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# Mutation of *lysine-specific demethylase 5* is associated with enhanced tumor immunity and favorable outcomes in pan-cancer immune checkpoint blockade

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**Abstract**

The lysine-specific demethylase 5 (KDM5) family, a key post-translational modification of chromatin, can shape tumor immune microenvironment. Here, we performed an extensive clinical and bioinformatic analysis to explore the association between *KDM5* mutation and tumor immunity and its impact on the outcomes in pan-cancer immunotherapy. In 2943 patients across 12 tumor types treated with immune checkpoint inhibitors, *KDM5*-mutant tumors were associated with favorable overall survival (hazard ratio, 0.72; 95% confidence interval, 0.59–0.87; $P=0.004$) and objective response rate (41.7% vs. 26.8%; $P=0.001$). Further multi-omics analysis revealed *KDM5* mutation was related to boosted tumor immunogenicity, enriched infiltration of immune cells, and improved immune responses. In summary, *KDM5* mutation indicates enhanced tumor immunity and favorable outcomes in pan-cancer immune checkpoint blockade. These results have implication for treatment decision-making and developing immunotherapy for personalized care.

**Keywords** *KDM5*, Cancer immunotherapy, Biomarker, Tumor immunity

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment in the last decade. However, it is difficult to determine which patients should be offered ICIs in clinical practice currently [1]. The KDM5 family, an enzymatic family including KDM5A/B/C/D, is a key post-translational modification of chromatin by removing the tri- or di-methyl groups from lysine 4 of histone H3 (H3K4) [2]. Interestingly, previous studies showed that *KDM5A* and *KDM5C* were ubiquitously expressed, whereas *KDM5B* was only discovered in testis, and *KDM5D* mainly in small intestine [3]. The dysregulation of *KDM5* affected numerous nuclear activities including the maintenance of genome integrity, epigenetic inheritance, and transcriptional regulation [2]. Recently, it was

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reported that KDM5 was also involved in shaping the tumor immune microenvironment. Indeed, the mutation of *KDM5* could regulate immune escape and immune response via its interaction with STING [4], or promote immune evasion by recruiting SETDB1 [5]. Accordingly, we speculated that the mutation of *KDM5* might impact the efficacy of immunotherapy and be treated as a potential predictive biomarker. Here, with accumulated information publicly available, we performed a comprehensive clinical and bioinformatic study to investigate the characteristics of *KDM5A/C* mutation and its association with the outcomes in pan-cancer immunotherapy (Suppl. methods 4).

To investigate the impact of *KDM5A/C* mutation on the efficacy of immunotherapy, 2943 patients with 12 distinct tumor types from 9 datasets were examined (Table S1). These patients were diagnosed as lung cancer ($n$=1137), melanoma ($n$=778), bladder urothelial cancer ($n$=238), renal cell carcinoma ($n$=178), head and neck cancer ($n$=141), esophagogastric cancer ($n$=118), glioma ($n$=116), colorectal cancer ($n$=109), cancer of unknown primary ($n$=85), breast cancer ($n$=41), anal cancer ($n$=1), and sarcoma ($n$=1). Information regarding objective response rate (ORR) and overall survival (OS) were collected. Patients who showed complete response (CR) or partial response (PR) were categorized as responders; patients who experienced stable disease (SD) or progressive disease (PD) were classified as non-responders. Totally, *KDM5*-mutant tumors were discovered in 196 patients (6.7%) and were associated with favorable OS (hazard ratio [HR]=0.72; 95% confidence interval [CI], 0.59–0.87; $P$=0.004; Fig. 1A). Additionally, compared with patients with *KDM5*-non-mutant tumors, more *KDM5*-mutant patients responded to ICIs (41.7% vs. 26.8%; $P$=0.001; Fig. 1B). Specifically, *KDM5A*-mutated tumors were identified in 105 patients (3.6%)

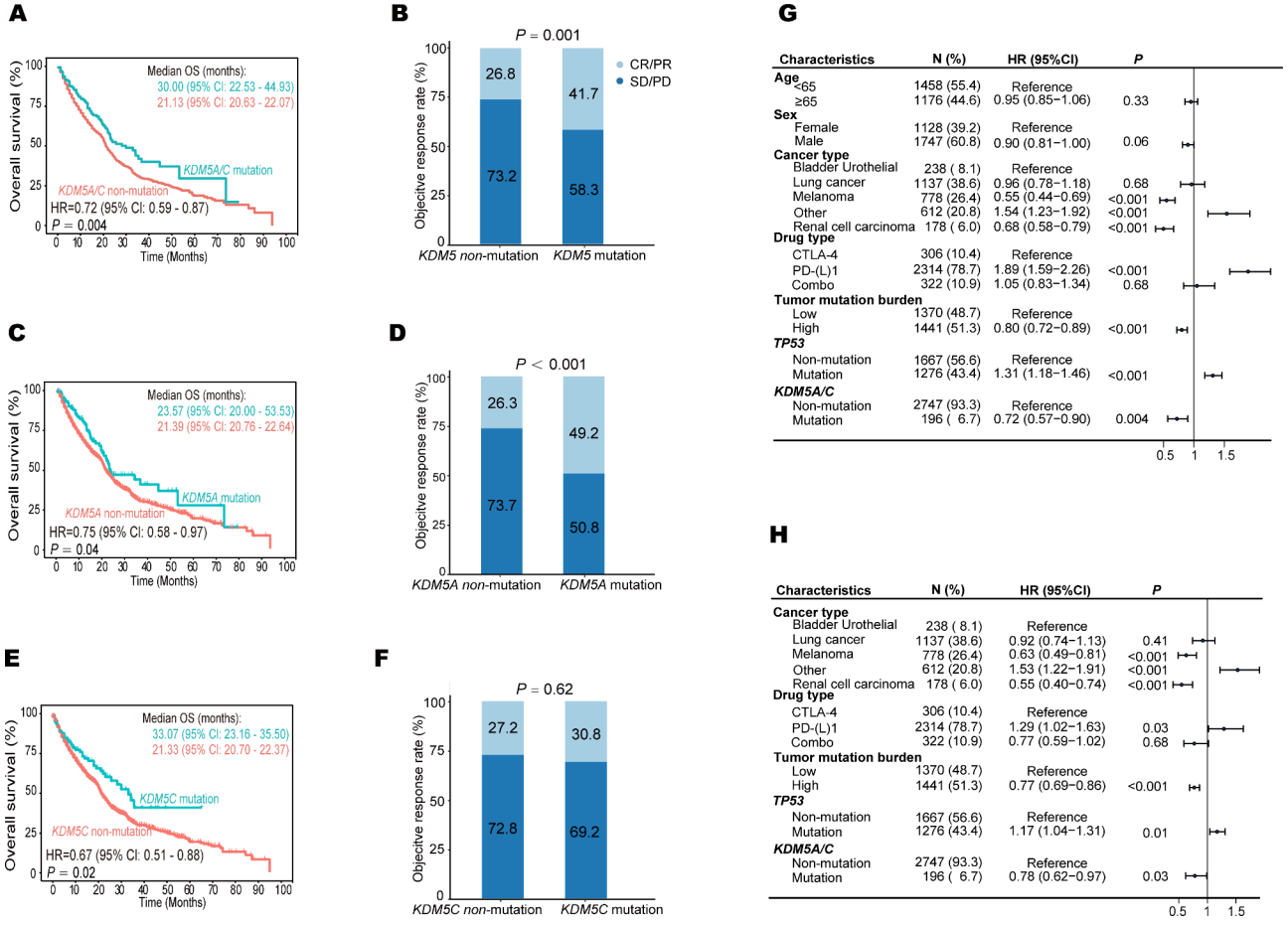


**Fig. 1** *KDM5* mutation as an independent biomarker for favorable outcomes in pan-cancer immune checkpoint blockade. **(A)** Pooled Kaplan–Meier survival analysis stratified by *KDM5A/C* mutation status in 2943 patients with 12 distinct tumor types treated with ICIs. **(B)** Comparison of objective response rate in patients with *KDM5A/C* mutation and patients with *KDM5A/C* non-mutation. **(C-F)** Association between *KDM5A* mutation and OS **(C)**, *KDM5A* mutation and ORR **(D)**, *KDM5C* mutation and OS **(E)**, *KDM5C* mutation and ORR **(F)** in patients treated with ICIs. **(G-H)** Univariate **(G)** and multivariate **(H)** Cox analysis of the association between *KDM5A/C* mutation and OS in 2943 patients treated with ICIs. CI, confidence interval; CR, complete response; HR, hazard ratio; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease

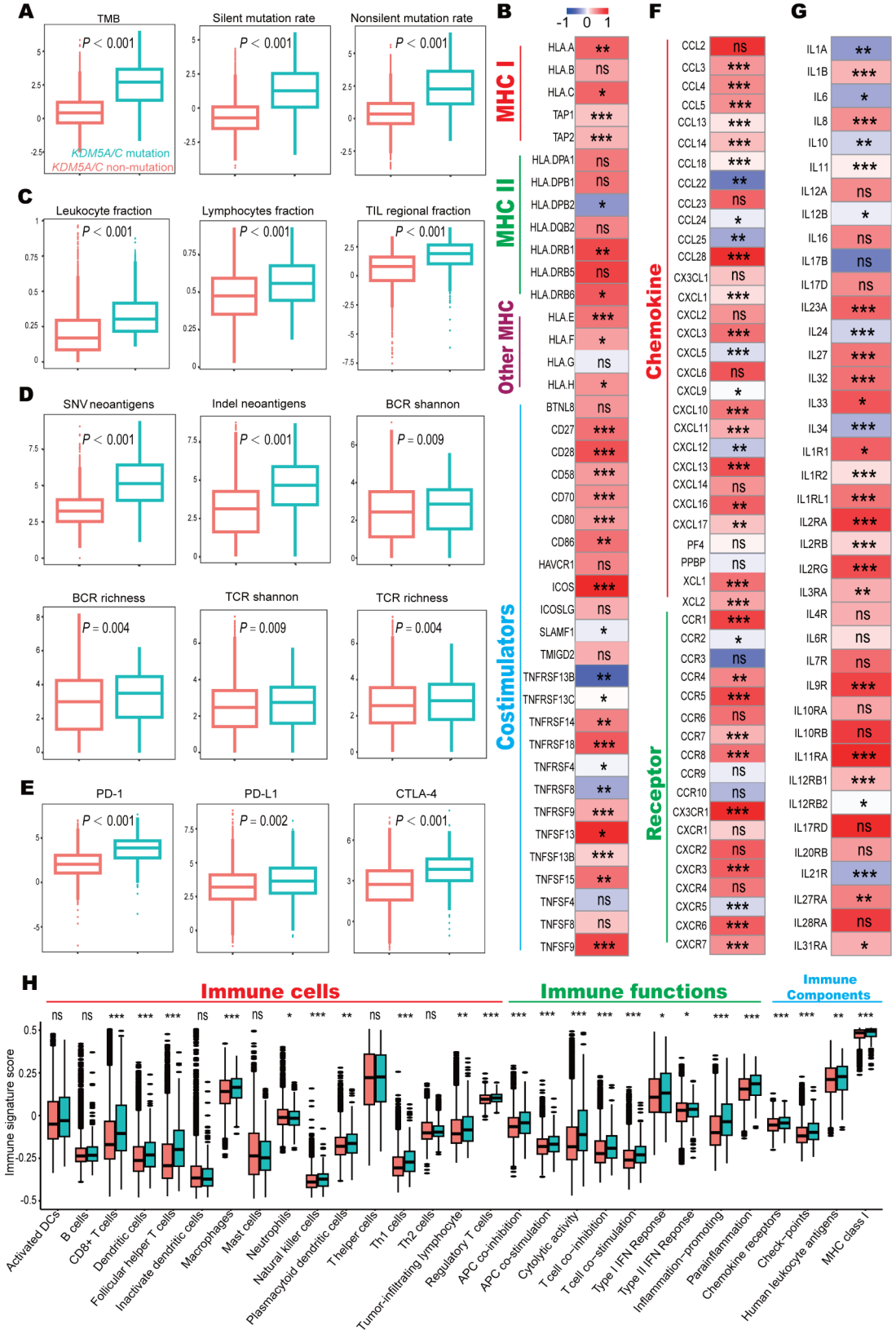


**Fig. 2** (See legend on next page.)

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**Fig. 2** Comparison of tumor immune microenvironment in*KDM5*-mutant and *KDM5*-non-mutant patients enrolled in TCGA cohort. **(A)** The differences of tumor mutation burden (TMB), silent mutation rate, and nonsilent mutation rate between *KDM5*-mutant and *KDM5*-non-mutant tumors examined by Wilcoxon test. Each dot represents one patient, box represents the median values and their interquartile ranges. Red, *KDM5*-mutant tumors; green, *KDM5*-non-mutant tumors. **(B)** The expression differences of 16 MHC-related antigen-presenting molecules and 25 co-stimulators between *KDM5*-mutant and *KDM5*-non-mutant tumors represented by heatmap. Red, the median expression values are higher in KDM5-mutant tumors; blue, the median expression values are lower in KDM5-mutant tumors. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$; ns, not significant. **(C)** The differences of leukocyte fractions, lymphocytes fraction and tumor-infiltrating lymphocyte fraction between *KDM5*-mutant and *KDM5*-non-mutant tumors. **(D)** Comparisons of the abundances of SNV/Indel neoantigens and the diversity of TCR/BCR. **(E)** Expression difference of *PD-1*, *PD-L1*, and *CTLA-4* in *KDM5*-mutant and *KDM5*-non-mutant tumors. **(F)** The expression differences of 48 chemokines and their receptors between *KDM5*-mutant and *KDM5*-non-mutant tumors represented by heatmap. **(G)** The expression differences of 39 immune-stimulators between *KDM5*-mutant and *KDM5*-non-mutant tumors represented by heatmap. **(H)** The differences of 29 immune signatures estimated by ssGSEA between *KDM5*-mutant and *KDM5*-non-mutant tumors. BCR, B cell receptor; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SNV, single nucleotide variants; TCGA, the cancer genome atlas; TCR, T cell receptor; TIL, tumor-infiltrating lymphocyte; TMB, tumor mutation burden

and associated with robust anti-cancer activities in terms of OS (HR=0.75; 95% CI, 0.58–0.97; $P=0.04$; Fig. 1C) and ORR (49.2% vs. 26.3%; $P<0.001$; Fig. 1D). *KDM5C* mutation ($n=99$) predicted similar outcomes but to a lesser extent in OS (HR=0.67; 95% CI, 0.51–0.88; $P=0.02$; Fig. 1E) and ORR (30.8% vs. 27.2%; $P=0.62$; Fig. 1F). To assess the value of various features as potential biomarkers for OS in immunotherapy, we performed univariate (Fig. 1G) and multivariate (Fig. 1H) Cox analysis. *KDM5* mutation was an independent positive predictor (HR=0.78; 95% CI, 0.62–0.97; $P=0.03$) after adjusting for confounding factors including age, sex, cancer type, drug type, tumor mutation burden (TMB), and *TP53* mutation status. Moreover, in patients with low TMB, *KDM5* mutation was also associated with longer OS (HR, 0.85; 95% CI, 0.71–0.99; $P=0.04$).

To investigate the underlying mechanisms between immunotherapy and *KDM5A/C* mutation, multi-omics information extracted from the cancer genome atlas (TCGA) pan-cancer cohort were explored. Totally, 429 (3.91%) of all 10,967 enrolled patients harbored *KDM5* somatic mutations. Specifically, *KDM5A* mutations were observed in 248 patients (2.26%), *KDM5C* mutations in 223 patients (2.03%). *KDM5* mutations were found in most tumor types (Figure S1), and the mutant frequencies differed significantly among various tumors ($P<0.001$). Totally, 504 mutations were identified, 435 (86.31%) were missense mutations, 46 (9.13%) were truncating mutations, 8 (1.59%) were fusion mutations, 8 (1.59%) was inframe mutation, and 7 (1.39%) were splice mutations. Further analysis revealed that OS was independent of *KDM5A/C* mutation (HR=0.98; 95% CI, 0.82–1.16; $P=0.77$), *KDM5A* mutation (HR=1.06; 95% CI, 0.85–1.33; $P=0.59$), or *KDM5C* mutation (HR=0.88; 95% CI, 0.70–1.11; $P=0.32$; Figure S2).

The key intrinsic immune response mainly referred to high tumor immunogenicity, activation of the antigen-processing machinery, and over-expression of co-stimulatory molecules [6]. In *KDM5*-mutant tumors, the mutation loads including TMB, silent mutation rate, and nonsilent mutation rate were increased significantly (Fig. 2A). Next, we investigated if there were any specific mutation patterns that were associated with the outcomes in *KDM5*-mutant patients treated with ICIs [7]. As shown in Figure S3A, the prevalence of SBS7a (known etiology, ultraviolet light exposure), SBS10b (*POLE* mutation), SBS31 (platinum chemotherapy treatment), and SBS86 (unknown chemotherapy treatment) were significantly different between *KDM5*-mutant and *KDM5*-non-mutant tumors. These SBSs were further identified as robust predictive biomarkers for survival in pan-cancer immunotherapy (Figure S3B). Indeed, the occurrence of SBS7a (HR=0.69; 95% CI, 0.58–0.82; $P<0.001$) and SBS10b (HR=0.73; 95% CI, 0.61–0.87; $P<0.001$) indicted favorable outcomes, while SBS31 (HR=1.41; 95% CI, 1.01–1.98; $P=0.01$) and SBS86 (HR=1.51; 95% CI, 1.08–2.10; $P=0.004$) were negative predictors. It was reported the dysfunctions of major histocompatibility complex (MHC) were main cause of tumor immune escape [8]. *KDM5* mutation was associated with higher expression of most known MHC-related antigen-presenting molecules and co-stimulators (Fig. 2B).

The major extrinsic immune characteristics included the infiltration of immune cells, high diversity of B/T cell receptors (BCRs/TCRs), activated immunogenicity of cancer cells contribute to the immune response, and high expression level of immune-stimulators and chemokines [9]. As shown in Fig. 2C, *KDM5* mutations were associated with enrichment of immune cell infiltration based on (1) leukocyte fractions measured by DNA methylation arrays; (2) lymphocytes fraction estimated from CIBERSORT algorithm [10]; and (3) the tumor-infiltrating lymphocyte (TIL) regional fraction evaluated by RNA-sequencing information. Mutations could induce potential tumor-associated neoantigens, which might be recognized by T/B cells with specific TCRs/BCRs [11]. Further analysis demonstrated the abundances of SNV neoantigens/Indel neoantigens and the diversity of TCR/BCR (measured by TCR/BCR richness and TCR/BCR Shannon) were significantly upregulated in *KDM5*-mutant tumors (Fig. 2D). The mRNA levels of three immune checkpoints (*PD-1*, *PD-L1* and *CTLA-4*) increased in *KDM5*-mutant tumors (Fig. 2E). Moreover, *KDM5* mutation was associated with higher levels of

most examined chemokines and their receptors (Fig. 2F) and immune-stimulators (Fig. 2G). Single sample gene set enrichment analysis (ssGSEA) was an approach quantifies 29 key immune cells, functions, and components [12], including activated dendritic cells, B cells, CD8+T cells, dendritic cells, follicular helper T cells, inactivated dendritic cells, macrophages, mast cells, neutrophils, natural killer cells, plasmacytoid dendritic cells, T helper cells, Th1 cells, Th2 cells, tumor-infiltrating lymphocytes, regulatory T cells, APC co-inhibition, APC co-stimulation, cytolytic activity, T cell co-inhibition, T cell co-stimulation, type I IFN response, type II IFN response, inflammation-promoting, para-inflammation, chemokine receptor, MHC class I, checkpoints, and human leukocyte antigens. As shown in Fig. 2H, the immune cell populations, immune activities, and immune-related components were clearly enriched in *KDM5*-mutant tumors.

Recent studies highlighted that KDM5 was associated with inflammatory disorders, autoimmune diseases, and tumor immune evasion through regulating cytokine production, inflammatory response, and immune checkpoints [3, 5, 13]. Moreover, pre-clinical studies discovered KDM5 could activate PI3K-AKT-S6K1 signaling cascade, resulting in the accumulation of tumor-associated macrophages, tumor-infiltrating dendritic cells, and increased T cell activation and expansion [14]. Consist with these investigations, our results from both extrinsic and intrinsic immune landscapes revealed *KDM5* mutation was associated with enhanced tumor immunogenicity, enriched infiltration of immune cells, and improved immune responses.

In summary, *KDM5* mutation was an independent biomarker for favorable outcomes in pan-cancer immune checkpoint blockade. Our study had implications for treatment decision-making and developing immunotherapy for personalized care.

#### Abbreviations

| | |
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| BCR | B cell receptor |
| CI | Confidence interval |
| CR | Complete response |
| CTLA-4 | Cytotoxic T-lymphocyte-associated antigen 4 |
| H3K4 | lysine 4 of histone H3 |
| HR | Hazard ratio |
| ICI | Immune checkpoint inhibitor |
| KDM5 | lysine-specific demethylase 5 |
| MHC | Major histocompatibility complex |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PD-1 | Programmed cell death protein 1 |
| PD-L1 | Programmed cell death ligand 1 |
| PR | Partial response |
| SBS | Single base substitution |
| SD | Stable disease |
| SNV | Single nucleotide variants |
| TCGA | The cancer genome atlas |
| TCR | T Cell receptor |
| TIL | Tumor-infiltrating lymphocyte |
| TMB | Tumor mutation burden |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12943-024-02197-3.

Supplementary Material 1: Figure 1. The mutation frequencies of KDM5 gene across 33 tumor types in TCGA cohort. (A) *KDM5A/C*; (B) *KDM5A*; (C) *KDM5C*.

Supplementary Material 2: Figure 2: Comparison of OS between patients with *KDM5* mutation and patients with *KDM5* non-mutation in 10967 subjects with 33 tumor types.

Supplementary Material 3: Fig. 3. COSMIC reference signatures associated with *KDM5* mutation. (A) The illustrations of four identified SBS signatures related with *KDM5* mutation and their frequencies in *KDM5*-mutant and *KDM5*-non-mutant tumors. Bold black, SBS signature and its known etiologies. Green, frequency in *KDM5*-mutant cancer. Orange, frequency in *KDM5*-non-mutant cancer. (B) The associations between four identified mutation signatures with OS in cancer immunotherapy.HR, hazard ratio; OS, overall survival; SBS, Single base substitution.

Supplementary Material 4

Supplementary Material 5

#### Author contributions

Dr. Bin Zhao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. XL, ZZ, YL, HZ and BZ conceived and designed the study. XL, ZZ, YL, LC, YH, LS, WX, YH, JL, MC and HY developed the protocol and performed the data analysis. XL, ZZ, YL, LC, YH, LS, WX, YH, JL, MC and HY collected data. XL, ZZ, YL, LC, YH, LS, WX, YH, JL, MC and HY conducted the statistical analysis. XL, ZZ, YL, HZ and BZ wrote the manuscript. BZ supervised this work.

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#### Data availability

No datasets were generated or analysed during the current study.

### Declarations

#### Consent to participate

Not applicable.

#### Ethics approval and consent to participate

Not applicable.

#### Role of the funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

#### Competing interests

The authors declare no competing interests.

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