## Supplementary Tables

## **Supplementary Table S1**. Overlap in biomarkers evaluated in OAM4558g

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | MET\_IHC | EGFR\_mutation | KRAS\_mutation | MET\_ex14\_mutation | MET\_N375S\_variant | FISH | qRT-PCR | plasma HGF |
| MET\_IHC | 128 | 110 | 110 | 87 | 111 | 96 | 67 | 91 |
| EGFR\_mutation | 110 | 112 | 112 | 87 | 107 | 90 | 67 | 82 |
| KRAS\_mutation | 110 | 112 | 112 | 87 | 107 | 90 | 67 | 82 |
| MET\_ex14\_mutation | 87 | 87 | 87 | 87 | 87 | 83 | 63 | 64 |
| MET\_N375S\_variant | 111 | 107 | 107 | 87 | 113 | 96 | 66 | 83 |
| FISH | 96 | 90 | 90 | 83 | 96 | 96 | 64 | 70 |
| qRT-PCR | 67 | 67 | 67 | 63 | 66 | 64 | 67 | 45 |
| plasma HGF | 91 | 82 | 82 | 64 | 83 | 70 | 45 | 96 |

## **Supplementary Table S2**. Primers/probes used in quantitative reverse transcription polymerase chain reaction profiling

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene** | **Probe sequence (FAM)** | **Forward primer sequence** | **Reverse primer sequence** |
| *MET* | TGTCTGCCTGCAATC | CGGGACATGGACTCAACAGA | TGCACTATTTGGGAAAACCTTGT |
| *HGF* | CACCTACAATAGTCAATTTA | CTATTTCTCGTTGTGAAGGTGATACC | GGCACAAGATATTACGGGATGGT |
| *EGFR* | ACCATGCAGAAGGAG | TGGGTGCGGAAGAGAAAGAA | CCATCCACTTGATAGGCACTTTG |
| *AREG* | From Life Technologies (cat. No. Hs00950669\_m1) | | |
| *EREG* | From Life Technologies (cat. No. Hs00914313\_m1) | | |

Supplementary Table S3.MET diagnostic scoring criteria

|  |  |  |
| --- | --- | --- |
| **Diagnostic** | **Clinical score** | **Scoring criteria** |
| Positive | 3+ | ≥50% tumor cells with membrane and/or cytoplasmic staining with strong intensity |
|  | 2+ | ≥50% tumor cells with membrane and/or cytoplasmic staining with moderate or higher intensity but <50% tumor cells with strong intensity |
| Negative | 1+ | ≥50% tumor cells with membrane and/or cytoplasmic staining with weak or higher intensity but <50% tumor cells with moderate or higher intensity |
|  | 0 | Samples with staining, or <50% tumor cells with membrane and/or cytoplasmic staining (could be combination of any staining intensities) |

**Supplementary Table S4.** SP44 IHC scores for tissue sections cut from separate tissue blocks representative of the same NSCLC lesion from 10 individuals

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Cells staining at respective intensity (%)** | | | | **Final call** | |
| **Patient ID** | **Tissue slide** | **Negative** | **Weak** | **Moderate** | **Strong** | **IHC score** | **Dx** |
| 1 | A | 15 | 70 | 15 | 0 | 1 | Negative |
| 1 | B | 45 | 50 | 5 | 0 | 1 | Negative |
| 2 | A | 0 | 0 | 60 | 40 | 2 | Positive |
| 2 | B | 0 | 0 | 90 | 10 | 2 | Positive |
| 2 | C | 0 | 0 | 100 | 0 | 2 | Positive |
| 3 | A | 0 | 20 | 70 | 10 | 2 | Positive |
| 3 | B | 0 | 25 | 70 | 5 | 2 | Positive |
| 4 | A | 100 | 0 | 0 | 0 | 0 | Negative |
| 4 | B | 100 | 0 | 0 | 0 | 0 | Negative |
| 5 | A | 0 | 0 | 90 | 10 | 2 | Positive |
| 5 | B | 0 | 0 | 90 | 10 | 2 | Positive |
| 5 | C | 0 | 0 | 90 | 10 | 2 | Positive |
| 5 | D | 0 | 0 | 90 | 10 | 2 | Positive |
| 5 | E | 0 | 0 | 90 | 10 | 2 | Positive |
| 6 | A | 0 | 0 | 100 | 0 | 2 | Positive |
| 6 | B | 0 | 0 | 100 | 0 | 2 | Positive |
| 7 | A | 0 | 70 | 30 | 0 | 1 | Negative |
| 7 | B | 0 | 75 | 25 | 0 | 1 | Negative |
| 8 | A | 0 | 20 | 50 | 30 | 2 | Positive |
| 8 | B | 25 | 0 | 75 | 0 | 2 | Positive |
| 9 | A | 0 | 0 | 100 | 0 | 2 | Positive |
| 9 | B | 0 | 0 | 100 | 0 | 2 | Positive |
| 10 | A | 80 | 0 | 20 | 0 | 0 | Negative |
| 10 | B | 100 | 0 | 0 | 0 | 0 | Negative |

Abbreviations: Dx, diagnostic

**Supplementary Table S5.** Objective response, PFS, and OS in patients with tumors carrying *EGFR* mutations and *KRAS* mutations, by MET diagnostic status, who received O+E or p+E

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **MET-positive** | | **MET-negative** | |
| **Tumor genotype** | **O+E** | **p+E** | **O+E** | **p+E** |
| ***EGFRmut***  *n*  Responders, n (%)  95% CI (%) | 7  3 (42.9)  9.9–81.6 | 2  1 (50)  1.3–98.7 | 0  0 | 4  2 (50)  6.8–93.2 |
| PFSa: HR  95% CI (%)  *P* value | 0.45  0.02–8.98  0.6 | | NA | |
| OSa: HR | NA | | NA | |
| ***KRASmut***  *n*  Responders, n (%)  95% CI (%) | 7  0 (0)  0–41.0 | 6  0 (0)  0–45.9 | 6  0 (0)  0–45.9 | 7  0 (0)  0–41.0 |
| PFSa: HR  95% CI (%)  *P* value | 0.64  0.16–2.60  0.53 | | 1.67  0.48–5.86  0.42 | |
| OSa: HR  95% CI (%)  *P* value | 1.22  0.33–4.43  0.77 | | 1.44  0.20–10.27  0.72 | |

Abbreviations: NA, not available

ap+E versus O+E.

MET-positive: ≥50% of tumor cells with moderate or strong IHC staining intensity.

**Supplementary Table S6.** Biomarker status in patients with *EGFR* mutations and/or objective responses on study

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Subject | Treatment | Response | Tumor Histology | *EGFR* Mutation Status | *KRAS* Mutation Status | *MET* Exon14 Variant Status | *MET* N375S Variant Status | Dx Score | *MET* Copy Number | Type of *MET* Copy g=gain | Plasma HGF Levels (pg/mL) |
| 1 | O+E | Partial response | Adenocarcinoma | ex19\_del | wt | nt | nt | 2 | nt | nt | nt |
| 2 | O+E | Partial response | Adenocarcinoma | ex19\_del | wt | wt | N375S | 2 | 3.67 | High polysomy | 212.2 |
| 3 | O+E | Partial response | Adenocarcinoma | L858R | wt | wt | wt | 2 | 2.81 | Other | 410.9 |
| 4 | O+E |  | Adenocarcinoma | ex19\_del | wt | wt | wt | 2 | 2.44 | Other | 252.4 |
| 5 | O+E |  | Adenocarcinoma | L858R | wt | wt | N375S | 3 | 10.32 | Gene amplification | 832.5 |
| 6 | O+E |  | Adenocarcinoma | L858R | wt | wt | wt | 2 | 3.57 | Other | 11374.5 |
| 7 | O+E |  | Adenocarcinoma | ex19\_del | wt | wt | wt | 2 | 2.43 | Other | 1152.3 |
| 8 | p+E | Partial response | Adenocarcinoma | ex19\_del | wt | wt | wt | 2 | 5.83 | High polysomy | 272.9 |
| 9 | p+E | Partial response | Adenocarcinoma | L858R | wt | wt | N375S | 0 | 2.7 | Other | 953.1 |
| 10 | p+E | Partial response | Adenocarcinoma | ex19\_del | wt | nt | wt | 1 | nt | nt | nt |
| 11 | p+E |  | Adenocarcinoma | L858R | wt | nt | wt | 1 | nt | nt | 775.1 |
| 12 | p+E |  | Adenocarcinoma | ex19\_del | wt | nt | wt | 2 | nt | nt | 681.4 |
| 13 | p+E |  | Squamous cell | G719X | wt | nt | N375S | 1 | 2.85 | other | nt |
| 14 | O+E | Partial response | Squamous cell | wt | wt | wt | wt | 1 | 3.22 | Other | 395.9 |

Abbreviations: nt, not tested; wt, wild-type

Supplementary Table S7.Association of *MET, HGF, EGFR, AREG*, and *EREG* expression with PFS

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| mRNA (median) |  | p+E | | O+E | | HR | 95% CI | *P* value |
| n/N\*\* | Median (months) | n/N\*\* | Median (months) |
| *MET* (3.16) | High\* | 11/12 | 2.6 | 13/22 | 2.7 | 0.76 | 0.33–1.74 | 0.51 |
| Low | 12/19 | 2.7 | 12/14 | 1.4 | 2.52 | 1.1–5.78 | 0.02 |
| *EGFR* (7.75) | High | 9/13 | 2.9 | 12/21 | 1.4 | 1.37 | 0.56–3.38 | 0.49 |
| Low | 14/18 | 2.2 | 13/15 | 1.4 | 1.71 | 0.79–3.74 | 0.17 |
| *AREG* (7.11) | High | 12/13 | 2.7 | 13/21 | 2.5 | 1.01 | 0.45–2.26 | 0.98 |
| Low | 11/18 | 2.6 | 12/15 | 1.4 | 2.4 | 1.02–5.66 | 0.04 |
| *EREG* (0.26) | High | 11/13 | 2.7 | 15/21 | 2.7 | 1.32 | 0.58–3.03 | 0.51 |
| Low | 12/18 | 2.6 | 10/15 | 1.4 | 2.29 | 0.95–5.55 | 0.06 |
| *HGF* (0.25) | High | 11/16 | 2.8 | 12/18 | 2.7 | 1.23 | 0.53–2.85 | 0.63 |
| Low | 12/15 | 2.0 | 13/18 | 1.4 | 1.97 | 0.86–4.5 | 0.10 |

\*High denotes mRNA levels ≥median; low denotes mRNA levels <median

\*\*: n denotes number of events; N denotes number of patients