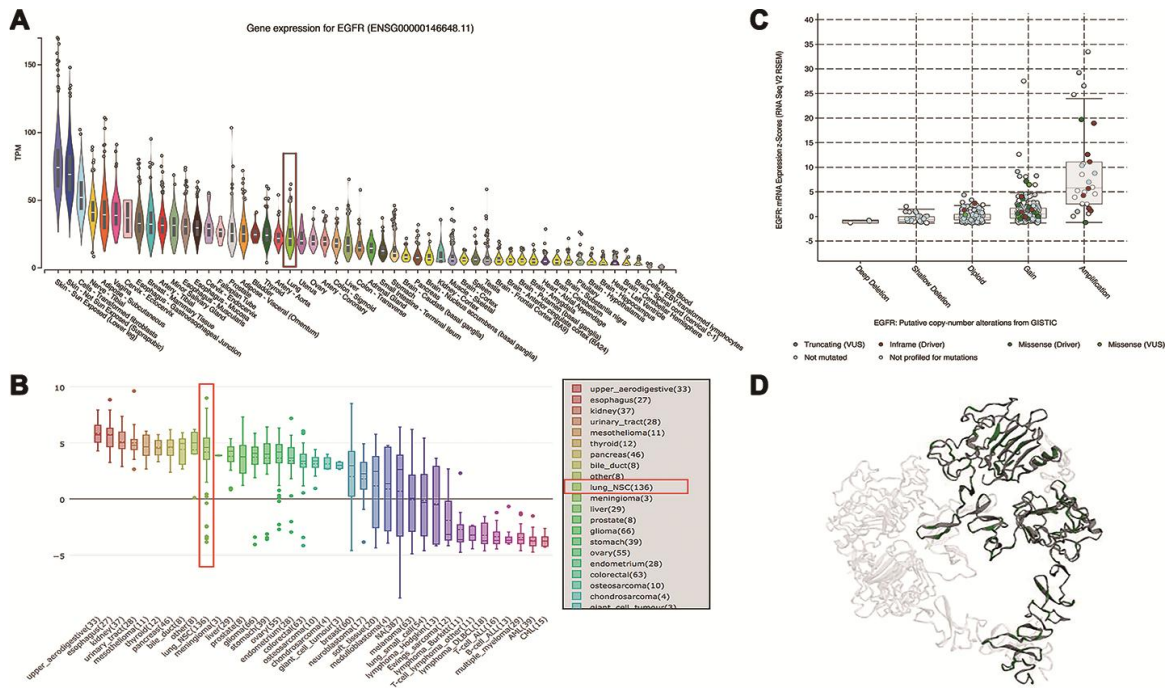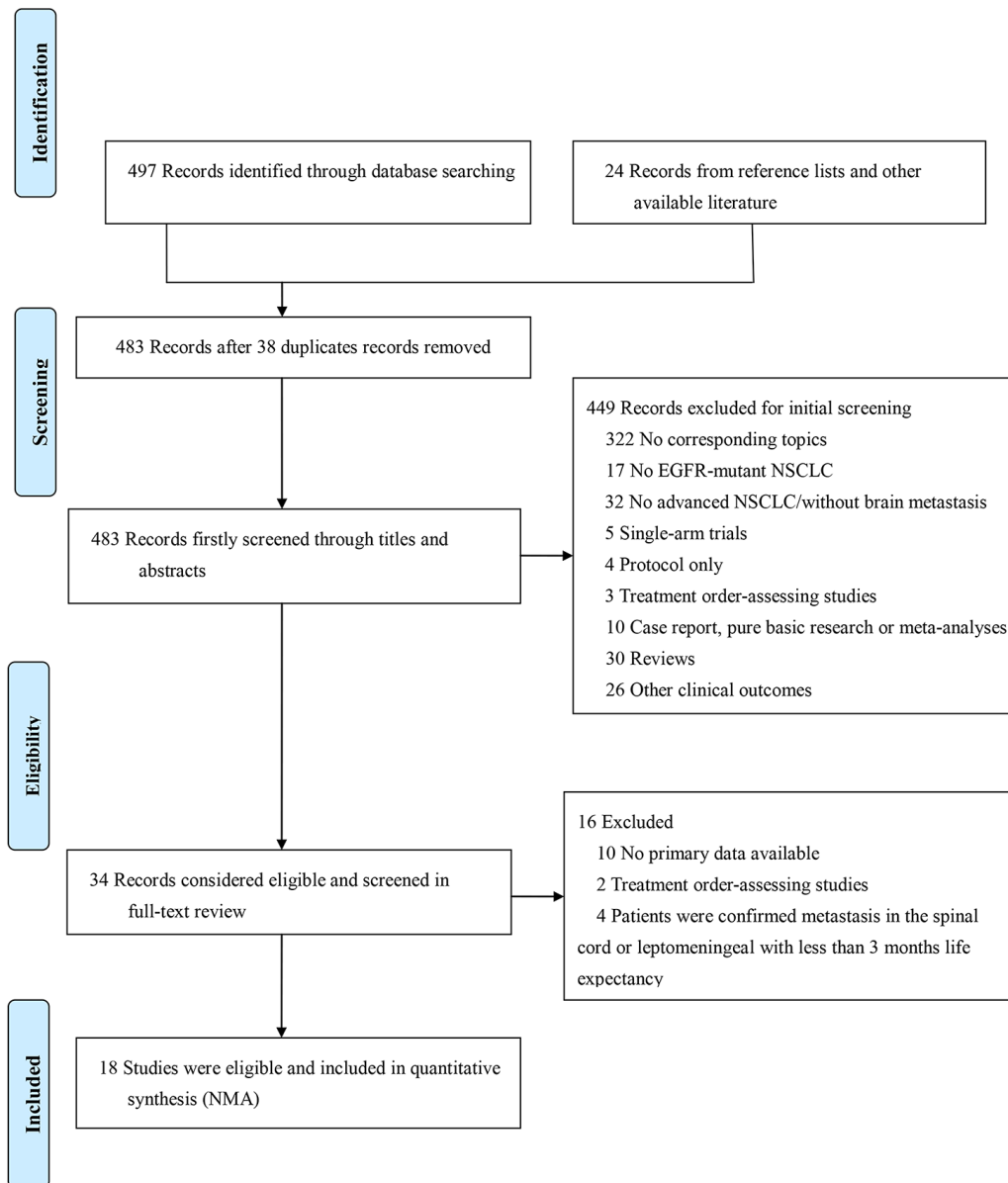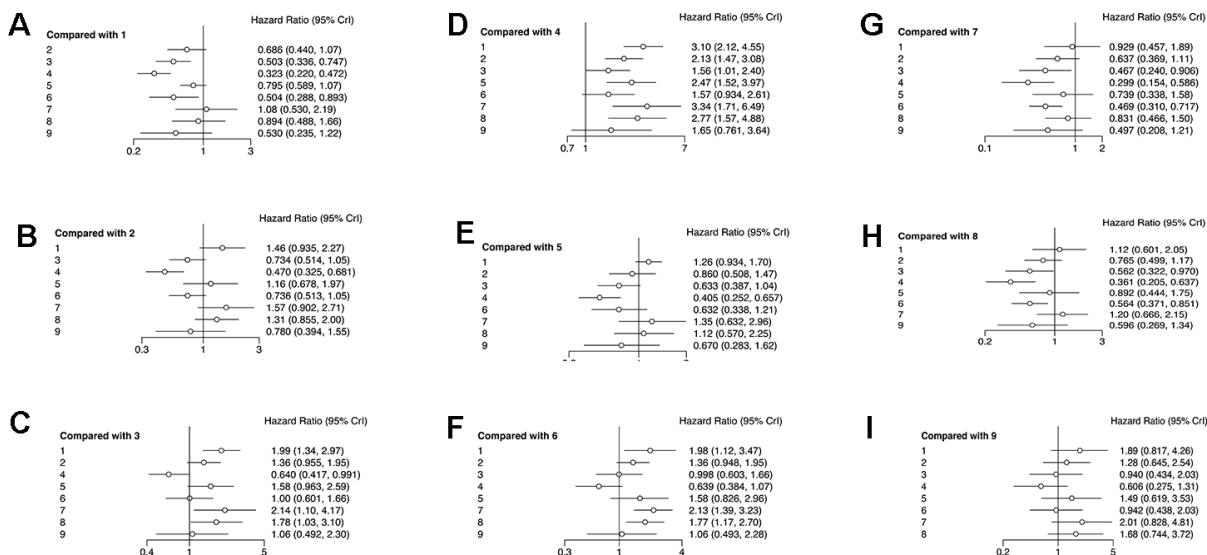Supplementary Figure 1. The landscape of the EGFR gene and mutations. (**A**) Gene expression for EGFR in normal tissues (CCLE analysis **https://portals.broadinstitute.org/ccle**), (**B**) gene expression for EGFR in cancer cell lines (CCLE analysis), (**C**) EGFR putative copy-number alternations from GISTIC (online source from **http://www.cbioportal.org/**), (**D**) 3D structure of the EGFR protein. EGFR mutations were commonly detected in normal lung tissues, ranking 21st in the 53 reported organ/tissue cells and 10th in the 37 pan-cancer types in NSCLC (Figure A1A, A1B). EGFR putative copy-number alternations from GISTIC based on 584 patients (containing 586 samples, from *CBioPortal*) harboured deep deletion, shallow deletion, diploid, gain and amplification mutations, among which amplification was the most commonly detected in the mRNA (A1C). The 3D structure of the EGFR protein is depicted in Figure A1D in dark green

Identification

497 Records identified through database searching

24 Records from reference lists and other available literature

Screening

483 Records after 38 duplicates records removed

483 Records firstly screened through titles and abstracts

449 Records excluded for initial screening

    322 No corresponding topics

    17 No EGFR-mutant NSCLC

    32 No advanced NSCLC/without brain metastasis

    5 Single-arm trials

    4 Protocol only

    3 Treatment order-assessing studies

    10 Case report, pure basic research or meta-analyses

    30 Reviews

    26 Other clinical outcomes

Eligibility

34 Records considered eligible and screened in full-text review

16 Excluded

    10 No primary data available

    2 Treatment order-assessing studies

    4 Patients were confirmed metastasis in the spinal cord or leptomeningeal with less than 3 months life expectancy

Included

18 Studies were eligible and included in quantitative synthesis (NMA)

Supplementary Figure 2. Study flow chart.

Forrest plots of multivariable interventions for PFS

A Compared with 1 — Hazard Ratio (95% CrI)
- 2: 0.686 (0.440, 1.07)
- 3: 0.503 (0.336, 0.747)
- 4: 0.323 (0.220, 0.472)
- 5: 0.795 (0.589, 1.07)
- 6: 0.504 (0.288, 0.893)
- 7: 1.08 (0.530, 2.19)
- 8: 0.894 (0.488, 1.66)
- 9: 0.530 (0.235, 1.22)
(axis: 0.2, 1, 3)

B Compared with 2 — Hazard Ratio (95% CrI)
- 1: 1.46 (0.935, 2.27)
- 3: 0.734 (0.514, 1.05)
- 4: 0.470 (0.325, 0.681)
- 5: 1.16 (0.678, 1.97)
- 6: 0.736 (0.513, 1.05)
- 7: 1.57 (0.902, 2.71)
- 8: 1.31 (0.855, 2.00)
- 9: 0.780 (0.394, 1.55)
(axis: 0.3, 1, 3)

C Compared with 3 — Hazard Ratio (95% CrI)
- 1: 1.99 (1.34, 2.97)
- 2: 1.36 (0.955, 1.95)
- 4: 0.640 (0.417, 0.991)
- 5: 1.58 (0.963, 2.59)
- 6: 1.00 (0.601, 1.66)
- 7: 2.14 (1.10, 4.17)
- 8: 1.78 (1.03, 3.10)
- 9: 1.06 (0.492, 2.30)
(axis: 0.4, 1, 5)

D Compared with 4 — Hazard Ratio (95% CrI)
- 1: 3.10 (2.12, 4.55)
- 2: 2.13 (1.47, 3.08)
- 3: 1.56 (1.01, 2.40)
- 5: 2.47 (1.52, 3.97)
- 6: 1.57 (0.934, 2.61)
- 7: 3.34 (1.71, 6.49)
- 8: 2.77 (1.57, 4.88)
- 9: 1.65 (0.761, 3.64)
(axis: 0.7, 1, 7)

E Compared with 5 — Hazard Ratio (95% CrI)
- 1: 1.26 (0.934, 1.70)
- 2: 0.860 (0.508, 1.47)
- 3: 0.633 (0.387, 1.04)
- 4: 0.405 (0.252, 0.657)
- 6: 0.632 (0.338, 1.21)
- 7: 1.35 (0.632, 2.96)
- 8: 1.12 (0.570, 2.25)
- 9: 0.670 (0.283, 1.62)

F Compared with 6 — Hazard Ratio (95% CrI)
- 1: 1.98 (1.12, 3.47)
- 2: 1.36 (0.948, 1.95)
- 3: 0.998 (0.271, 1.66)
- 4: 0.639 (0.384, 1.07)
- 5: 1.58 (0.826, 2.96)
- 7: 2.13 (1.39, 3.23)
- 8: 1.77 (1.17, 2.70)
- 9: 1.06 (0.493, 2.28)
(axis: 0.3, 1, 4)

G Compared with 7 — Hazard Ratio (95% CrI)
- 1: 0.929 (0.457, 1.89)
- 2: 0.637 (0.369, 1.11)
- 3: 0.467 (0.240, 0.906)
- 4: 0.299 (0.154, 0.586)
- 5: 0.739 (0.338, 1.58)
- 6: 0.469 (0.310, 0.717)
- 8: 0.831 (0.466, 1.50)
- 9: 0.497 (0.208, 1.21)
(axis: 0.1, 1, 2)

H Compared with 8 — Hazard Ratio (95% CrI)
- 1: 1.12 (0.601, 2.05)
- 2: 0.765 (0.499, 1.17)
- 3: 0.562 (0.322, 0.970)
- 4: 0.361 (0.205, 0.637)
- 5: 0.892 (0.444, 1.75)
- 6: 0.564 (0.371, 0.851)
- 7: 1.20 (0.666, 2.15)
- 9: 0.596 (0.269, 1.34)
(axis: 0.2, 1, 3)

I Compared with 9 — Hazard Ratio (95% CrI)
- 1: 1.89 (0.817, 4.26)
- 2: 1.28 (0.845, 2.54)
- 3: 0.940 (0.434, 2.03)
- 4: 0.606 (0.275, 1.31)
- 5: 1.49 (0.619, 3.53)
- 6: 0.942 (0.438, 2.03)
- 7: 2.01 (0.828, 4.81)
- 8: 1.68 (0.744, 3.72)
(axis: 0.2, 1, 5)

Interventions note:
1: Platinum-based chemotherapy
2: First generation EGFR-TKI
3: Second generation EGFR-TKI
4: Third generation EGFR-TKI
5: EGFR-TKIs + platinum-based chemotherapy
6: EGFR-TKIs + SRS/WBRT
7: Deferring SRS/WBRT
8: WBRT
9: EGFR-TKIs + anti-VEGFR

**Supplementary Figure 3. Forrest plots for network comparisons of multiple-treatments on PFS**

Forrest plots of multivariable interventions for OS

A Compared with 1 — Hazard Ratio (95% CrI)
- 2: 1.41 (0.551, 3.72)
- 3: 1.14 (0.712, 1.78)
- 4: 1.18 (0.377, 3.87)
- 5: 1.39 (0.912, 2.16)
- 6: 0.730 (0.252, 2.20)
- 7: 1.81 (0.492, 6.79)
- 8: 1.52 (0.753, 3.11)
- 9: 1.03 (0.286, 3.60)
(axis: 0.2, 1, 7)

B Compared with 2 — Hazard Ratio (95% CrI)
- 1: 0.707 (0.269, 1.82)
- 3: 0.804 (0.270, 2.27)
- 4: 0.833 (0.434, 1.59)
- 5: 0.982 (0.421, 2.28)
- 6: 0.517 (0.305, 0.875)
- 7: 1.28 (0.491, 3.23)
- 8: 1.07 (0.563, 2.01)
- 9: 0.718 (0.306, 1.68)
(axis: 0.2, 1, 4)

C Compared with 3 — Hazard Ratio (95% CrI)
- 1: 0.879 (0.560, 1.40)
- 2: 1.24 (0.440, 3.71)
- 4: 1.04 (0.311, 3.68)
- 5: 1.23 (0.665, 2.31)
- 6: 0.642 (0.201, 2.16)
- 7: 1.59 (0.397, 6.57)
- 8: 1.34 (0.586, 3.13)
- 9: 0.895 (0.232, 3.41)
(axis: 0.2, 1, 7)

D Compared with 4 — Hazard Ratio (95% CrI)
- 1: 0.848 (0.258, 2.65)
- 2: 1.20 (0.630, 2.30)
- 3: 0.965 (0.271, 3.21)
- 5: 1.18 (0.406, 3.42)
- 6: 0.621 (0.264, 1.42)
- 7: 1.54 (0.495, 4.78)
- 8: 1.29 (0.519, 3.20)
- 9: 0.860 (0.294, 2.56)
(axis: 0.2, 1, 5)

E Compared with 5 — Hazard Ratio (95% CrI)
- 1: 0.719 (0.464, 1.10)
- 2: 1.02 (0.438, 2.37)
- 3: 0.816 (0.432, 1.50)
- 4: 0.850 (0.292, 2.46)
- 6: 0.526 (0.197, 1.40)
- 7: 1.31 (0.374, 4.52)
- 8: 1.10 (0.624, 1.93)
- 9: 0.737 (0.221, 2.37)
(axis: 0.1, 1, 5)

F Compared with 6 — Hazard Ratio (95% CrI)
- 1: 1.37 (0.454, 3.97)
- 2: 1.93 (1.14, 3.28)
- 3: 1.56 (0.462, 4.98)
- 4: 1.61 (0.702, 3.78)
- 5: 1.90 (0.713, 5.07)
- 7: 2.47 (1.14, 5.34)
- 8: 2.08 (0.906, 4.73)
- 9: 1.40 (0.512, 3.78)
(axis: 0.4, 1, 6)

G Compared with 7 — Hazard Ratio (95% CrI)
- 1: 0.551 (0.147, 2.03)
- 2: 0.781 (0.310, 2.04)
- 3: 0.629 (0.152, 2.52)
- 4: 0.651 (0.209, 2.02)
- 5: 0.766 (0.221, 2.67)
- 6: 0.404 (0.187, 0.874)
- 8: 0.840 (0.274, 2.62)
- 9: 0.559 (0.161, 2.00)
(axis: 0.1, 1, 3)

H Compared with 8 — Hazard Ratio (95% CrI)
- 1: 0.657 (0.322, 1.33)
- 2: 0.930 (0.498, 1.78)
- 3: 0.747 (0.319, 1.71)
- 4: 0.776 (0.313, 1.93)
- 5: 0.911 (0.519, 1.60)
- 6: 0.480 (0.212, 1.10)
- 7: 1.19 (0.381, 3.65)
- 9: 0.672 (0.229, 1.92)
(axis: 0.2, 1, 4)

I Compared with 9 — Hazard Ratio (95% CrI)
- 1: 0.975 (0.278, 3.50)
- 2: 1.39 (0.595, 3.27)
- 3: 1.12 (0.293, 4.31)
- 4: 1.16 (0.391, 3.40)
- 5: 1.36 (0.422, 4.52)
- 6: 0.717 (0.264, 1.95)
- 7: 1.79 (0.500, 6.21)
- 8: 1.49 (0.520, 4.37)
(axis: 0.2, 1, 7)

Interventions note:
1. Platinum-based chemotherapy
2 First generation EGFR-TKI
3. Second generation EGFR-TKI
4. Third generation EGFR-TKI
5. EGFR-TKIs + platinum-based chemotherapy
6. EGFR-TKIs + SRS/WBRT
7. Deferring SRS/WBRT
8.WBRT
9. EGFR-TKIs + MET-TKIs

Supplementary Figure 4. Forrest plots for network comparisons of multiple-treatments on OS
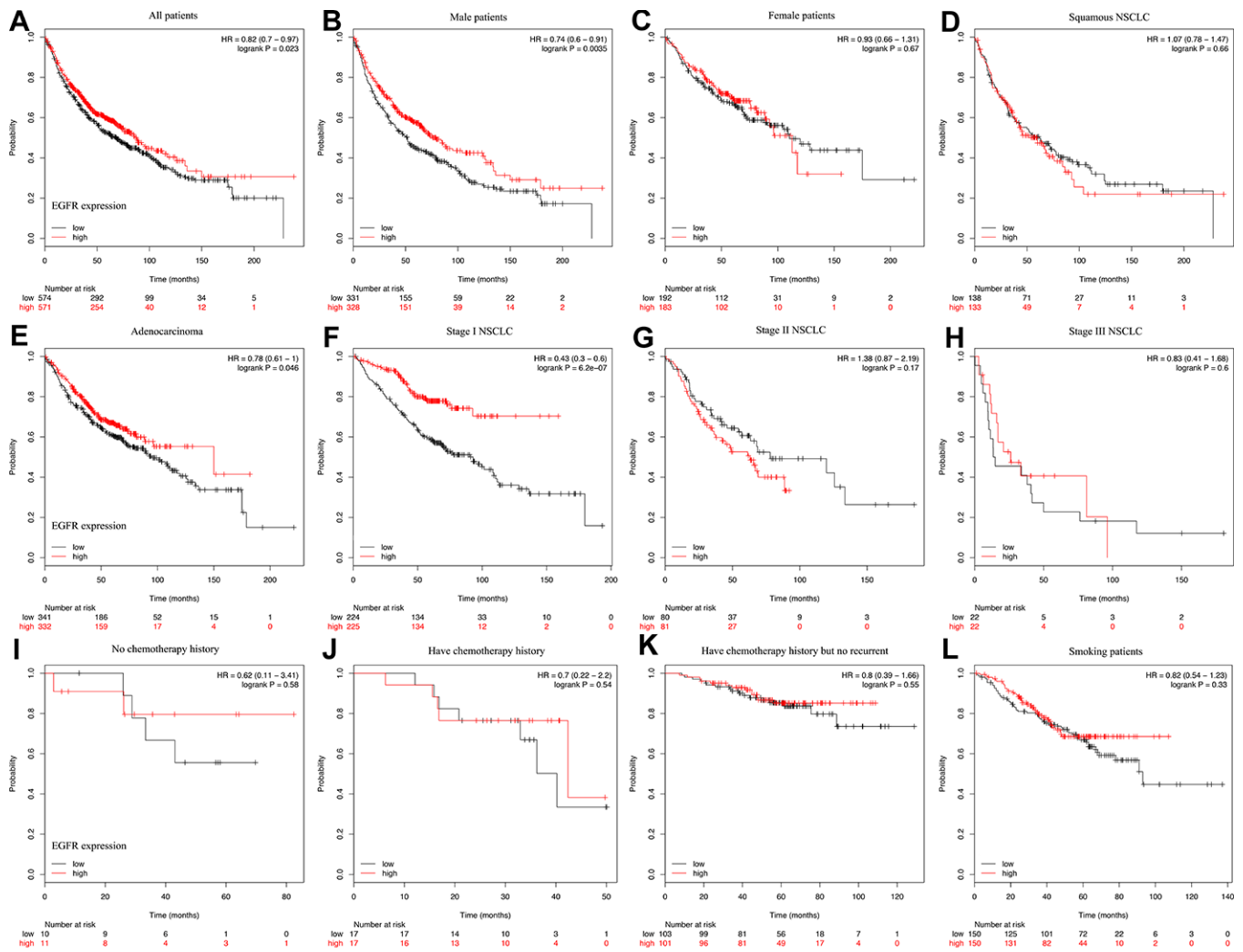
Supplementary Figure 5. Kaplan-Meier plots by EGFR mutations for OS
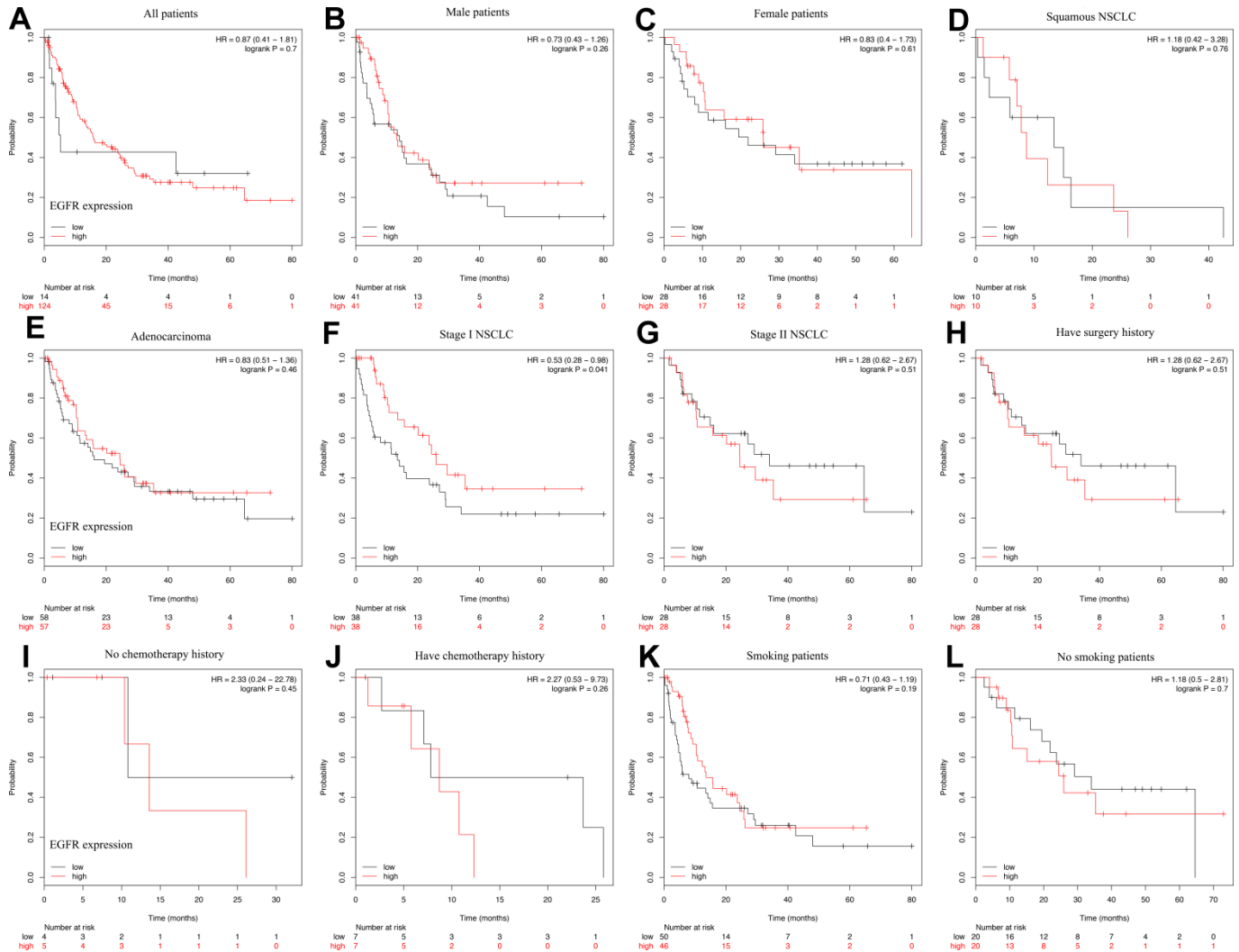
Supplementary Figure 6. Kaplan-Meier plots by EGFR mutations for PFS.