1.39) | 1467 (2.04) | 0.68/ p=0.42 | 1 (0.62) | 6 (1.75) | inf/ p=0.32 | 0 (0.00) | 7 (1.79) | 0.00/ p=1.00 | 3 (2.94) | 4 (1.00) | 0.00/ p=1.00 | 2 (4.00) | 5 (1.10) | 0.00/ p=1.00 |
| ***CCNE1*** | 7 (1.39) | 2324 (3.23) | 0.42/ p=0.06 | 3 (1.86) | 4 (1.17) | 0.35/ p=0.44 | 3 (2.68) | 4 (1.02) | 0.00/ p=0.36 | 0 (0.00) | 7 (1.75) | 3.01/ p=0.15 | 0 (0.00) | 7 (1.55) | 3.73/ p=0.15 |
| ***CDK4*** | 27 (5.37) | 2391 (3.33) | 1.65/ p=0.06 | 11 (6.83) | 16 (4.68) | 1.60/ p=1.00 | 6 (5.36) | 21 (5.37) | 2.66/ p=1.00 | 5 (4.90) | 22 (5.49) | 0.00/ p=1.00 | 2 (4.00) | 25 (5.52) | 0.00/ p=1.00 |
| ***CDKN2A*** | 140 (27.83) | 22234 (30.93) | 0.86/ p=0.31 | 52 (32.30) | 88 (25.73) | 1.49/ p=1.00 | 30 (26.79) | 110 (28.13) | 1.00/ p=1.00 | 16 (15.69) | 124 (30.92) | 0.89/ p=1.00 | 9 (18.00) | 131 (28.92) | 0.71/ p=1.00 |
| ***CDKN2B*** | 102 (20.28) | 13296 (18.50) | 1.12/ p=0.44 | 39 (24.22) | 63 (18.42) | 1.38/ p=0.97 | 22 (19.64) | 80 (20.46) | 0.93/ p=1.00 | 11 (10.78) | 91 (22.69) | 0.42/ p=0.17 | 4 (8.00) | 98 (21.63) | 0.54/ p=1.00 |
| ***CHEK2*** | 11 (2.19) | 1240 (1.73) | 1.28/ p=0.50 | 3 (1.86) | 8 (2.34) | 1.42/ p=0.97 | 1 (0.89) | 10 (2.56) | 0.95/ p=1.00 | 2 (1.96) | 9 (2.24) | 0.41/ p=0.36 | 1 (2.00) | 10 (2.21) | 0.31/ p=1.00 |
| ***FGF12*** | 1 (0.20) | 2803 (3.90) | 0.05/ p<0.05 | 0 (0.00) | 1 (0.29) | 2.15/ p=1.00 | 0 (0.00) | 1 (0.26) | 0.70/ p=1.00 | 0 (0.00) | 1 (0.25) | 0.00/ p=1.00 | 0 (0.00) | 1 (0.22) | 1.83/ p=1.00 |
| ***FGF3*** | 15 (2.98) | 3519 (4.90) | 0.60/ p=0.14 | 5 (3.11) | 10 (2.92) | 0.00/ p=1.00 | 3 (2.68) | 12 (3.07) | 0.00/ p=1.00 | 3 (2.94) | 12 (2.99) | 0.00/ p=1.00 | 1 (2.00) | 14 (3.09) | 0.00/ p=1.00 |
| ***FGFR1*** | 4 (0.80) | 3189 (4.44) | 0.17/ p<0.05 | 0 (0.00) | 4 (1.17) | 0.00/ p=0.97 | 1 (0.89) | 3 (0.77) | 1.17/ p=1.00 | 0 (0.00) | 4 (1.00) | 0.00/ p=1.00 | 1 (2.00) | 3 (0.66) | 3.06/ p=1.00 |
| ***FGFR2*** | 2 (0.40) | 378 (0.53) | 0.76/ p=1.00 | 0 (0.00) | 2 (0.58) | 0.00/ p=1.00 | 1 (0.89) | 1 (0.26) | 3.51/ p=1.00 | 0 (0.00) | 2 (0.50) | 0.00/ p=1.00 | 0 (0.00) | 2 (0.44) | 0.00/ p=1.00 |
| ***FGFR3*** | 1 (0.20) | 661 (0.92) | 0.22/ p=0.23 | 0 (0.00) | 1 (0.29) | 0.00/ p=1.00 | 0 (0.00) | 1 (0.26) | 0.00/ p=1.00 | 0 (0.00) | 1 (0.25) | 0.00/ p=1.00 | 0 (0.00) | 1 (0.22) | 0.00/ p=1.00 |
| ***KEAP1*** | 15 (2.98) | 9711 (13.51) | 0.20/ p<0.05 | 10 (6.21) | 5 (1.46) | 4.46/ p=0.36 | 1 (0.89) | 14 (3.58) | 0.24/ p=1.00 | 1 (0.98) | 14 (3.49) | 0.27/ p=1.00 | 1 (2.00) | 14 (3.09) | 0.64/ p=1.00 |
| ***KMT2D*** | 10 (1.99) | 4690 (6.53) | 0.29/ p<0.05 | 6 (3.73) | 4 (1.17) | 3.27/ p=0.97 | 1 (0.89) | 9 (2.30) | 0.38/ p=1.00 | 1 (0.98) | 9 (2.24) | 0.43/ p=1.00 | 1 (2.00) | 9 (1.99) | 1.01/ p=1.00 |
| ***KRAS*** | 12 (2.39) | 22226 (30.92) | 0.05/ p<0.05 | 5 (3.11) | 7 (2.05) | 1.53/ p=1.00 | 2 (1.79) | 10 (2.56) | 0.69/ p=1.00 | 1 (0.98) | 11 (2.74) | 0.35/ p=1.00 | 1 (2.00) | 11 (2.43) | 0.82/ p=1.00 |
| ***MDM2*** | 45 (8.95) | 3083 (4.29) | 2.20/ p<0.05 | 18 (11.18) | 27 (7.89) | 1.47/ p=0.97 | 5 (4.46) | 40 (10.23) | 0.41/ p=1.00 | 10 (9.80) | 35 (8.73) | 1.14/ p=1.00 | 5 (10.00) | 40 (8.83) | 1.15/ p=1.00 |
| ***MET*** | 6 (1.19) | 3772 (5.25) | 0.22/ p<0.05 | 4 (2.48) | 2 (0.58) | 4.33/ p=0.97 | 2 (1.79) | 4 (1.02) | 1.76/ p=1.00 | 0 (0.00) | 6 (1.50) | 0.00/ p=1.00 | 0 (0.00) | 6 (1.32) | 0.00/ p=1.00 |
| ***MTAP*** | 80 (15.90) | 9948 (13.84) | 1.18/ p=0.35 | 30 (18.63) | 50 (14.62) | 1.34/ p=0.97 | 17 (15.18) | 63 (16.11) | 0.93/ p=1.00 | 9 (8.82) | 71 (17.71) | 0.45/ p=0.95 | 4 (8.00) | 76 (16.78) | 0.43/ p=1.00 |
| ***NF1*** | 10 (1.99) | 5791 (8.06) | 0.23/ p<0.05 | 5 (3.11) | 5 (1.46) | 2.16/ p=0.97 | 2 (1.79) | 8 (2.05) | 0.87/ p=1.00 | 0 (0.00) | 10 (2.49) | 0.00/ p=1.00 | 0 (0.00) | 10 (2.21) | 0.00/ p=1.00 |
| ***NF2*** | 3 (0.60) | 1192 (1.66) | 0.36/ p=0.19 | 1 (0.62) | 2 (0.58) | 1.06/ p=1.00 | 0 (0.00) | 3 (0.77) | 0.00/ p=1.00 | 1 (0.98) | 2 (0.50) | 1.98/ p=1.00 | 0 (0.00) | 3 (0.66) | 0.00/ p=1.00 |
| ***NFE2L2*** | 13 (2.58) | 3427 (4.77) | 0.53/ p=0.06 | 4 (2.48) | 9 (2.63) | 0.94/ p=1.00 | 2 (1.79) | 11 (2.81) | 0.63/ p=1.00 | 3 (2.94) | 10 (2.49) | 1.18/ p=1.00 | 0 (0.00) | 13 (2.87) | 0.00/ p=1.00 |
| ***NSD3*** | 5 (0.99) | 3583 (4.98) | 0.19/ p<0.05 | 0 (0.00) | 5 (1.46) | 0.00/ p=0.97 | 1 (0.89) | 4 (1.02) | 0.87/ p=1.00 | 1 (0.98) | 4 (1.00) | 0.98/ p=1.00 | 1 (2.00) | 4 (0.88) | 2.29/ p=1.00 |
| ***PBRM1*** | 3 (0.60) | 1671 (2.32) | 0.25/ p=0.03 | 2 (1.24) | 1 (0.29) | 4.29/ p=0.97 | 0 (0.00) | 3 (0.77) | 0.00/ p=1.00 | 0 (0.00) | 3 (0.75) | 0.00/ p=1.00 | 0 (0.00) | 3 (0.66) | 0.00/ p=1.00 |
| ***PIK3CA*** | 13 (2.58) | 8231 (11.45) | 0.21/ p<0.05 | 5 (3.11) | 8 (2.34) | 1.34/ p=1.00 | 2 (1.79) | 11 (2.81) | 0.63/ p=1.00 | 1 (0.98) | 12 (2.99) | 0.32/ p=1.00 | 2 (4.00) | 11 (2.43) | 1.67/ p=1.00 |
| ***PRKCI*** | 12 (2.39) | 3257 (4.53) | 0.52/ p=0.06 | 5 (3.11) | 7 (2.05) | 1.53/ p=1.00 | 0 (0.00) | 12 (3.07) | 0.00/ p=1.00 | 1 (0.98) | 11 (2.74) | 0.35/ p=1.00 | 1 (2.00) | 11 (2.43) | 0.82/ p=1.00 |
| ***RB1*** | 20 (3.98) | 5988 (8.33) | 0.46/ p<0.05 | 6 (3.73) | 14 (4.09) | 0.91/ p=1.00 | 8 (7.14) | 12 (3.07) | 2.43/ p=1.00 | 1 (0.98) | 19 (4.74) | 0.20/ p=1.00 | 4 (8.00) | 16 (3.53) | 2.38/ p=1.00 |
| ***RBM10*** | 3 (0.60) | 5176 (7.20) | 0.08/ p<0.05 | 2 (1.24) | 1 (0.29) | 4.29/ p=0.97 | 0 (0.00) | 3 (0.77) | 0.00/ p=1.00 | 1 (0.98) | 2 (0.50) | 1.98/ p=1.00 | 0 (0.00) | 3 (0.66) | 0.00/ p=1.00 |
| ***SETD2*** | 54 (10.74) | 2078 (2.89) | 4.05/ p<0.05 | 12 (7.45) | 42 (12.28) | 0.58/ p=0.97 | 13 (11.61) | 41 (10.49) | 1.12/ p=1.00 | 12 (11.76) | 42 (10.47) | 1.14/ p=1.00 | 7 (14.00) | 47 (10.38) | 1.41/ p=1.00 |
| ***SMARC4*** | 10 (1.99) | 5019 (6.98) | 0.27/ p<0.05 | 4 (2.48) | 6 (1.75) | 1.43/ p=1.00 | 2 (1.79) | 8 (2.05) | 0.87/ p=1.00 | 1 (0.98) | 9 (2.24) | 0.43/ p=1.00 | 2 (4.00) | 8 (1.77) | 2.32/ p=1.00 |
| ***SOX2*** | 3 (0.60) | 4553 (6.33) | 0.09/ p<0.05 | 2 (1.24) | 1 (0.29) | 4.29/ p=0.97 | 0 (0.00) | 3 (0.77) | 0.00/ p=1.00 | 0 (0.00) | 3 (0.75) | 0.00/ p=1.00 | 0 (0.00) | 3 (0.66) | 0.00/ p=1.00 |
| ***STK11*** | 12 (2.39) | 11641 (16.20) | 0.13/ p<0.05 | 6 (3.73) | 6 (1.75) | 2.17/ p=0.97 | 2 (1.79) | 10 (2.56) | 0.69/ p=1.00 | 1 (0.98) | 11 (2.74) | 0.35/ p=1.00 | 1 (2.00) | 11 (2.43) | 0.82/ p=1.00 |
| ***TERC*** | 12 (2.39) | 3357 (4.67) | 0.50/ p=0.05 | 5 (3.11) | 7 (2.05) | 1.53/ p=1.00 | 1 (0.89) | 11 (2.81) | 0.31/ p=1.00 | 0 (0.00) | 12 (2.99) | 0.00/ p=1.00 | 1 (2.00) | 11 (2.43) | 0.82/ p=1.00 |
| ***TP53*** | 211 (41.95) | 50329 (70.02) | 0.31/ p<0.05 | 83 (51.55) | 128 (37.43) | 1.78/ p=0.31 | 49 (43.75) | 162 (41.43) | 1.10/ p=1.00 | 36 (35.29) | 175 (43.64) | 0.70/ p=1.00 | 17 (34.00) | 194 (42.83) | 0.69/ p=1.00 |
| ***ZNF703*** | 6 (1.19) | 2650 (3.69) | 0.32/ p<0.05 | 0 (0.00) | 6 (1.75) | 0.00/ p=0.97 | 1 (0.89) | 5 (1.28) | 0.70/ p=1.00 | 1 (0.98) | 5 (1.25) | 0.78/ p=1.00 | 2 (4.00) | 4 (0.88) | 4.68/ p=1.00 |
| **MSI High** | 1 (0.20) | 356 (0.49) | 0.40/ p=0.65 | 0 (0.00) | 1 (0.29) | 0.00/ p=1.00 | 0 (0.00) | 1 (0.26) | 0.00/ p=1.00 | 0 (0.00) | 1 (0.25) | 0.00/ p=1.00 | 1 (2.00) | 0 (0.00) | inf/ p=0.38 |
| **N** | **503** | **71997** |  | 161 | 342 |  | 84 | 300 |  | 102 | 401 |  | 50 | 453 |  |
| **Median TMB (Range)** | 2.41 (0-45) | 6.25 (0-1977.8) |  | 2.5 (0-45) | 1.25 (0-36.26) |  | 2.41 (0-15) | 2.41 (0-45) |  | 1.25 (0-36.256) | 2.41 (0-45) |  | 1.25 (0-27.76) | 2.41(0-45) |  |
| **TMB ≥10 mut/Mb** | 32 (6.36) | 23881 (33.17) | 0.14/ p<0.05 | 16 (9.94) | 16 (4.68) | 2.25/ p=0.14 | 3 (2.68) | 29 (7.42) | 0.71/ p=1.00 | 5 (4.90) | 27 (6.73) | 0.71/ p=1.00 | 3 (6.00) | 29 (6.40) | 0.93/ p=1.00 |
| **TMB≥20 mut/Mb** | 5 (0.99) | 6812 (9.46) | 0.10/ p<0.05 | 2 (1.24) | 3 (0.88) | 1.42/ p=0.96 | 0 (0.00) | 5 (1.28) | 0.98/ p=1.00 | 1 (0.98) | 4 (1.00) | 0.98/ p=1.00 | 2 (4.00) | 3 (0.66) | 6.25/ p=0.38 |
| **N** | **503** | **72003** |  | 161 | 342 |  | 84 | 300 |  | 102 | 401 |  | 50 | 453 |  |
| ***MMR*** | 3 (0.60) | 1485 (2.06) | 0.00/ p<0.05 | 2 (1.24) | 1 (0.29) | 4.29/ p=0.76 | 0 (0.00) | 3 (0.77) | 0.00/ p=1.00 | 0 (0.00) | 3 (0.75) | 0.00/ p=1.00 | 0 (0.00) | 3 (0.66) | 0.00/ p=1.00 |
| **N** | **250** | **42318** |  | 82 | 168 |  | 50 | 200 |  | 53 | 197 |  | 30 | 220 |  |
| **PD-L1 low positive** | 95 (38) | 13711 (32.4) | 1.28/ p=0.10 | 26 (31.71) | 69 (41.07) | 0.67/ p=0.61 | 18 (36.00) | 77 (38.50) | 0.90/ p=1.00 | 22 (41.51) | 73 (37.06) | 1.21/ p=1.00 | 17 (56.67) | 78 (35.45) | 2.38/ p=0.21 |
| **PD-L1 high positive** | 100 (40) | 13542 (32) | 1.44/p=0.009 | 46 (56) | 54 (32) | 2.7/p=0.007 | 20 (40) | 80 (40) | 1/p=1 | 20 (38) | 81 (41) | 1/ p=0.89 | 3 (10) | 97 (44) | 0.14/ p=0.005 |
| **Other signatures** | | | | | | | | | | | | | | | |
| **N** | **384** | **55023** |  | 129 | 255 |  | 84 | 300 |  | 77 | 307 |  | 37 | 347 |  |
| ***HRD* signature positive** | 4 (1.04) | 2176 (3.95) | 0.26/ p=0.003 | 1 (0.78) | 3 (1.18) | 0.66/ p=1.00 | 1 (1.19) | 3 (1.00) | 1.19/ p=1.00 | 2 (2.60) | 2 (0.65) | 4.07/ p=0.80 | 0 (0.00) | 4 (1.15) | 0.00/ p=1.00 |
| **N** | **503** | **72003** |  | 161 | 342 |  | 112 | 391 |  | 102 | 401 |  | 50 | 453 |  |
| ***APOBEC*** | 13 (2.58) | 3491 (4.85) | 0.52 p=0.03 | 4 (2.48) | 9 (2.63) | 0.94/ p=1.00 | 3 (2.68) | 10 (2.56) | 1.05/ p=1.00 | 2 (1.96) | 11 (2.74) | 0.71/ p=1.00 | 2 (4.00) | 11 (2.43) | 1.67/ p=0.75 |
| ***POLE*** | 0 (0.00) | 47 (0.07) | 0.00/ p=1.00 | 0 (0.00) | 0 (0.00) | For/ p=1.00 | 0 (0.00) | 0 (0.00) | nan/ p=1.00 | 0 (0.00) | 0 (0.00) | nan/ p=1.00 | 0 (0.00) | 0 (0.00) | nan/ p=1.00 |
| ***Tobacco signature*** | 4 (0.80) | 7321 (10.17) | 0.07/ p<0.05 | 1 (0.62) | 3 (0.88) | 0.71/ p=1.00 | 1 (0.89) | 3 (0.77) | 1.17/ p=1.00 | 1 (0.98) | 3 (0.75) | 1.31/ p=1.00 | 1 (2.00) | 3 (0.66) | 3.06/ p=0.75 |