Supplementary Figure legends

Fig S1. Flowchart of the procedures in the development and validation of genomic mutation signature. GMS, genomic mutation signature; MSK, Memorial Sloan Kettering; TCGA, The Cancer Genome Atlas; ICIs, immune-checkpoint inhibitors; ORR, objective response rate.

Fig S2. Relationship between GMS score and treatment response to anti–PD-(L1) therapy. The association of GMS score with progression-free survival time and objective response rate in (A) MSK training cohort and (B) MSK internal validation cohort respectively. Vertical and horizontal dashed line were indicated as GMS cut-point (0.565) and progression-free survival ≥ 6 months (durable clinical benefit) respectively. GMS, genomic mutation signature; MSK, Memorial Sloan Kettering

Fig S3. (A) A Venn diagram showing the overlap patients with GMS > cut-point (0.565) and PD-L1 IHC ≥ 50%; (B) A Venn diagram showing the overlap patients with GMS > cut-point (0.565) and TMB ≥ upper quartile.

Fig S4. Kaplan-Meier estimates of progression-free survival classified by the status of GMS and PD-L1 in (A) MSK cohort and (B) external validation cohorts. GMS^{high} $PD\text{-}L1^{low}$ group and GMS^{low} $PD\text{-}L1^{high}$ group were discriminated.

Fig S5. Relationship between GMS and TMB.

The correlation analysis between GMS and TMB in (A) MSK and (B) external validation cohort respectively. The spearman correlation coefficient and *P* value are shown. TMB, tumor mutation burden; GMS, genomic mutation signature; MSK, Memorial Sloan Kettering

Fig S6. Kaplan-Meier estimates of progression-free survival classified by the status of two markers (A, GMS and TMB) and three markers (B, GMS, PD-L1, and TMB).

Note: 2/3 markers (+) denotes these three situations: $GMS^{high}TMB^{high}PD\text{-}L1^{low}$, $GMS^{high}TMB^{low}PD\text{-}L1^{high}$, $GMS^{low}TMB^{high}PD\text{-}L1^{high}$; 1/3 markers (+) denotes these three situations: $GMS^{high}TMB^{low}PD\text{-}L1^{low}$, $GMS^{low}TMB^{low}PD\text{-}L1^{high}$, $GMS^{low}TMB^{high}PD\text{-}L1^{low}$.

Fig S7. Survival analysis in MSK training cohort and MSK internal validation cohort using the optimal cutoff determined by ROC method. (A)Receiver–operating characteristic (ROC) curves in the MSK training cohort. The optimal cutoff value was determined by Youden Index. Kaplan-Meier curves of progression-free survival according to GMS status in (B) MSK training cohort and (C) MSK internal validation cohort. Kaplan-Meier curves of overall survival according to GMS status in (D) MSK training cohort and (E) MSK internal validation cohort. GMS, genomic mutation signature; MSK, Memorial Sloan Kettering.

Fig S8. Parsimony analysis of GMS in the training, internal validation and external validation cohorts. Kaplan-Meier curves of progression free survival and overall survival of (A) a three-gene model, whose members (MLL3/KMT2C, SMAD4 and HGF) achieve $P \leq 0.05$ in the multivariate Cox regression analysis, and (B) a four-gene model developed with four well-established genes (TP53, KRAS, EGFR and STK11). GMS, gene mutation-based signature.

Fig S9. Kaplan-Meier estimates of progression-free survival classified by the status of GMS in all the CR/PR cases.