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Original Article

Identifying predictors of overall survival among patients with TMB-low metastatic cancer treated with immune checkpoint inhibitors

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have significantly advanced cancer therapy, yet their efficacy in tumors with low tumor mutational burden (TMB) remains suboptimal. In this study, we aimed to elucidate the impact of somatic mutations on overall survival (OS) in TMB-low patients treated with ICIs and to explore the potential for personalized treatment selection through machine learning.

Methods: We conducted a comprehensive analysis of 1172 TMB-low (TMB < 10 mutations per megabase) patients with cancer receiving ICIs, examining the association between specific gene mutations and OS. Additionally, we developed a decision tree model (DTM) to predict OS based on clinical features and tumor mutational profiles.

Results: Our findings reveal that mutations in *DAXX, HLA-A, H3C2, IGF1R, CTNNB1, SMARCA4, KMT2D, and TP53* are significantly associated with poorer survival outcomes in the multivariate analysis. Remarkably, for renal cell carcinoma (RCC) patients, VHL mutations predicted improved OS following ICI even when adjusted for age, sex, and microsatellite instability (MSI) status in both multivariate analysis and the DTM model.

Conclusions: These results reinforce the prevailing notion that TMB alone does not predict ICI response, highlighting the critical role of individual gene mutations in TMB-low tumors under ICI therapy. Furthermore, our study demonstrates the promise of machine learning models in optimizing ICI treatment decisions, paving the way for more precise and effective therapeutic strategies in this patient population.

Key words: tumor mutation burden; immune checkpoint inhibitors; immunotherapy; machine learning.

Implications for practice

This study identified that mutations in MAP2K1, SETD2, KDM5C, PBRM1, and BRAF are associated with improved survival in TMB-low patients receiving immune checkpoint inhibitors therapy. A particular association between VHL mutations and improved survival was identified in renal cell carcinoma patients, which remained significant after adjusting for clinical factors. The investigators developed a decision tree model incorporating tumor histology and mutation status, highlighting the predictive value of renal cell carcinoma histology, VHL mutations (in RCC), CTNNB1 status (in melanoma), and TP53 status (in other cancers) to predict survival among TMB-low patients receiving immune checkpoint inhibitors therapy.

Introduction

The relationship between tumor mutational burden (TMB) and the efficacy of immune checkpoint inhibitor (ICI) therapy is well-established in recent literature.[1-3] This relationship is based on the rationale that tumors with high TMB harbor more mutations, increasing the likelihood of generating neoantigens.[4] These neoantigens can be recognized by the immune system as foreign, triggering an immune response.[5] However, tumor cells often develop mechanisms to suppress immune responses, evading detection, and destruction.[6] ICI therapies work by blocking these inhibitory signals, allowing immune cells to more effectively recognize and attack

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cancer cells.[7] Therefore, tumors with high TMB present more potential targets for activated T cells, potentially leading to improved responses to ICIs.

In clinical practice, stratifying patients with cancer based on their tumor mutational burden (TMB) status is commonly used for determining eligibility for immune checkpoint inhibitor (ICI) therapy.[8,9] Patients are typically classified as either TMB-high (≥10 mutations per megabase (Mb) or TMB-low (<10 mutations per Mb).[10] While patients with TMB-high tumors, irrespective of tumor type, are often eligible for ICI therapy due to increased likelihood of response,[11] those with TMB-low tumors are frequently excluded from this treatment option.[12]

However, TMB alone is not a perfect predictor of patient response to ICIs.[3,6] Factors like tumor microenvironment and immune cell infiltration also play a role.[13] Furthermore, recent studies (including our own) have shown that for TMB-high tumors, the specific somatic mutation profile can significantly impact survival outcomes in patients treated with ICIs, suggesting a potential role in determining ICI response.[14] However, similar investigations are lacking for patients with TMB-low tumors undergoing ICI treatment.[15]

Given this knowledge gap and the potential benefits of ICIs for TMB-low patients, in this study we comprehensively examine the impact of somatic mutation profiles and TMB sub-stratification on the outcomes of 1172 patients with cancer with TMB-low status receiving ICI therapy.

Methods

Patient cohort

We gathered somatic mutational profiles, clinical information, and survival data from a pan-cancer dataset, which included 1661 patients with advanced cancer treated with at least one dose of immune checkpoint inhibitors (ICIs) such as anti-PD-1/PD-L1, anti-CTLA-4, or combinations thereof.[9] Tumor histology was informed per the Oncotree Code. The survival time was measured from the date of first ICIs treatment to time of death or most recent follow-up. Selected ICIs included atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, or tremelimumab as monotherapy or in combination. Patients must had received at least one dose of ICIs therapy. Information regarding previous targeted therapies were not available and therefore not considered. The mutational profiles had previously been established based on somatic mutations identified in 468 cancer-related genes, utilizing both tumor-derived and matched germline normal DNA samples (MSK-IMPACT). The timing of tissue pathology on which somatic mutation profiling was performed relative to ICI administration was heterogeneous, with a small portion of patients with testing after ICI administration. Tumor mutational burden (TMB) was calculated based on the number of nonsynonymous somatic mutations amidst 4,976 exons corresponding to canonical transcripts of 341 genes (468 in the most recent version), and selected introns of oncogenes and tumor suppressor genes corresponding to approximately 1.5 Mb of the human genome. Germline alterations were excluded using paired normal blood samples. Specifically, we focused on the analyses of 1172 patients classified as TMB-low (TMB < 10 mutations per megabase). In order to estimate microsatellite instability (MSI) status in these samples, we individually assessed somatic mutations in MLH1, MSH2, MSH6, PMS2, and SETD2, following the methodology proposed by Yamamoto and Imai in 2015[16] and beforehand used in the TMB-high cohort assessment.[14] All the data we utilized in this study is publicly accessible via the cBioPortal database (https://www.cbioportal.org/, accessed on September 26, 2023).

Study design and impact of somatic gene mutations on overall survival

We investigated the mutational profiles in 468 key cancer-related genes from the MSK-IMPACT panel. Our focus was to understand their influence on overall survival (OS) in patients with a TMB-low across 8 cancer histologies, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), bladder cancer, head and neck, glioma, esophagogastric cancers, and colorectal cancers.

For the initial analysis on overall survival, patients were categorized into 2 groups: those with mutated genes and those with wild-type genes. We included only genes that were mutated in at least 5 patients ($N = 210$). Genes whose mutations were significantly associated with OS (P-value < .05) in the univariate analysis per Kaplan-Meier survival curves and log-rank tests were then included in multivariate Cox analyses. These analyses were adjusted for sex, median age, microsatellite instability (MSI) status, and histology, specifically covering melanoma, non-small cell lung cancer (NSCLC), bladder, colorectal, and renal cell carcinoma (RCC).

For RCC patients, we explored the most frequently mutated genes related to carcinogenesis (VHL, PBRM1, SETD2, BAP1, and KDM5C) and examined their co-occurrence. A multigene multivariate Cox analysis was subsequently conducted, adjusting for sex and median age.

Decision tree modeling

We employed decision tree modeling (DTM) to predict whether TMB-low patients receiving ICI treatment would have a median OS shorter or longer than the cohort median OS of 15 months. The decision boundaries in the DTM were established based on the following features: TMB as a continuous variable, somatic mutations in 24 genes significantly correlated with OS (P-value < .05) during univariate assessments, sex, and cancer type. These features were selected after induction and cutoff phases. For this analysis, our initial cohort (1,172 patients) was reduced to exclude those censored patients (243) before the median survival of 15 months.

Statistical analyses

Univariate and multivariate Cox analyses, Kaplan-Meier survival curves and Forest plots were conducted using R (https://www.r-project.org/), with the following packages: survival (v. 3.5.7), survminer (v. 0.4.9), OptimalCutpoints (v. 1.1.5), survivalROC (v. 1.0.3.1), and forestmodel (v. 0.6.2). For decision tree modeling, the Python programming language (https://www.python.org/) with Lifelines package (version 0.26.4) was used, following the methodology described by Davidson-Pilon.[17]

Results

This study included a total of 1172 patients with advanced tumors exhibiting a tumor mutational burden (TMB) below 10 mutations per megabase (mut/Mb). The cancer types

comprised non-small cell lung cancer (NSCLC) (*N* = 234; 20.0%), melanoma (*N* = 168; 14.3%), renal cell carcinoma (RCC) (*N* = 149; 12.7%), bladder cancer (*N* = 126; 10.8%), head and neck cancer (*N* = 111; 9.5%), glioma (*N* = 108; 9.2%), esophagogastric cancers (*N* = 107; 9.1%), colorectal cancer (*N* = 64; 5.5%), breast cancer (*N* = 41; 3.5%), and cancer of unknown primary (*N* = 64; 5.5%).

The median follow-up time for these patients was 19 months (range 0-78 months). Among the cases, 6.1% showed evidence of surrogate markers for microsatellite instability (MSI). The majority of patients received anti-PD-(L)1 monotherapy (79.5%), followed by ICI combination therapy (15.6%) and anti-CTLA-4 therapy (4.9%). Other preceding or concurrent non-ICI treatments were not recorded or accounted for in this analysis. The most frequently mutated genes were *TP53* (*N* = 467; 39.8%), *TERT* (*N* = 256; 21.8%), *KRAS* (*N* = 138; 11.8%), *VHL* (*N* = 105; 9%), *PIK3CA* (*N* = 104; 8.9%), *PTEN* (*N* = 80; 6.8%), *APC* (*N* = 73; 6.2%), and *PBRM1* (*N* = 72; 6.1%). A total of 5617 somatic nonsynonymous mutations were identified, with missense (*N* = 3595; 64.0%), frameshift (*N* = 662; 11.8%), and nonsense (*N* = 650; 11.6%) mutations being the most common types (Supplementary Table S1). These and other additional patient and tumor characteristics can be found in **Table 1**.

Somatic gene mutations impact survival of TMB-low patients treated with ICI

We first assessed the impact of somatic gene mutations on overall survival (OS) in all TMB-low patients treated with ICIs. OSl analysis was performed from the date of first infusion of any ICI. For patients who received multiple courses of ICI, the first treatment was used for analysis. With a maximum follow up of 80 months, the median OS for the cohort was 15 months. Focusing on gene mutations present in at least five patients, 24 out of 210 cancer-related genes were significantly associated with OS after ICI treatment (*P*-value < .05). Of these, 5 genes (*MAP2K1, SETD2, KDM5C, PBRM1*, and *BRAF*) were associated with improved OS, while 19 genes were associated with worse OS (*TP53, H3C2, DAXX, SMARCA4, STK11, SOX17, RB1, PIK3CA, CTNNB1, KMT2D, HLA-A, FBXW7, CDH1, RBM10, KEAP1, IGF1R, H3C11, EGFR*, and *RUNX1*)—Supplementary Table S1, Figure S1.

Subsequent multivariate Cox regression analysis adjusted by sex, median age, MSI status, and histology of these 24 genes identified 8 genes independently associated with reduced OS, regardless of other clinical factors: *DAXX, HLA-A, H3C2, IGF1R, CTNNB1, SMARC4, KMT2D*, and *TP53* (*P*-value < .05) melanoma, bladder, and renal cell carcinoma (RCC) histologies were associated with better OS, independent of gene mutations (*P*-values < .05). In these cases, the

Table 1. Tumor characteristics, patient demographics, treatment details, and mutation profiles in the dataset used for this study (*n* = 1172).

Tumor Type	NSCLC	234 (20%)
	Melanoma	168 (14.3%)
	Renal cell carcinoma	149 (12.7%)
	Bladder cancer	126 (10.8%)
	Head and neck cancer	111 (9.5%)
	Glioma	108 (9.2%)
	Esophagogastric cancer	107 (9.1%)
	Colorectal cancer	64 (5.5%)
	Unknown primary	64 (5.5%)
	Breast cancer	41 (3.5%)
Median age		62 years
Sex	Female	447 (38.1%)
	Male	725 (61.9%)
MSI (%)		72 (6.1%)
ICI type	ANTI-PD-(L)1	932 (79.5%)
	ANTI-CTLA-4	57 (4.9%)
	ICI combination	183 (15.6%)
Most frequently found mutations	TP53	467 (39.8%)
	TERT	256 (21.8%)
	KRAS	138 (11.8%)
	VHL	105 (9%)
	PIK3CA	104 (8.9%)
	PTEN	80 (6.8%)
	APC	73 (6.2%)
	PBRM1	72 (6.1%)

Abbreviations:ANTI-CTLA-4, monoclonal antibody directed against cytotoxic T lymphocyte-associated antigen; ANTI-PD-(L)1, monoclonal antibody directed against programmed cell death protein-1 or monoclonal antibody directed against programmed cell death ligand 1; ICI COMBINATION, combined treatment regimen including one ANTI-PD-(L)1 and one ANTI-CTLA-4, ICI, immune checkpoint inhibitor; MSI, microsatellite instability; N, number; NSCLC, non-small cell lung cancer.

presence of MSI surrogates, age, and gender did not significantly influence OS—**Figure 1A**, Supplementary **Table S1**.

Next, we decided to evaluate somatic gene mutations associated with OS of TMB-low patients depending on their tumor histologies. We found 8 genes significantly impacting OS of patients with 4 distinct tumor histologies at both uni and multivariate assessments adjusted by sex, median age, MSI status, and histology (*P*-value < .05). Interestingly, *VHL* mutations were significantly associated with increased OS after ICI treatment in patients with renal cell carcinoma, while for the remaining histologies gene mutations were associated with reduced OS: *CTNNB1* and *BAP1* for melanoma; *TP53* for head and neck cancer; *PBRM1*, *BRAF* and *TP53* for NSCLC; and *PIK3CA* for patients with bladder cancer—**Figure 1B**, **Supplementary Table S2**, **Figure S2**).

RCC carcinogenesis-related genes impact survival of TMB-low patients treated with ICI

Given the significant association between VHL mutation and improved OS in patients with RCC, we further investigated this relationship. The VHL gene, a tumor suppressor, encodes a 214 amino acid protein containing the VHL beta domain (VHL BD).[18] Inactivation of VHL is a pivotal molecular event in RCC tumorigenesis. To understand the role of VHL somatic mutations in the context of ICI treatment, we first performed univariate and multivariate analyses to assess their impact on survival prediction (**Figure 2**A-B). The median OS for VHL-mutated RCC patients was 24 months, compared to 17 months for VHL wild-type patients (*P*-value = .001)—**Figure 2A**. This survival benefit remained significant in a multivariate model adjusted for sex, median age (61 years), and MSI status (HR 0.43 [95% CI, 0.25-0.74]; *P*-value = .002), supporting VHL mutation as a strong predictor of improved OS—**Figure 2B**.

To gain further insights, we examined the distribution and frequency of *VHL* somatic mutations within the *VHL* BD—**Figure 2C**. Mutations were observed throughout the domain, with hotspots at protein positions 114 (10.5%; X114 splice and G114A), 155 (4.8%; V155L and X155 splice), and 65 (3.8%; S65L and S65P). Of the 105 *VHL*-mutated RCC patients, 38 (36.2%) had frameshift mutations, 37 (35.2%) had missense mutations, and the remaining patients presented nonsense (14.3%), splice-site (11.4%), or in-frame (2.9%) mutations—**Figure 2C**.

To better characterize the impact of VHL mutations on the survival of patients with RCC receiving ICI, we analyzed

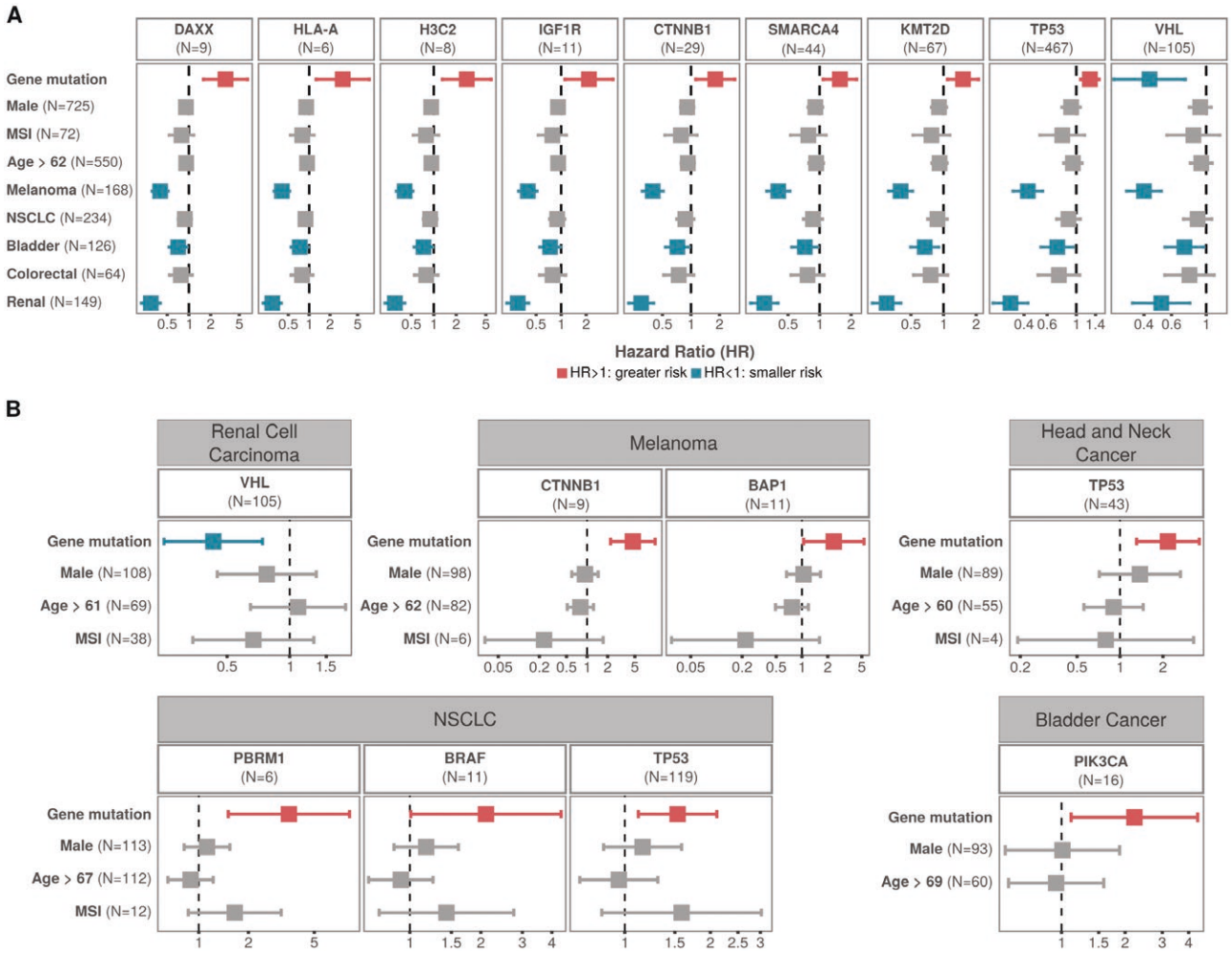

Figure 1. Impact of gene mutations on survival of TMB-low patients treated with ICI. A. Gene mutations associated with patients' overall survival (OS), adjusted for sex, age, microsatellite instability (MSI) status, and tumor histologies. B. Gene mutation effect on overall survival analyzed by tumor histology, adjusted for sex, median age, and microsatellite instability (MSI) status. Abbreviations: N, number. NSCLC, non-small cell lung cancer. Reference: Hazard Ratio (95% confidence interval).

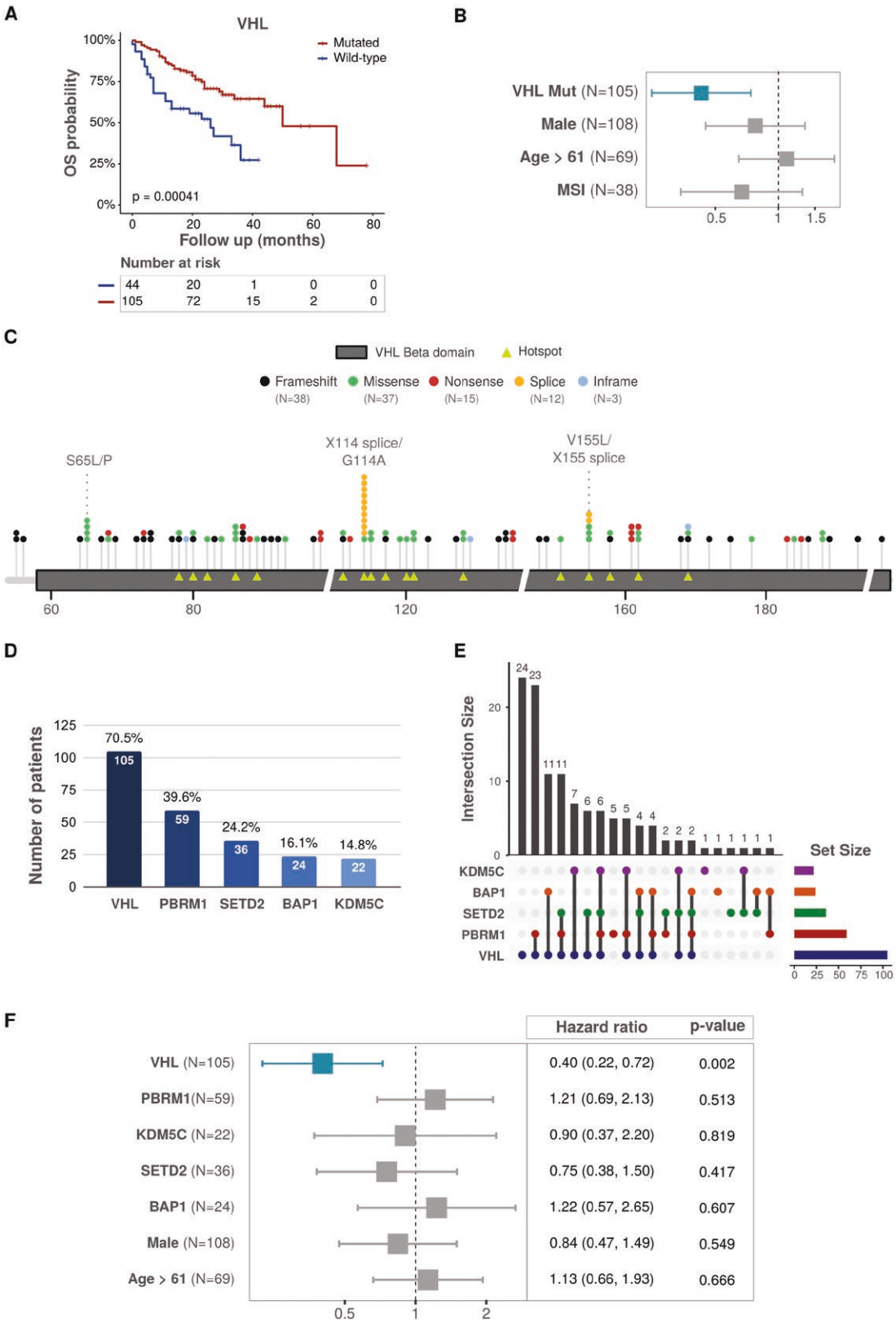

Figure 2. RCC carcinogenesis-related genes impact survival of TMB-low patients. (A) Kaplan Meier curve for OS of VHL-mutated RCC patients versus the wild-type ones; B) Forest plot adjusted by sex, median age, and MSI status; (C) schematic representation of VHL gene, its protein domains, and mutational profiles found in patients used in this study. (D) Five most frequently mutated genes among RCC patients; (E) co-occurrence of RCC carcinogenesis-related gene mutations among patients. (F) Multi-gene forest plot adjusted by sex and median age. Reference: hazard ratio (95% confidence interval).

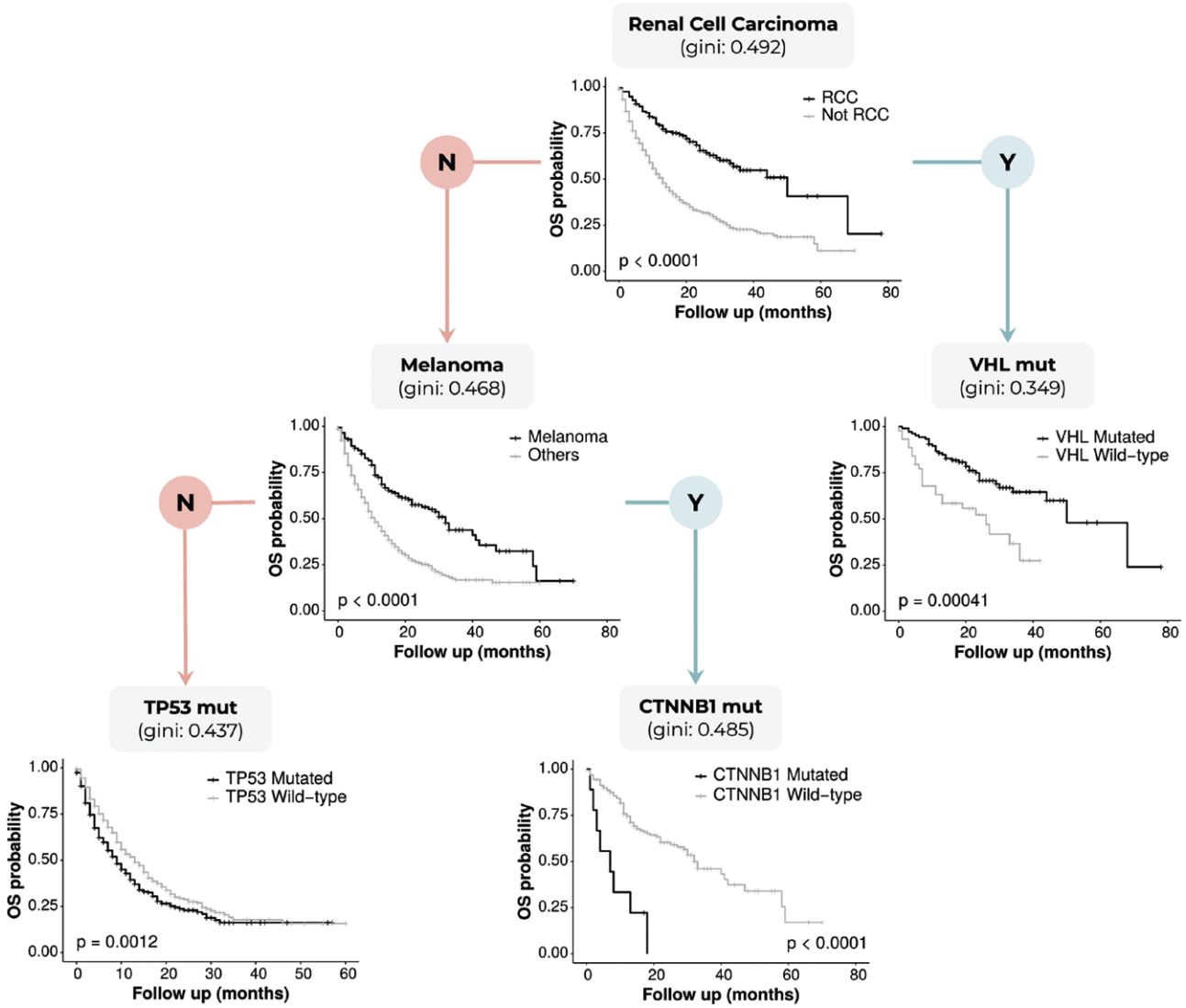

Figure 3. Decision tree model for predicting ICI response in TMB-low patients, with corresponding Kaplan-Meier survival curves. The model identifies RCC histology, VHL mutation status (in RCC), melanoma histology, CTNNB1 mutation status (in melanoma), and TP53 mutation status (in other cancers) as key determinants of overall survival following ICI therapy in the TMB-low setting.

their mutation profiles. The 5 most frequently mutated genes, including *VHL* ($N = 105$; 70.5%), were *PBRM1* ($N = 59$; 39.6%), *SETD2* ($N = 36$; 24.2%), *BAP1* ($N = 24$; 16.1%), and *KDM5C* ($N = 22$; 14.8%)—Figure 2D. Co-occurring mutations were common, with *VHL* and *PBRM1* being the most frequent ($N = 24$), followed by VHL and *BAP1* ($N = 11$), and *VHL*, *PBRM1*, and *SETD2* ($N = 11$)—Figure 2E. Notably, *KDM5C* mutations were more often found in combination with *VHL* mutations ($N = 7$), while *VHL* mutations were the most frequently observed alone ($N = 24$). Multivariate analysis incorporating these genes, sex, and median age confirmed the independent association of *VHL* mutations with improved OS (HR 0.40 [95% CI, 0.22–0.72]; p-value = 0.002)—Figure 2F.

Decision tree modeling

To investigate whether a machine learning approach could better stratify TMB-low patients undergoing ICI treatment based on their mutational profiles, we employed a DTM. This supervised learning algorithm is favored for its interpretability and ease of use. DTM works by recursively partitioning data into subsets based on input features, creating a tree-like structure where each node represents a decision based on a feature, each branch an outcome of that decision, and each leaf node a predicted outcome (eg, survival or death). Notably, DTM uses the Gini Index to evaluate the quality of each split, quantifying how often a randomly chosen element from a set would be incorrectly labeled if it were labeled according to the distribution of labels in the subset.

For this DTM analysis, our low-TMB patient cohort was split into a 75% training set and a 25% model testing. For the utilized model, with a depth of 3, the model exhibited accuracy of 68.07% and recall of 86.25%—Supplementary Figure S3. Consistent with our previous findings, the DTM identified RCC histology as the primary factor influencing survival outcomes in TMB-low patients (gini index = 0.492, Figure 3; Supplementary Figure S3). Within the RCC subgroup, VHL mutation status emerged as the second most important factor (gini index = 0.349, Figure 3). In non-RCC patients, melanoma histology was the primary determinant

(gini index = 0.468), followed by CTNNB1 mutation status in melanoma patients and TP53 mutation status in the remaining non-RCC, non-melanoma patients—**Figure 3**.

Overall, our DTM analysis suggests that within the TMB-low population, patients with, particularly those with VHL mutations, may derive greater benefit from ICI therapy compared to other tumor types. Additionally, melanoma patients with low TMB and wild-type CTNNB1 may also experience favorable outcomes with ICI treatment. Conversely, the presence of TP53 mutations appears associated with poorer prognosis in TMB-low patients receiving ICIs, consistent with previous findings.

Discussion

Our study comprehensively investigated the impact of somatic mutations on OS of TMB-low cancer patients treated with ICIs. These analyses revealed significant associations between specific gene mutations and overall survival within this theoretically "immune-cold" tumor subset.

Notably, we observed that mutations in several genes (*MAP2K1, SETD2, KDM5C, PBRM1,* and *BRAF*) were associated with improved survival in the univariate setting amidst TMB-low patients receiving ICI therapy. Conversely, mutations in a larger set of genes, including HLA-A and *TP53*, were linked to poorer outcomes in the uni- and multivariate settings. Specifically, HLA-A is a classical class I component of the major histocompatibility complex MHC, which holds an important antigen presentation function, enabling the immune system to discern between self and non-self, and driving immune-related responses.[19] Previously, McGranahan et al. reported that loss of heterozygosity (LOH) in HLA genes is associated with a high subclonal neoantigen burden, APOBEC mutational signature, upregulation of cytolytic activity, and PD-L1 overexpression.[20] However, the focal nature of these alterations (subclonal) and occurrence as parallel events suggests that HLA LOH can be understood as an immune escape mechanism subjected to evolutionary pressure. Altogether, these findings challenge the conventional view that TMB is the sole predictor of ICI response and emphasize the importance of considering individual gene mutation status in treatment decision-making.

Interestingly, our study identified a particular association between the VHL mutation and improved survival in RCC patients. This finding remained significant even after adjusting for other clinical factors such as age, sex, and presence of MSI. Recently, Zhang *et. al.* developed an immune-related gene signature for VHL-mutated RCC based on the expression of 10 genes (SEMA3B, KCNH2, INHA, BPIFA2, FGF19, IL20, GDNF, ANGPTL7, MUC5AC, and HLA-DQA1) related to survival, pointing that co-occurrence of VHL-mutations and other gene signatures can predict tumor immune status.[21]

Finally, to explore the potential for personalized treatment selection, we developed a decision tree model incorporating tumor histology and mutation status. This model reinforced our findings, highlighting the predictive value of RCC histology, VHL mutations (in RCC), CTNNB1 status (in melanoma), and TP53 status (in other cancers). First, this comes across the data from the CheckMate 214 trial that investigated the efficacy of the ICI combination of ipilimumab plus nivolumab in at first-line setting for advanced RCC patients. After a median follow-up of 25.2 months, the median OS was not reached for the interventional group.[22] Unfortunately, the information on whether our cohort's RCC patients received ICI at first or late lines is lacking. Interestingly, although most melanoma patients usually exhibit a TMB above 10 mut/Mb,[23] our results suggest that TMB-low melanoma patients can also benefit from ICI due to the existence of other predictive biomarkers like tumor-infiltrating lymphocytes (TILs).[24] In summary, these results demonstrate the potential of machine learning algorithms in refining ICI treatment decisions for TMB-low patients.

Importantly, our study has limitations. First, the retrospective setting of our study may introduce biases, however, they can be minimized by multivariable analysis and training and test groups validation. Second, the analyses were based on clinical and molecular data available in a public database, which did not guarantee the accuracy and update of the data. Third, the cohort was enriched with some specific tumor phenotypes such as NSCLC and melanoma that drive therapeutic advantage from ICI regardless of the TMB, which could have enhanced the magnitude of the ICI benefit.

Also, a particular confounding factor for RCC is that previous targeted therapies were not considered for this cohort and may confound the association of these genes with improved survival. Specifically, RCC patients may have previously received antiangiogenic drugs. Recent biomarker analyses from the CLEAR trial, which evaluated the efficacy of combining pembrolizumab with lenvatinib compared with sunitinib, indicate that the overall response rate (ORR) with the combination was numerically higher among patients with VHL mutations compared with the wild-type correlates. However, the deleterious mutation status of the *VHL* and other RCC carcinogenesis genes (*BAP1*, *PBRM1*, *SETD2*, and *KDM5C*—the same frequently mutated genes in RCC used in our analysis) failed to predict progression free survival (PFS) or OS benefit with the combination compared to the antiangiogenic treatment alone.[25] Finally, given that VHL loss is a key therapeutic target in RCC, further investigation is warranted to explore potential synergistic effects between ICIs and existing VHL-targeted therapies like HIF-2α inhibitors. Unfortunately, for the LITESPARK-005 trial which compared belzutifan, an HIF-2α inhibitor, with everolimus for previously treated RCC patients, the entire cohort received ICI as a primary treatment, combined or not with antiangiogenic drugs, making it impossible to bisect subgroups to evaluate the possible prognostic impact of the VHL mutations. Also, it bounded the evaluation of the potential synergistic interaction between ICI and HIF-2α inhibitor.[26] In our analysis, no separation of exploration and validation sets was done for the uni- and multivariate analysis. Training and test group separation were performed only for the Decision Tree Modeling to avoid overfitting. Also, we explored a validation cohort from the TCGA including patients who received various treatments, making it impossible to exclude a prognostic role of the VHL mutation. Ideally, an independent cohort of patients with RCC treated with and without ICIs should be selected for this objective.

Our investigation provides valuable insights into the impact of somatic mutations on ICI OS in TMB-low tumors. By demonstrating the predictive significance of specific gene mutations for personalized treatment selection, we pave the way for future research aimed at optimizing ICI therapy for the TMB-low patient population. However, among this particular group of patients, the molecular profiling based on NGS findings alone is deficient in defining patients that can

benefit from ICI, and the evidence provided is still contingent on clinical features. Additionally, we highlight the need to explore novel artificial intelligence (AI) methodologies that could further enhance clinical decision-making in the era of precision oncology. Our DTM brought out some information that is already established in the clinical practice, as RCC and melanoma patients meet FDA-approved ICI-based therapies for advanced disease scenarios regardless of the TMB count and molecular findings. Ideally, AI models should allow investigators to escalate the number of molecular features included in a model to adjudicate in patient selection for ICI-based therapies. Recently, researchers from the National Institutes of Health (NIH) have developed an AI tool incorporating five clinical features (age, cancer type, history of systemic therapy, blood albumin level, and blood neutrophil-to-lymphocyte ratio) associated with TMB to predict a patient's likelihood of benefiting (ORR and short and long term survival) from ICI.[27] The model was developed without the inclusion of detailed gene alteration information due to data restrictions. This reinforces that collaborative efforts to develop research in larger cohorts, incorporating comprehensive genomic profiling and detailed clinic information, are exceedingly needed.

Author contributions

Camila B. Xavier (Conceptualization, Formal analysis, Methodology, Investigation, Writing – original draft), Gabriela D. A. Guardia (Data curation, Formal analysis, Software, Visualization, Writing – original draft), João Pedro B. Alves (Data curation, Formal analysis, Software, Visualization), Carlos Diego H. Lopes (Investigation, Writing – original draft), Beatriz M. Awni (Investigation, Writing – original draft), Eduardo F. Campos (Investigation, Writing – original draft), Denis L. Jardim (Conceptualization, Project administration, Supervision, Writing – review & editing), Pedro A. F. Galante (Project administration, Supervision, Writing – review & editing).

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Conflict of interest

The authors declare no competing financial interests.

Data availability

The datasets analyzed during the current study are publicly available via the cBioPortal database (https://www.cbioportal.org/).

Supplementary material

Supplementary material is available at *The Oncologist* online.

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