LETTER

Self-limited cancer progression with increasing tumor mutations

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Dear Editor,

For most patients, cancer is a devastating disease leading to death, which is the consequence of malignant cancer progression. Self-limited cancer progression is rare but may occur. Identifying self-limited cancers is particularly important, not only for understanding the nature of the disease, but also for designing therapeutic strategies to limit cancer mortality. To date, most of the evidence for self-limited cancers remains indirect, primarily because the etiological agent driving such self-limited nature is unknown.

Somatic mutations inevitably accumulate over a lifetime of cell divisions, underpinning the malignant transition from normal cells to cancer. As an important hallmark of cancer, tumor mutation can confer a selective advantage by increasing genetic diversity and adaptability, which contributes to malignant cancer progression; however, the progressive accumulation of mutations also leads to the production of mutant proteins that can be recognized as neoantigens by the immune system, posing a significant risk to cancer cells selves. In summary, tumor mutations can contribute to oncogenicity and immunogenicity, resulting in pro- and anti-tumor effects. Due to its immunogenic anti-tumor effect, tumor mutation may be a potential agent mediating self-limited cancer progression.

Real-world data on tumor mutation and cancer progression

Although it is now widely accepted that cancer is caused by the accumulation of genetic mutations, the causal role of tumor mutations in cancer progression is obscure owing to the difficulty of analyzing the entanglement between the double-edged effects of tumor mutation —oncogenicity and immunogenicity. To date, the impact of increasing tumor mutations on cancer progression has been extensively studied in patients receiving immune checkpoint blockade (ICB) therapy, in which ICB therapy abrogates the suppression of the anti-tumor immunity against tumor neoantigens. ICB therapy can induce sustained disease remission and prolonged patient survival for those tumors with higher tumor mutation burden (TMB) >10 mutations/megabase (mut/Mb),[1] and has therefore been approved by the US Food and Drug Administration (FDA) approval.[2] However, patients eligible for ICB therapy only account for approximately 10% of cancer patients,[3] and there is still a lack of data conclusively demonstrating the role of TMB in patients not receiving ICB treatment. The inherent prognostic value of TMB, independent of ICB therapy, is also important in providing a benchmark for evaluating TMB-related cancer progression.

By far, TMB does not appear to be associated with cancer progression in cancer patients not treated with ICB therapy.[4] However, the previous study only analyzed TMB-H defined by TMB >10 mut/Mb.[4] The prevalence of TMB ranges from 0.01 mut/Mb to over 400 mut/Mb.[5] Previous studies used a TMB cutoff of 10 mut/Mb to assess clinical relevance, thereby ignoring differences in patients with much higher TMB. Furthermore, previous studies have not analyzed the cumulative effects of increasing TMB levels. In contrast, this study has advantages over previous reports. Unlike previous studies, this study sought to comprehensively analyze the cumulative impact of TMB on the clinical outcomes in cancer patients, while particularly investigating those patients with the highest TMB levels.

Data sources for this study

At present, the previous efforts of collecting large and clinical representative cohorts, coupled with recent advances in developing TMB assays, are beginning to enable the study of the precise role of tumor mutation in cancer progression. In this study, a contemporary cohort of 10,233 patients with cancer was acquired from Dr. Morris' study.[6] To eliminate the potential bias caused by the mutagenic effect of chemotherapy or radiotherapy,[7] patients who received any cytotoxic chemotherapy or radiotherapy before TMB detection were excluded. Next, 6,978 previously treatment-naïve patients were used for further analysis. The 6,978 patients were composed of 1,147 patients who subsequently received treatment with immune checkpoint inhibitors (ICIs) and 5,831 patients without ICI treatment.

Statistical analysis

To determine the dynamic of cancer progression attributable to increasing tumor mutations, this study conducted a non-linear analysis of hazard ratio (HR) by spline-based smoothing method. By taking the value of TMB = 0 mut/Mb as a reference, HRs were estimated across the continuous spectrum of TMB levels. A statistical method known as smoothHR[8] was applied to construct the natural cubic regression spline curve of HR with 95% confidence intervals (CIs). The log-HR curve with 95% CIs provided a straightforward interpretation that the 95% CIs above or below zero is equivalent to a significance of two-sided p <0.05.

Self-limited cancer progression with increasing tumor mutations

Through interrogating 6,978 previously treatment-naïve patients with cancer, this study analyzed the dynamics of overall survival (OS) with increasing TMB levels. As shown in Figure 1A, TMB was significantly associated with OS in dose-dependent manners. In ICB-treated patients, TMB was positively associated with a favorable OS (Figure 1A; left panels). In the context of ICB treatment, the accumulation of TMB can directly limit cancer progression in a dose-dependent manner. In contrast, in non-ICB-treated patients, TMB showed an inverted S-shaped relationship with OS: the initial increase of TMB (0-30 mut/Mb) was associated with inferior OS, while the further increase of TMB (> 30 mut/Mb) was associated with improved OS (Figure 1A; right panels).

Since the improved or inferior cancer progression could scale with different TMB levels, to explore the trend of this apparent discrepancy, Kaplan-Meier analysis was conducted, and patients of low and high TMB (TMB-L and TMB-H) groups were stratified by the FDA-approved TMB cutoff — 10 mut/Mb; further, TMB-H group was equally divided into three subgroups by TMB level. Figures 1B-C shows that increasing TMB levels can contribute to both reduction and improvement in OS. Notably, in non-ICB-treated patients, a remarkably improved OS was observed in the TMB-H subgroup of high TMB (subgroup IV) (p < 0.0001; Figure 1C). In summary, those patients with the highest TMB levels represent an important subset of cancer patients that have superior prognosis and high responsiveness to ICB therapy. Moreover, increasing TMB can eventually give rise to self-limited cancer progression even without ICB therapy.

The self-limited cancer progression was observed in patients with the highest TMB levels, which could be attributed to a minority (3.81%) of cancer patients, mainly derived from colorectal cancer, endometrial cancer, and non-small cell lung cancer (NSCLC) (Figure 1D). Of note, colorectal cancer, endometrial cancer, and NSCLC are markedly different in cancer mortalities. According to the cancer statistics from Surveillance, Epidemiology, and End Results (SEER) Program, the 5-year survival rates for NSCLC, colorectal cancer, and endometrial cancer are 26%, 64-67%, and 84%, respectively.[9] Here, according to different cancer types, patients of low and high TMB (TMB-L and TMB-H) groups were stratified by 10 mut/Mb; TMB-L and TMB-H groups were equally divided into subgroups by TMB level. Albeit with different survival rates and times and varying TMB levels, the findings of self-

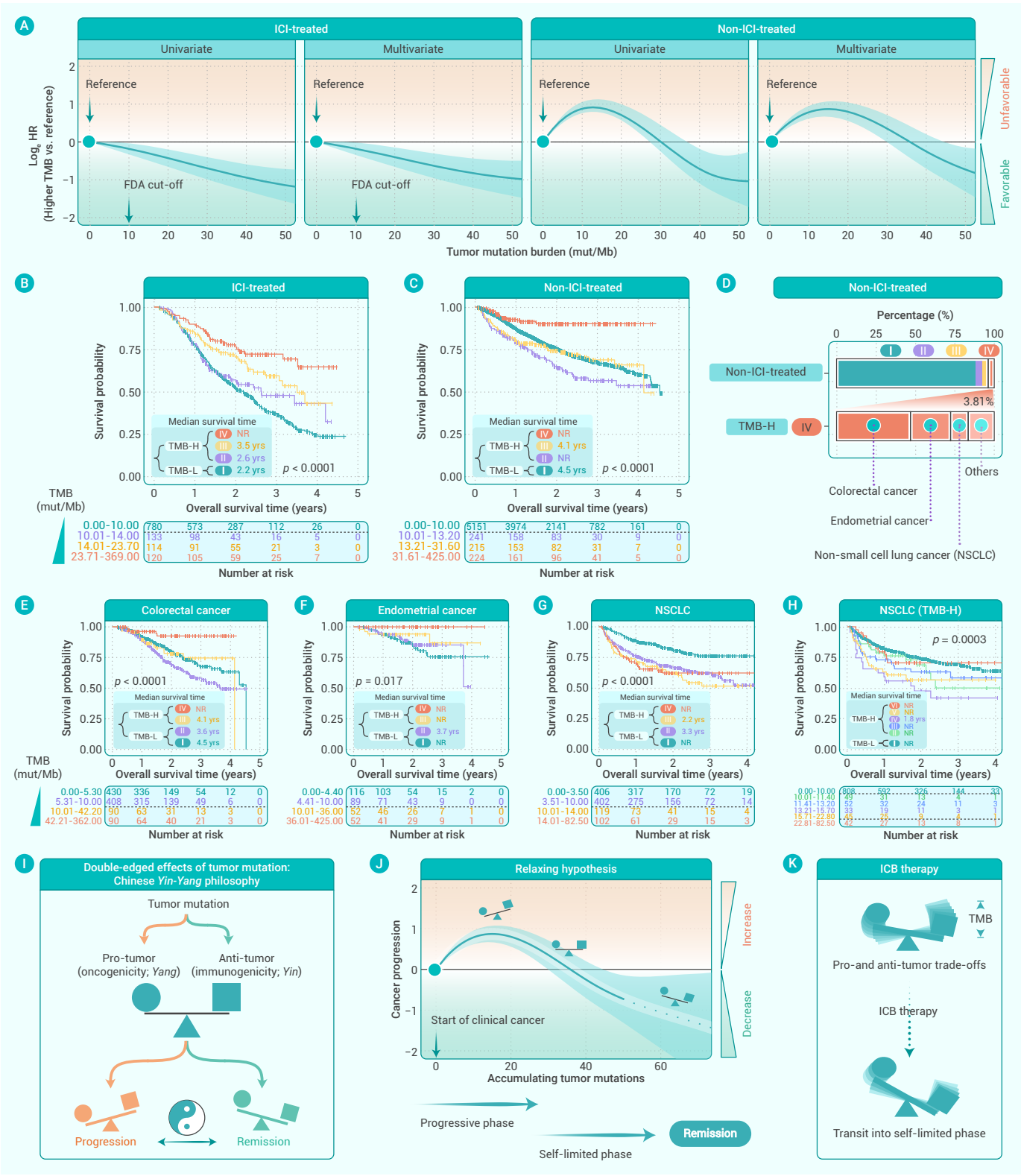

Figure 1. Landscape of cancer progression across increasing tumor mutation burden (TMB) levels (A) The smoothing estimate of hazard ratio (HR) with 95% confidence intervals (CIs) across the increasing TMB level. The log-HR curves (solid line) with 95% CIs (shading) show the impact of TMB increase on the overall survival (OS) in cancer patients with or without treatment using immune checkpoint inhibitors. The HRs were fitted by univariate and multivariate analyses using Cox proportional hazards regression model. Multivariate analysis was performed using covariates of cancer type, sex, age, ICB drug class, and year of ICB treatment start. To rule out the outliers at the distal end of log-HR curve, truncation was performed to remove TMB values above the 95th percentile. The x-axis shows the TMB level (mut/Mb), and the y-axis shows $\log_e$-HR taking TMB = 0 mut/Mb as the reference. (B-C) The Kaplan-Meier curves show the OS in ICB-treated (B) and non-ICB-treated (C) patients with cancer. Patients of low and high TMB (TMB-L and TMB-H) groups were stratified by the FDA-approved TMB cutoff — 10 mut/Mb; further, TMB-H group was equally divided into three subgroups by TMB level. The significance was measured by the log-rank test. The bottom panel shows the number of patients at risk every one year. (D) The bar plot shows the percentage of non-ICB-treated patients by TMB level and cancer type. (E-H) The Kaplan-Meier curves show the OS according to TMB level in non-ICB-treated patients with colorectal cancer (E), endometrial cancer (F), and non-small-cell lung cancer (G-H). The significance was measured by the log-rank test. (I) Double-edged effects of tumor mutation: Chinese Yin-Yang philosophy. The dynamic seesaw model shows the pro-and anti-tumor trade-offs following tumor mutation leading to cancer progression or remission. (J) Relaxing hypothesis. Cancer progression could undergo a smooth transition from progressive to self-limited phases with the accumulation of tumor mutations. The dashed line shows the extrapolation of cancer progression outside the common range of TMB in human cancer. (K) ICB therapy enhances anti-tumor response to direct the transition into a self-limited phase.

limited cancer progression were considerably consistent in patients with the highest TMB levels in colorectal cancer, endometrial cancer, and NSCLC (Figures 1E-H).

To the best of my knowledge, this is the first sufficiently powered post-hoc analysis revealing the dose-dependent relationship between continuous TMB levels and cancer progression. Scaled across the continuous spectrum of TMB levels, in cancer types with markedly different survival rates and times, this finding may promise to transform our understanding of the multiple roles of tumor mutation and its effect on cancer progression. Of note, this study identified that self-limited cancer progression could be achieved in patients with higher TMB of >30 mut/Mb even without ICB treatment (Figure 1A). Thus, this discovery is important for the clinical decision-making for cancer patients as well as for regulatory agencies to evaluate the efficacy of ICB treatment according to TMB levels.

Double-edged effects of tumor mutation: Chinese Yin-Yang philosophy

Tumor mutations can contribute to pro- and anti-tumor effects (oncogenicity and immunogenicity). These double-edged effects arise very early during tumorigenesis, representing hallmarks of cancer that are present in all tumors. The double-edged effects of tumor mutation embody a basic tenet of Chinese philosophy—the Yin-Yang theory (Figure 1I). Oncogenicity represents the *Yang* (阳; positive) side that promotes cancer progression, whereas immunogenicity represents the *Yin* (阴 ; negative) side that inhibits cancer progression. Just as described in Yin-Yang philosophy, these opposite but interconnected forces interact to form a dynamic system. As such, the trade-offs between the pro- and anti-tumor effects of tumor mutations effectively determine inter-individual differences in TMB-related cancer progression or remission.

Next, this study proposes a theoretical framework based on the "dynamic seesaw model" to illustrate the underlying conceptual basis for explaining how cancer progression changes with increasing TMB levels (Figures 1J-K). Based on real-world data from cancer patients, this study found that cancer progression exhibits a seesaw-like pattern, which can transition from a progressive phase to a self-limited phase as tumor mutations increase (Figure 1J). Furthermore, the "dynamic seesaw model" is in agreement with the clinical data of immunotherapy with respect to the clinical implications of TMB in ICB responsiveness, in which ICB treatment abolishes the suppression of anti-tumor immunity and enhances the recognition of immunogenic mutations and thus induces self-limited cancer progression (Figure 1K). This finding has important ramifications for understanding the root cause of cancer progression as well as for reducing cancer mortality by ICB-based precision medicine.

Moreover, the findings described above strongly suggest the existence of self-limited cancers, that is, malignancies that do not or slowly progress to fatal disease. From this perspective, cancers encompass lethal and self-limited subtypes that are scaled across the broad spectrum of TMB levels. This discovery revolutionized our understanding of the boundary between benign and lethal cancers. Currently, there is no known indicator used to distinguish self-limited cancers from lethal cancers. When new cancer cases are diagnosed, the detection of TMB—a well-established and readily available technique—may be one of the promising approaches to identify self-limited cancers that are less lethal, presumably benign with superior prognosis, and highly sensitive to immunotherapy.

Perspective

In this study, the role of tumor mutations in cancer progression has been analyzed in depth through sophisticated clinical investigations, leading to the notable finding of a previously unrecognized self-limited cancer. The key insight is the recognition of tumor mutation as a causative agent driving cancer progression. By mediating varying levels of pro- and anti-tumor effects, tumor mutations can exacerbate cancer progression while interacting with the immune system that influences tumor fitness. As for cancer cells selves, when tumor mutations increase, the benefits of tumor fitness must be balanced against the costs of excessive mutations. As such, tumor mutation is not an unmitigated good, but it is caught in risk-benefit trade-offs. By modulating such trade-offs, ICB therapy has been shown to improve clinical benefit by promoting self-limited cancer progression. Therefore, cancer is not undefeatable due to its intrinsic design flaw.

In summary, as a major determinant of oncogenicity and immunogenicity, tumor mutation is the etiological agent driving cancer progression, albeit with varying contributions and different metrics in the therapeutic context with or without ICB treatment. As in the Yin-Yang philosophy, since the pro-tumor effect (*Yang*) of tumor mutation is integral and indispensable in tumorigenesis and cancer progression (termed tumor fitness), considering that it is interconnected with its anti-tumor effect (*Yin*), such double-edged effects (Yin-Yang interaction) can be omnipresent in any tumors. The dynamic balance between the *Yin* and *Yang* sides of tumor mutation jointly determines cancer progression or remission.

This theory helps explain the natural pathogenesis of cancer and its responsiveness to immunotherapy. Moreover, the discovery—self-limited cancer progression with increasing tumor mutations—provides a natural prescription for cancer patients. For example, therapeutic priming with alkylating agent temozolomide can inactivate mismatch repair (MMR) genes, leading to increased TMB levels and promoting the generation of neoepitopes, thereby stimulating immune surveillance and boosting responsiveness to subsequent ICB therapy, thus ultimately inducing self-limited cancers.[10] As such, we can exploit the natural design flaw of cancer to develop novel strategies for cancer therapy.

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DECLARATION OF INTERESTS

The author declares no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

No human subjects were directly involved in this study. All the data used in this study were derived from existing deidentified biological samples and data from prior studies. Thus, ethical and patient consent were not required in this study.

DATA AND CODE AVAILABILITY

Data are available on reasonable request.