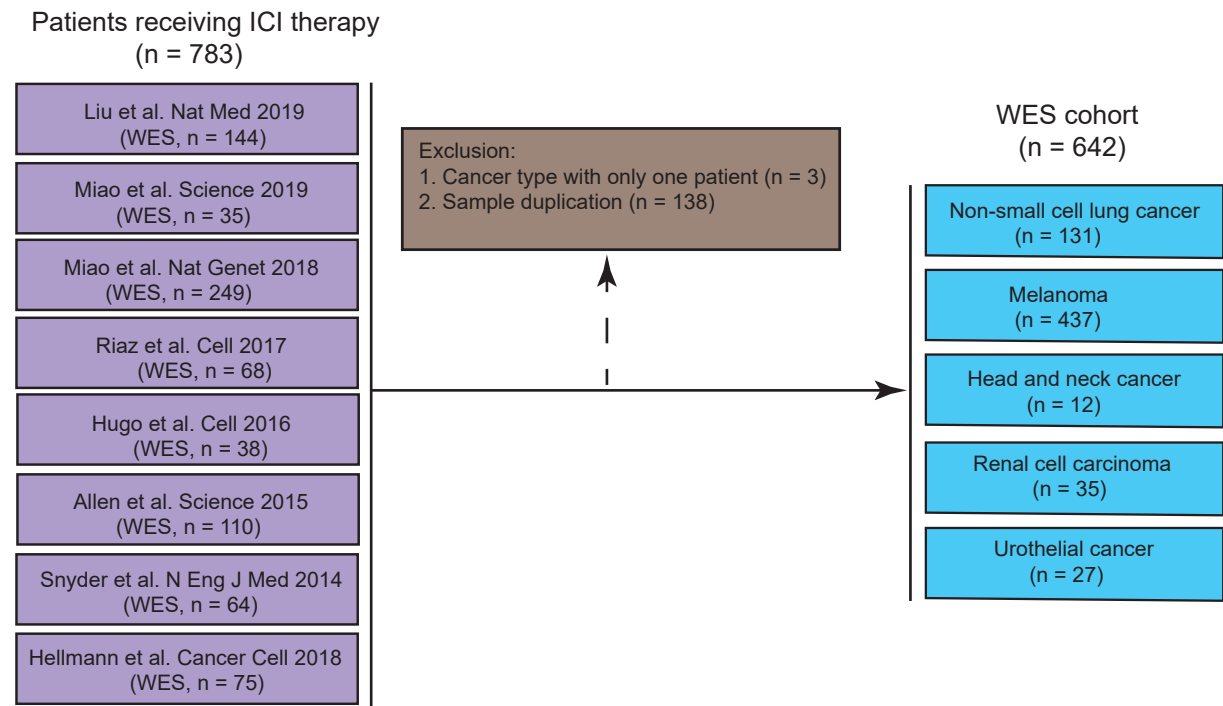


A Discovery Cohort



B Validation Cohort

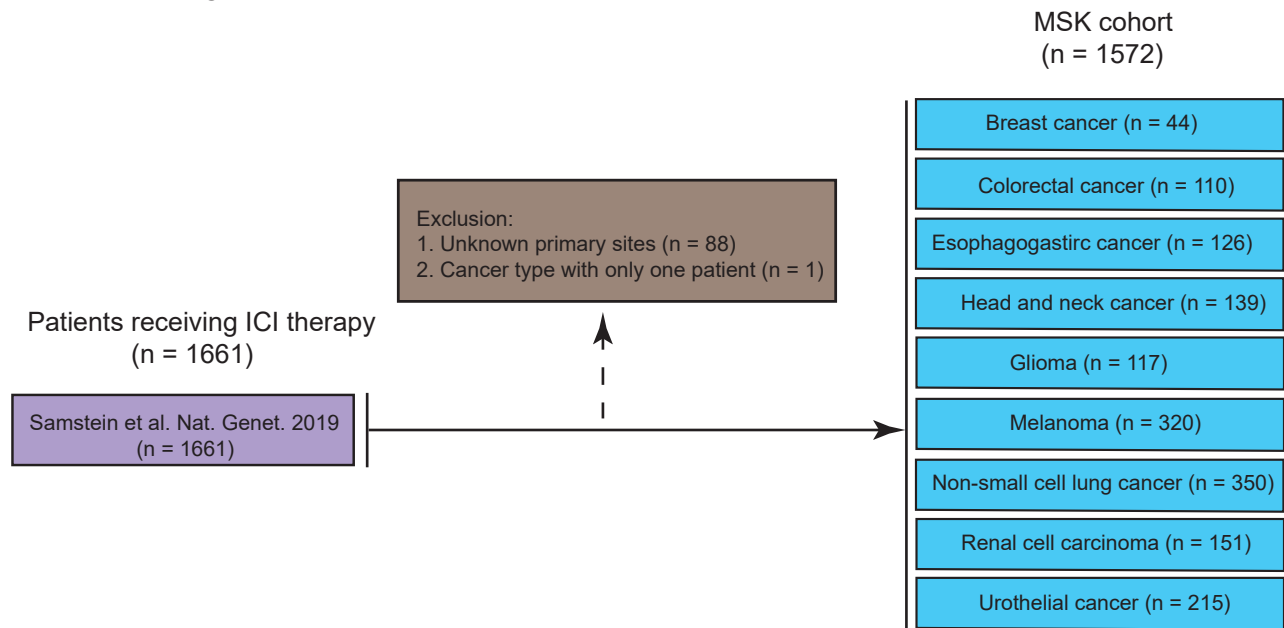


Figure S1. The inclusion and exclusion of the discovery and validation cohorts.

Step1: Discovery

Liu (N=144); Miao 2019 (N=35);
Miao 2018 (N=249); Riaz (N=68);
Hugo (N=38); Allen (N=110);
Snyder (N=64); Hellmann (N = 75);

NTRK3-Mut VS. NTRK3-Wild:

- 1) ICB treatment response: ORR and DCB.
- 2) ICB treatment outcomes: OS and PFS.

Step2: Validation

Samstein (N=1572)

NTRK3-Mut VS. NTRK3-Wild:

- 1) ICB treatment response: ORR and DCB.
- 2) ICB treatment outcomes: OS.

Step3: Prognosis

Zehir (N=10336) ;
TCGA pan-cancer (N=10350)

NTRK3-Mut VS. NTRK3-Wild:

- 1) Non-ICB treatment outcomes: OS.

Step4: Intrinsic immune landscapes

Discovery cohort (N=642)
Validation cohort (N=1572)
TCGA pan-cancer (N=10350)

NTRK3-Mut VS. NTRK3-Wild:

- 1) TMB analysis.
- 2) Neoantigen analysis. (Thorsson's data)
- 3) PD1/PDL1/CTLA4 mRNA expression analysis.
- 4) MHC molecules mRNA expression analysis.

Step5: Extrinsic immune landscapes

TCGA pan-cancer (N=10350)

NTRK3-Mut VS. NTRK3-Wild:

- 1) Leukocyte fraction, TIL regional fraction, TCR /BCR diversity analysis. (Thorsson's data)
- 2) Immune infiltration score analysis. (Danaher's data)
- 3) Immune signatures enrich analysis. [GSVA]
- 4) Microenvironment immune cell abundance. [CIBERSORT & MCP-Counter]
- 5) Cytolytic activity (CYT) score analysis.
- 6) Chemokines and interleukin analysis.

Step6: Generation of the mutation-based gene set

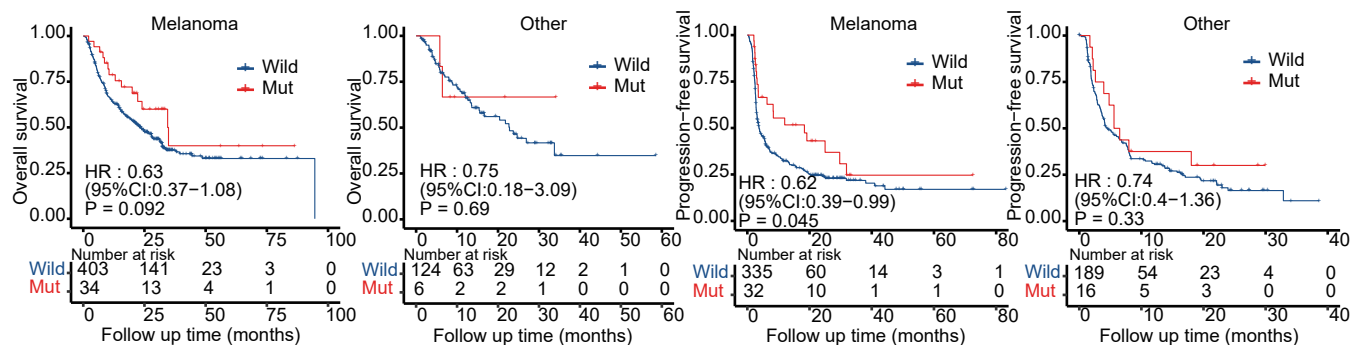
Discovery cohort (N= 642)
Validation cohort (N=1572)
Rizvi. cohort (N=34)

GMB-High vs. GMB-Low:

- 1) ICB treatment response: DCB.
- 2) ICB treatment outcomes: OS and PFS.
- 3) Comparing the predictive efficacy of GMB vs. TMB.

Figure S2. The flow chart of this study.

A WES Cohort



B MSK Cohort

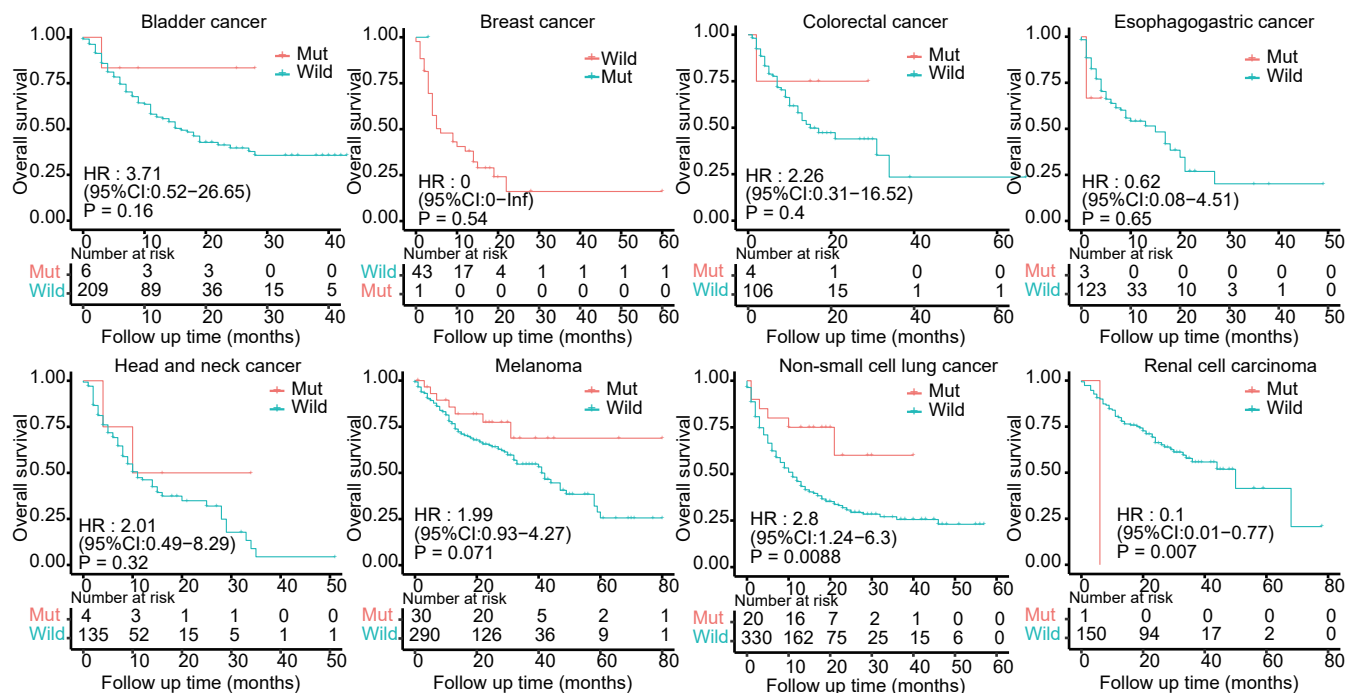


Figure S3. Subgroup survival analyses of different cancer types in the WES and MSK cohorts.

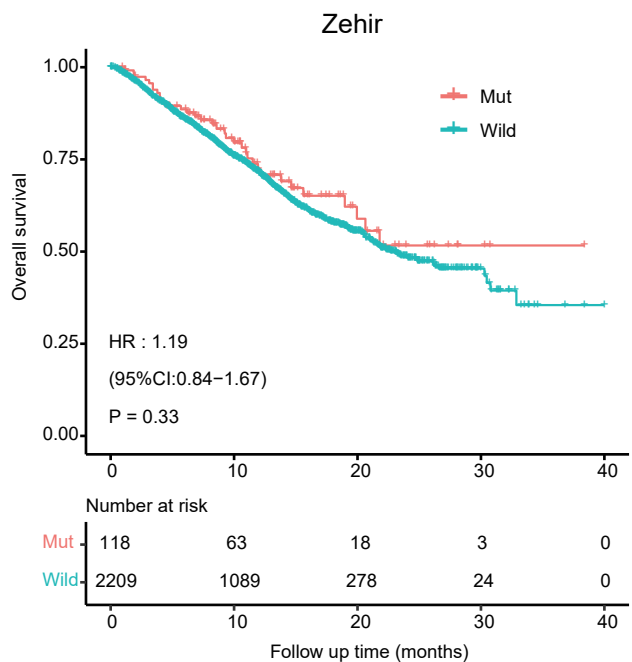
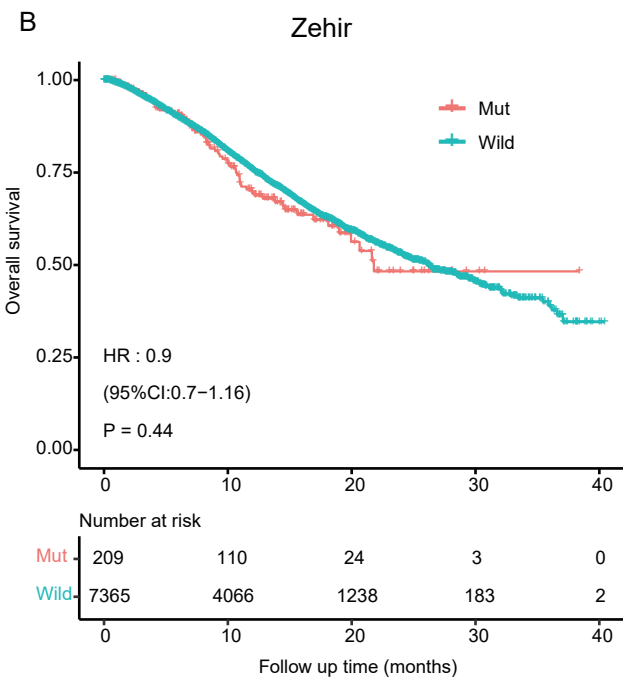
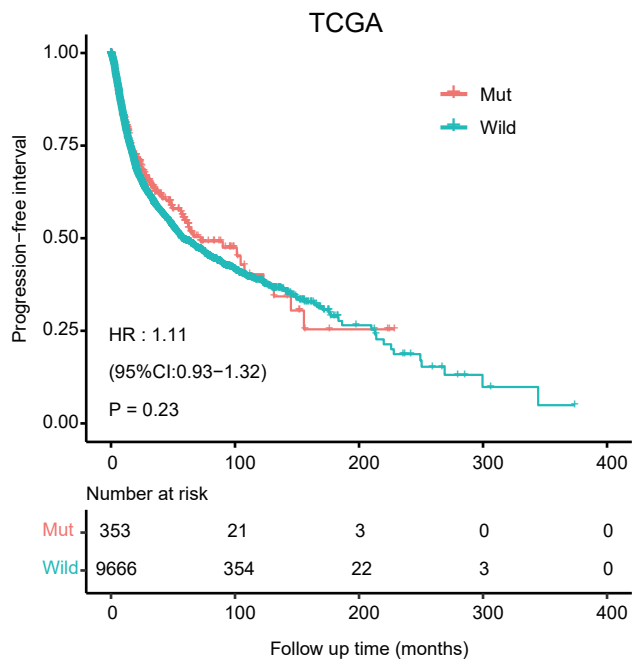
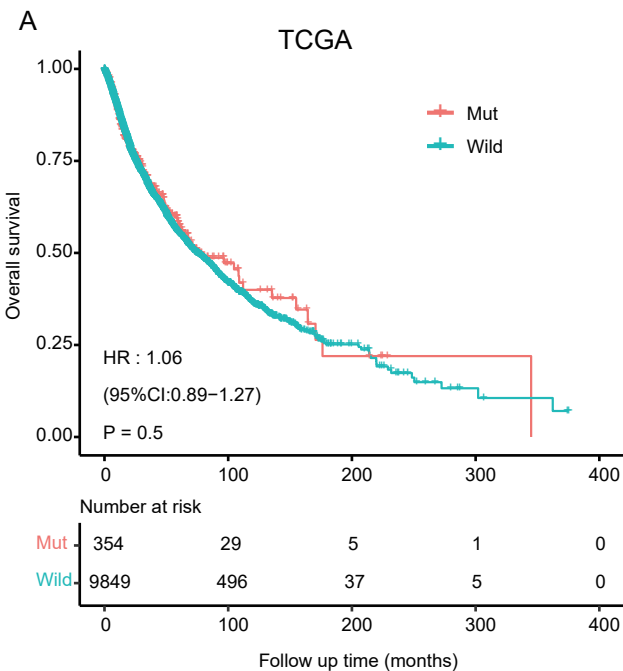


Figure S4. The survival analysis of NTRK3 mutation in the TCGA (A) and Zehir (B) cohorts.

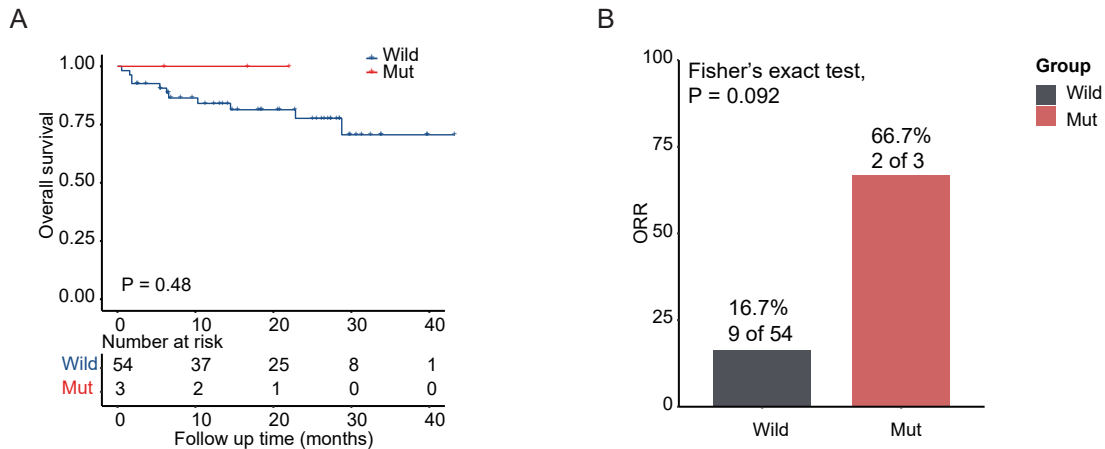


Figure S5. The association between NTRK3-Mut, overall survival and response in the internal cohorts (n = 57).

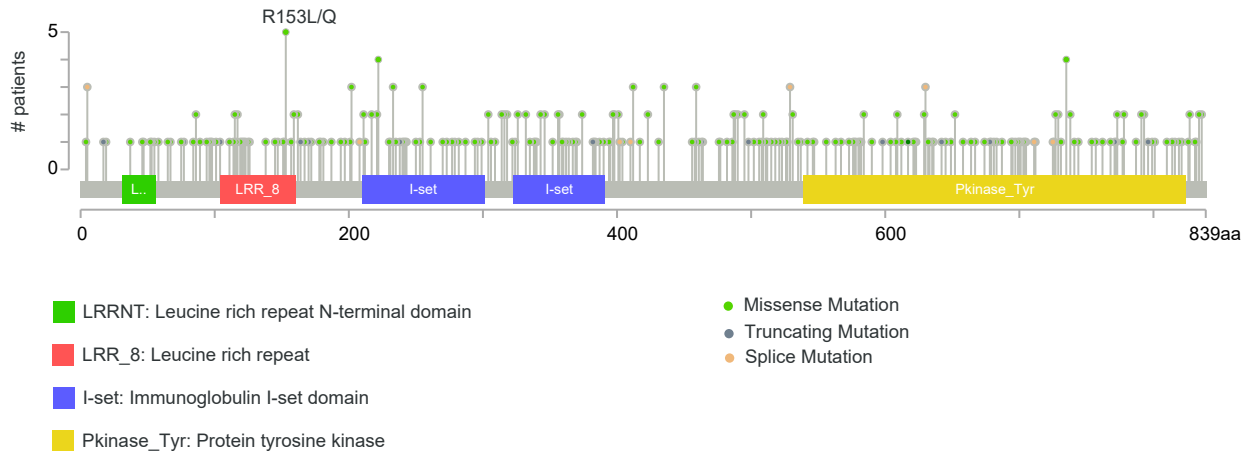


Figure S6. The mutation landscape of NTRK3 genome.

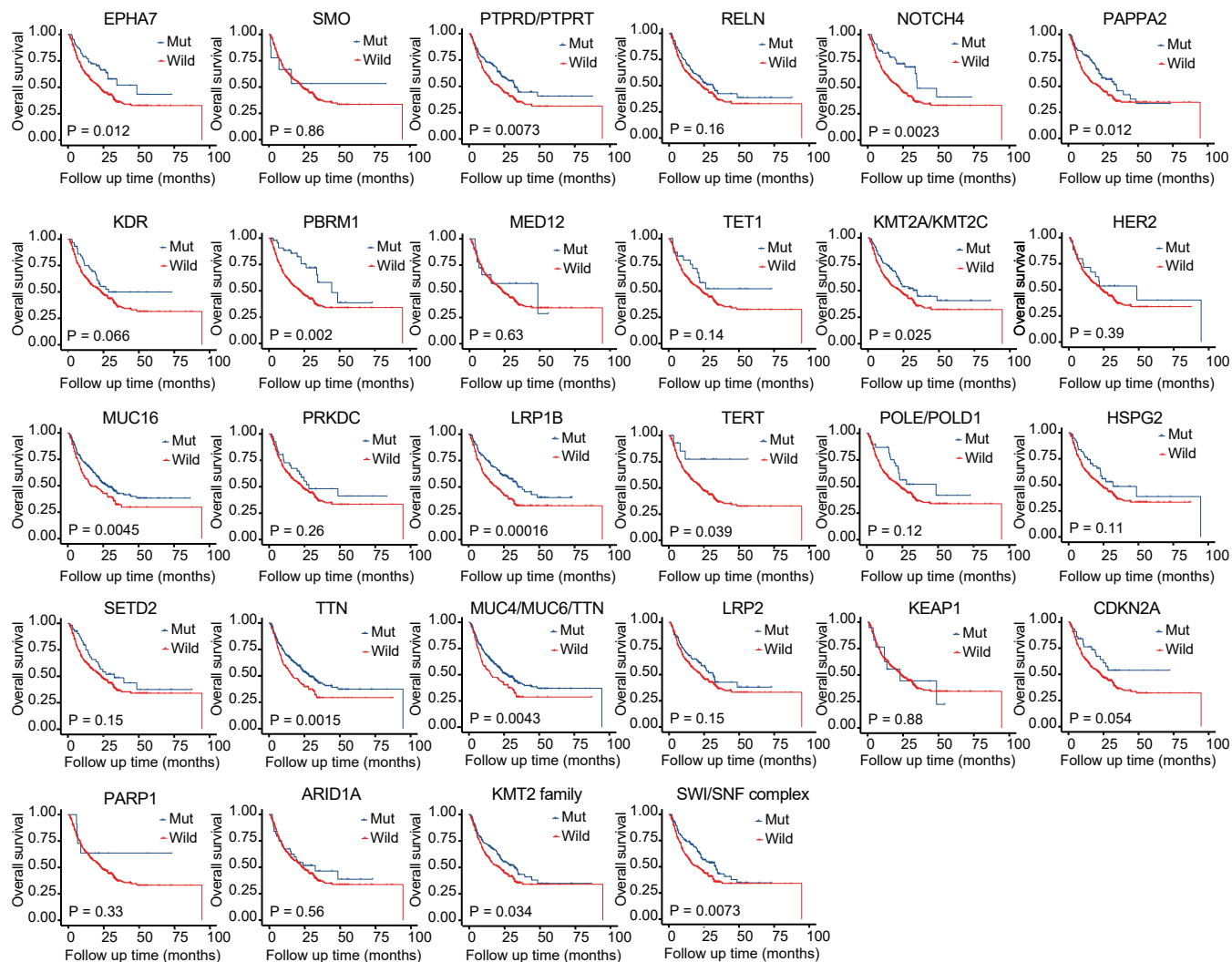


Figure S7. Overall survival analysis of candidate genes in the WES cohort.

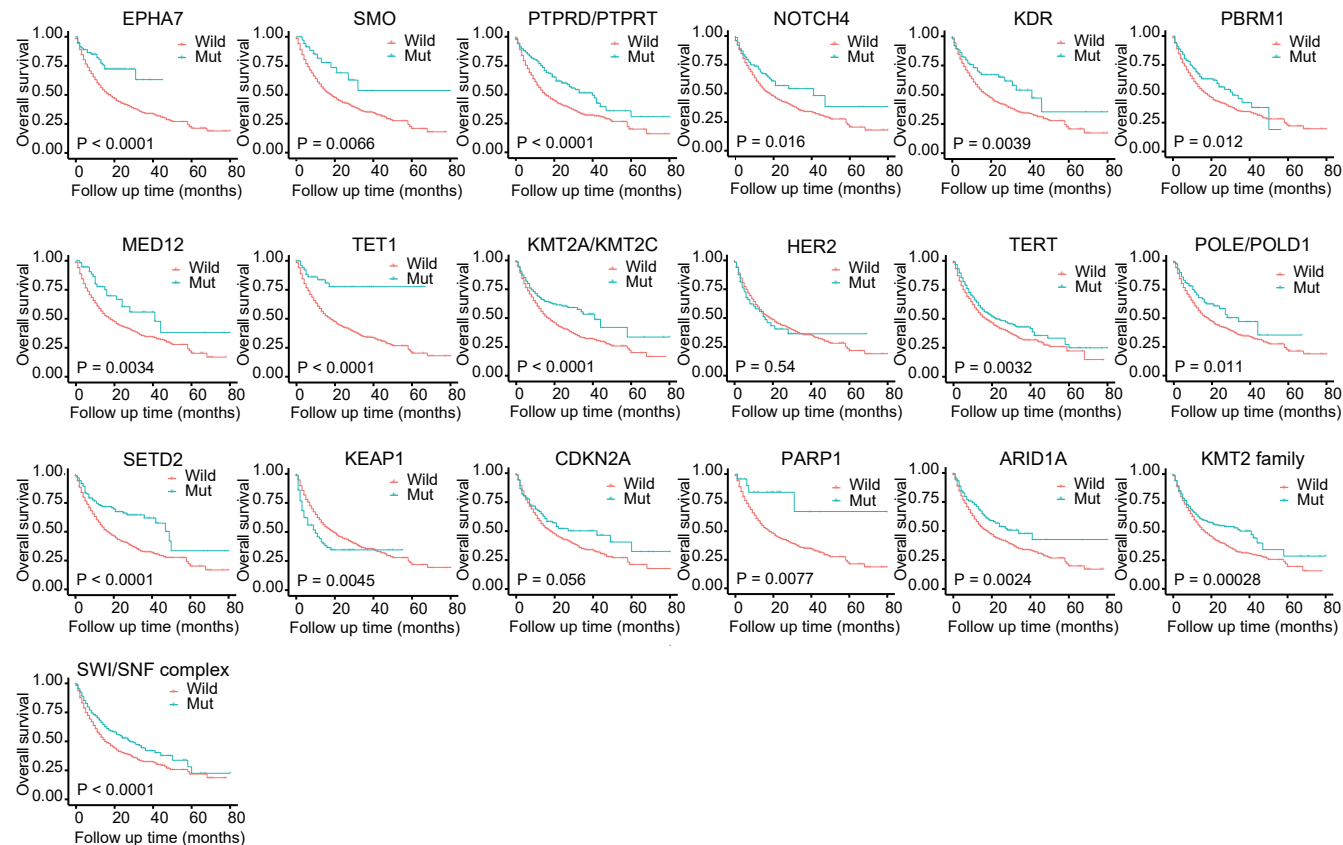


Figure S8. Overall survival analysis of candidate genes in the MSK cohort.

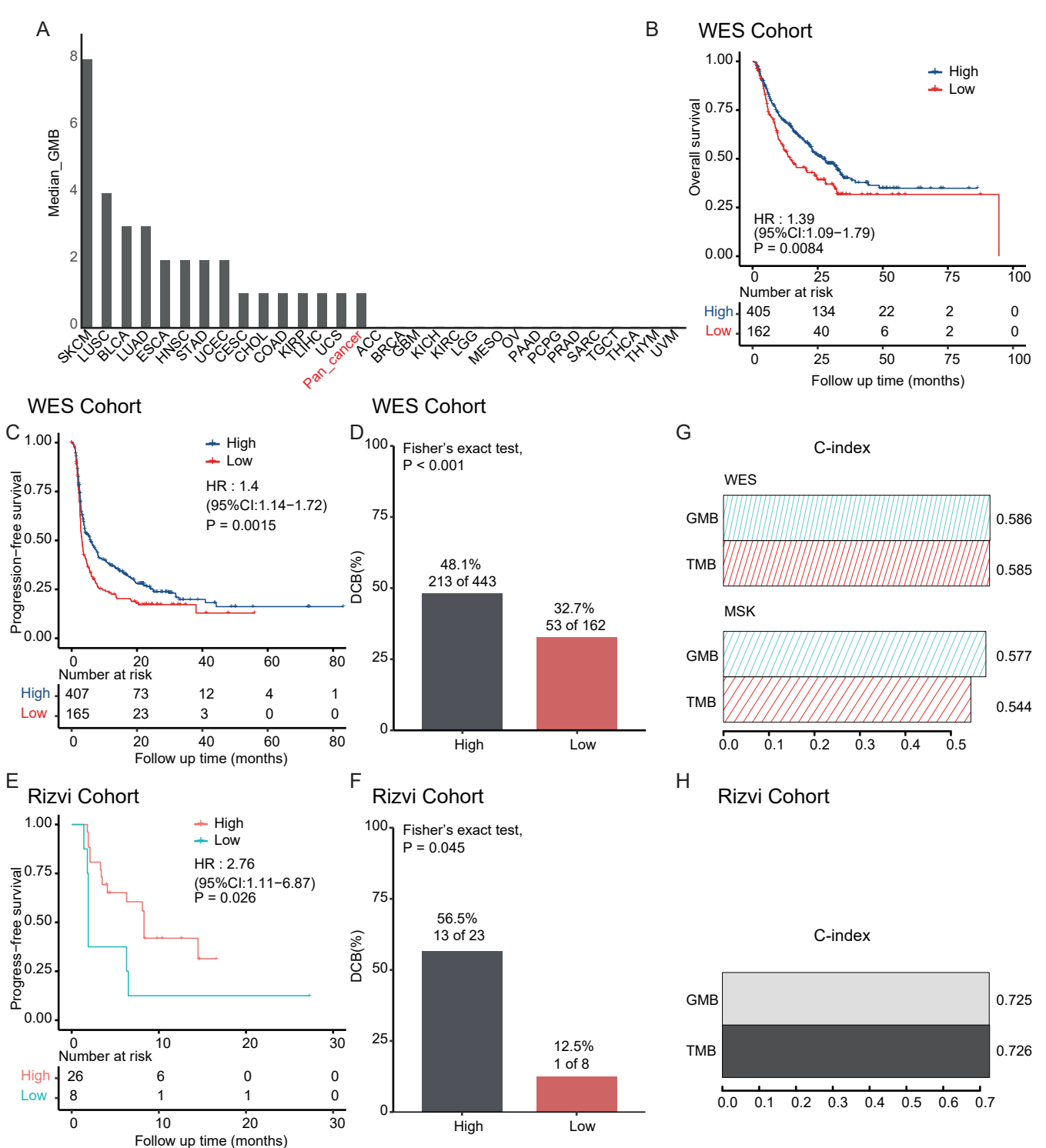
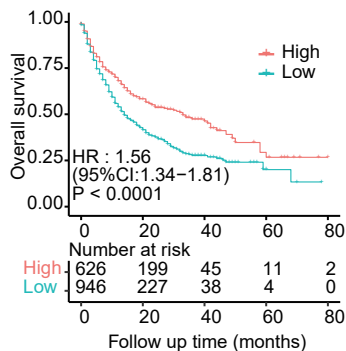


Figure S9. Construction and validation of the mutation-based gene set. (A) The median mutation number of the mutation-based gene set in TCGA solid tumors. (B) Overall survival (OS) analysis of the mutation-based gene set in the WES cohort. (C) Progression-free survival (PFS) analysis of the mutation-based gene set in the WES cohort. (D) Durable clinical benefit (DCB) comparison of the mutation-based gene set in the WES cohort. (E) P-rgression-free survival (PFS) analysis of the mutation-based gene set in the Rizvi cohort. (F) Durable clinical benefit (DCB) comparison of the mutation-based gene set in the Rizvi cohort. (G-H) Comparison of the efficacy between TMB and the mutation-based gene set in the WES, MSK, and Rizvi cohorts.

A MSK Cohort



B WES Cohort

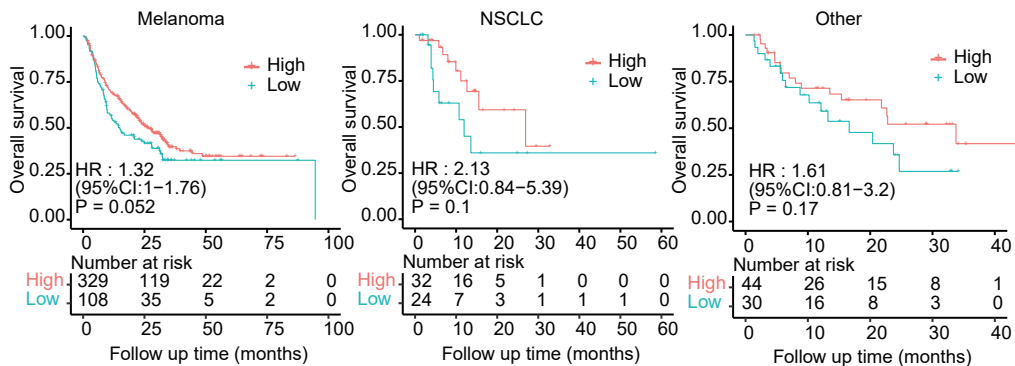


Figure S10. Overall analysis of the mutation-based gene set in the MSK cohort (A) and different types of cancers in the WES cohort (B).