Decoding Tumor Mutation Burden: A Predictor of Immunotherapy Efficacy Across Diverse Cancer Types

By

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School of Pharmacy

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Declaration

It is hereby declared that

- The thesis submitted is my own original work while completing degree at BRAC University.
- The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
- The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
- I have acknowledged all main sources of help.

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Approval

The thesis titled "Decoding Tumor Mutation Burden: A Predictor of Immunotherapy Efficacy Across Diverse Cancer Types" submitted by Md Muntasir (19346072) of Summer, 2026 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

The study does not involve any animal or human clinical trials.

Abstract

Tumor Mutation Burden (TMB) has become one of the most popular predictive biomarkers to determine the application of immune checkpoint inhibitors (ICIs) in cancer treatment, on the grounds that a higher somatic mutation burden has a higher neoantigen load and, as such, is more easily recognized by the immune system. TMB has become a solid part of tumor-agnostic clinical decision-making, with the tumor-agnostic approval of pembrolizumab on solid tumors with TMB of ten or more mutations per megabase by the United States Food and Drug Administration, but its predictive capabilities across cancer types, sequencing systems, and pipelines can vary significantly. This study discusses TMB's biological nature, estimation methods, and clinical results in diverse cancers using peer-reviewed literature, breakthrough clinical studies, and regulatory data. The results reveal that TMB is a context-specific but significant biomarker. Its predictive capacity in classifications with mutational load as the leading driver of immunogenicity such as melanoma, non-small cell lung cancer, and microsatellite instability-high tumors, but is diluted in histologies with low mutational loads or in tumors that contain immunosuppressive microenvironment, intra-tumoral heterogeneity, and other immune-evasion strategies. The lack of a universally validated cut-off, variability based on platforms and inequities in access to genomic testing are the main obstacles to wider adoption. TMB is always better predicted with complementary biomarkers including PD-L1, microsatellite instability, and tumor-infiltrating lymphocyte signals. It concludes that TMB is part of a multi-biomarker system to select immunotherapy patients and that future developments will rely on harmonized measurement standards, histology-specific thresholds, prospective real-world validation, artificial intelligence, and liquid-biopsy systems.

Keywords: Tumor Mutation Burden; Immunotherapy; Immune Checkpoint Inhibitors; Neoantigens; Predictive Biomarker; Microsatellite Instability; PD-L1; Pembrolizumab; Precision Oncology; Next-Generation Sequencing.

Dedication

Dedicated to my family, whose encouragement and patience supported me through every stage of my undergraduate studies, and to the teachers and mentors at the School of Pharmacy, BRAC University, who guided me through this work.

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List of Acronyms

AI	Artificial Intelligence
AMP	Association for Molecular Pathology
APC	Antigen-Presenting Cell
bTMB	Blood-Based Tumor Mutation Burden
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CDx	Companion Diagnostic
ctDNA	Circulating Tumor DNA
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
dMMR	Deficient Mismatch Repair
DNA	Deoxyribonucleic Acid
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FOCR	Friends of Cancer Research
HLA	Human Leukocyte Antigen
ICI	Immune Checkpoint Inhibitor

INDEL	Insertion/Deletion Mutation
ITH	Intratumoral Heterogeneity
IVDR	In Vitro Diagnostic Regulation
LAG-3	Lymphocyte Activation Gene 3
MDSC	Myeloid-Derived Suppressor Cell
MHC	Major Histocompatibility Complex
ML	Machine Learning
mRNA	Messenger Ribonucleic Acid
MSI	Microsatellite Instability
MSI-H	Microsatellite Instability-High
Mut/Mb	Mutations per Megabase
NGS	Next-Generation Sequencing
ns-SNV	Non-Synonymous Single-Nucleotide Variant
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1

PFS	Progression-Free Survival
RNA	Ribonucleic Acid
TAM	Tumor-Associated Macrophage
TCR	T-Cell Receptor
TIL	Tumor-Infiltrating Lymphocyte
TIM-3	T-cell Immunoglobulin and Mucin Domain-Containing Protein 3
TMB	Tumor Mutation Burden
TMB-H	Tumor Mutation Burden-High
TME	Tumor Microenvironment
Treg	Regulatory T Cell
tTMB	Tissue-Based Tumor Mutation Burden
UV	Ultraviolet
WES	Whole-Exome Sequencing
WGS	Whole-Genome Sequencing

Chapter 1

Introduction

Tumor Mutation Burden (TMB) is a measure of the number of mutations in a tumor, which is calculated in mutations per megabase (Mb) of DNA in a specific area of the genome (Wood et al., 2020). A greater increase in TMB leads to the generation of immunogenic neopeptides, which are bundles of tiny protein fragments expressed on tumor cells surfaces through major histocompatibility complexes (MHC), and which can elicit immune responses, especially in patients treated with immune checkpoint inhibitors (ICIs) (Kim et al., 2024; Yoshino et al., 2023). The TMB has since been confirmed as an effective predictive biomarker of ICI efficacy in certain types of cancer (Klempner et al., 2019). The initial signs were in melanoma and non-small cell lung cancer, which has a high mutation burden due to the exposure to UV radiation and smoking (Klempner et al., 2019). Recently, high TMB has been linked to improved ICI results in a broader spectrum of solid tumors (Budczies et al., 2024).

One of the problems still is measurement. The most accurate TMB estimate is provided by whole-exome sequencing (WES), although cost and turnaround limit clinical use. The viable alternative is targeted gene panels, although they vary in size, mutation coverage, and bioinformatics pipelines resulting in inconsistent TMB values across platforms (Makrooni et al., 2022). TMB is also similar to microsatellite instability-high (MSI-H) status that is caused by the impaired DNA mismatch repair (dMMR) pathways in some tumors (Yao et al., 2020).

Immunotherapy of cancer does not act in the same way as chemotherapy or radiation. This does not attack the tumor, but rather enhances the immune system to identify and kill malignant cells and is a method that has yielded long-term outcomes in patients who would not have responded to a standard therapy (Tanegashima et al., 2025; Chen and Emens, 2013). The involvement of the immune system here is not in passive form: tumor-infiltrating lymphocytes (TILs) identified in or near tumors demonstrate the active engagement of the immune system, and an increased TIL density always predicts improved prognosis (Mukherjee et al., 2022; Whiteside, 2022).

Tumor mutational burden refers to the total number of somatic mutations present in a tumor's DNA (Jardim et al., 2020). Tumors with high TMB carry a greater mutational load, and this drives the production of neoantigens, which are novel protein fragments arising directly from those mutations (Budczies et al., 2024). Unlike normal self-proteins, neoantigens are recognized by the immune system as foreign, triggering a targeted response against the cells that display them (Xie et al., 2023; Efremova et al., 2017). This is the core mechanism linking mutational burden to immune reactivity: the more mutations a tumor accumulates, the more targets it presents (Han et al., 2020).

TMB is determined by counting the number of somatic mutations in the DNA of a tumor and dividing the number by the size of the sequenced genomic region. There are three major sequencing methods in current use: Whole Exome Sequencing (WES), regarded as the reference standard; Targeted Next-Generation Sequencing (NGS) Panels, which are more clinically practical but depend heavily on panel size and gene composition; and Whole Genome Sequencing (WGS), which provides the most detailed measurement but is limited by high cost and computational demands (Elbehi, 2024). TMB may also be quantified using either tumor tissue (tTMB) or

peripheral blood (bTMB), each with distinct clinical usability and limitations (Ba et al., 2021). TMB is stratified into TMB-high and TMB-low, which has direct clinical implications to identify patients with the highest likelihood of responding to immune checkpoint inhibitor therapy (Jardim et al., 2020; Jun et al., 2025). Although a threshold of 10 or more mutations per megabase (mut/Mb) is frequently used, the threshold definition does not have a universal standard and has different values depending on the type of cancer and sequencing platform (Bai et al., 2020; Meléndez et al., 2018).

In spite of its clinical utility and widespread usage in immuno-oncology (Bai et al., 2020), TMB as a predictive biomarker is still subject to quite significant limitations. TMB also has some unsolved methodological debates that constrain it to be a reliable application across tumor types and clinical scenarios (Jun et al., 2025). Higher TMB is not a sure sign of an effective immune response and the mechanisms behind this discordance are becoming more fully understood (Zhu et al., 2020). A dense population of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) may form an immunosuppressive tumor microenvironment that excludes the access of cytotoxic T cells to the tumor and their functional performance (Velez, 2022). In addition to immune exclusion, the quality of neoantigens is a key factor: a high mutational load does not guarantee the presence of neoantigens properly presented on MHC molecules or sufficiently immunogenic to trigger T cell responses (Halima et al., 2022). The non-standardization of TMB is one of the basic impediments to its consistent application as a clinical biomarker. The lab-to-lab comparability of TMB scores based on various sizes of gene panels, bioinformatics pipeline, and variant-calling thresholds remains uncertain, which affects the decision-making regarding treatment based on the accurate classification of biomarkers (Fenizia et al., 2021; Galuppini et al., 2019). TMB's predictive value is not equal for all types of cancers: it is a reliable predictor in

cancers where the high level of mutational burden is the major contributor to immunogenicity, including melanoma and MSI-H colorectal cancer, but in other cases, the relationship fails due to mutational load not dominating as the determinant of immune engagement.

Despite growing clinical adoption, no universally validated TMB threshold exists across all cancer histologies, and significant variability persists across sequencing platforms and laboratories. This review is significant because it synthesizes evidence from landmark clinical trials, meta-analyses, and regulatory decisions to provide a comprehensive cross-cancer evaluation of TMB's predictive value and limitations. By mapping when TMB succeeds and when it fails as a stratification tool, this article offers actionable guidance for clinicians and researchers seeking to integrate TMB into precision oncology practice.

What is novel about this study is its side-by-side comparison of patient sex distribution across the major TMB trials, paired with the strengths and limitations of each, so that readers can see in one place how heavily the existing evidence base for TMB rests on male-dominated cohorts and where this bias may distort the biomarker's reported performance.

Chapter 2

Aim, Objectives and Rationale

2.1 Aim and Objectives

The proposed study will investigate TMB as a predictive biomarker of immunotherapy response in various types of solid tumors, with overall survival as the main clinical outcome of the study to determine which patients are most likely to respond positively to immune checkpoint inhibition. The study attempts to base its findings on clinically meaningful outcomes as opposed to surrogate measures by itself by emphasizing the importance of including clinically meaningful outcomes in the study instead of surrogate measures alone. Another objective is to explore the behavior of the relationship between TMB and survival by cancer of various tissue origin, mutational profile, and immune microenvironment, as not all tumors respond to prediction based on one predictor. Another objective of the study is to determine whether tumor-agnostic TMB cutoff can be a reliable cutoff, or whether tumor-specific calibration is needed to maintain the predictive accuracy. All these objectives are meant to help demystify the strengths as well as the limitations of TMB as a decision tool in immunotherapy.

The objectives of this study include: First, to assess TMB as a predictive biomarker of immunotherapy response in the context of various solid tumor types, as primary clinical outcome measures, treatment response, progression-free survival, and overall survival. This set of endpoints enables the analysis to get both short-term tumor control and the long-term clinical benefit. Second, to define how variable TMB is among different types of tumors, it is necessary to determine which oncological scenarios TMB best predicts probable responders versus non-responders. This involves taking into account the possibility of factors like tumor immunogenicity,

prior exposure to treatment, and underlying mutational mechanisms modulate the intensity of TMB-outcome correlation. Third, to identify which subpopulations of patients, based on high TMB, show the most clinical benefits in response to immune checkpoint inhibition, and to take into account whether any further clinical or molecular characteristics further narrow down the identification of likely responders. Fourth, to convert these results into actionable criteria that can be used in the clinical treatment of TMB-high cancers, considering how such criteria can be incorporated into the current diagnostic processes and shared decision-making between oncologists and patients.

2.2 Rationale of the Study

This study is justified by the fact that there is an inherent gap in precision oncology: the immune checkpoint inhibitors have generated long-term responses in several malignancies, though a significant number of patients will not benefit. This variability has clinical implications, since patients who fail to respond are left at risk of possible immune-related toxicity, economic cost, and missed chance to seek other treatments within a critical period of disease control. It thus requires biomarkers that can be used in predicting future responders prior to initiating treatment. In this aspect, TMB is known to have attracted significant clinical interest in this field of research. As high mutational load tumors are able to produce neoantigens more frequently this then enhances the chance of a long-lasting anti-tumor immune response. There is a growing sector of clinical data, based on cancer types with high TMB, that demonstrate that patients with high TMB respond more, have a longer progression-free and overall survival in response to immunotherapy. Nonetheless, the predictive value of TMB to tumors is not all inclusive. Differences in the genomic profiling platforms, the size of the panel and mutational threshold have yielded opposing outcomes

and decelerated clinical uptake. The disparities in the definitions and reporting of TMB by laboratories have also complicated the comparison of the results of studies between studies, making the creation of standard clinical guidelines challenging. Whether or not a single set of TMB-based patient stratification is feasible across histologically different cancers, or whether predictive thresholds will have to be defined on a tumor-type by tumor-type basis, remains unknown. This uncertainty is proportionately relevant to the system of how TMB testing is ordered, interpreted and acted upon in everyday practice. The paper will answer this question by methodically assessing the association between TMB and immunotherapy outcomes in different tumor types to evaluate in which situations TMB is a valid stratification factor and in which the predictive power fails.

Chapter 3

Methodology

Research articles were searched in academic databases such as PubMed, Google Scholar, and Scopus using keywords including 'Tumor Mutation Burden', 'immune checkpoint inhibitors', 'TMB biomarker', 'neoantigen', 'immunotherapy response', 'pembrolizumab', and 'predictive biomarker'. Articles published between 2010 and 2024 were included. Studies were selected based on their relevance to TMB measurement methodology, clinical trial outcomes, regulatory decisions, and pan-cancer biomarker analysis. Articles were then screened to ensure pertinence, and essential details were gathered regarding TMB's biological mechanism, measurement approaches, clinical evidence, limitations, and emerging trends. The results were arranged thematically to provide a comprehensive and structured overview of the current state of TMB as a predictive tool in cancer immunotherapy.

Chapter 4

Results

In recent times, TMB has emerged as a clinically validated prognostic biomarker for the prediction of patient response to ICIs (immune checkpoint inhibitors). Data from important and landmark clinical trials along with data from real medical cases are consistent with the information that tumors with high levels of TMB are more likely to respond to ICI therapy (Huang et al., 2023; Özdoğan et al., 2021).

4.1 Major Findings

TMB differs significantly among the types of cancer, and these differences have direct implications to immunotherapy response. Melanoma is one of the most high-TMB tumor types that are consistent. The extent of the DNA damage caused by chronic UV radiation has resulted in the high mutational burden underlying the immune checkpoint inhibitor-responsive nature of melanoma (Galuppini et al., 2019; Wang et al., 2022). The same case applies to non-small cell lung cancer (NSCLC), with a significant percentage of patients having high TMB as a result of mutagenesis caused by tobacco carcinogens. Microsatellite instability-high (MSI-H) tumors are caused by defective DNA mismatch repair machinery which results in a large rate of errors in replication throughout the genome, producing one of the highest TMB values in clinical practice (Shimozaki et al., 2021; Wang et al., 2022).

Accelerated approval of pembrolizumab was granted by the FDA against adult and pediatric patients with metastatic or unresectable solid tumors, which have a high tumor mutational burden (TMB-H). This was the initial regulatory approval of a cancer treatment on the basis of a molecular

biomarker and not the anatomic origin of the cancer. This approval was based on the information of a pre-specified subgroup of 102 patients participating in the KEYNOTE-158 trial, in which pembrolizumab demonstrated an ORR of 29% and many patients exhibited long-term response greater than 12 months (Marabelle et al., 2020; Marcus et al., 2021). At the same time, the FDA approved the FoundationOne CDx assay as a companion diagnostic to identify TMB-H eligible patients (Wang et al., 2021).

4.2 Summary Table of Clinical Trials

The following table summarises the key clinical trials and studies that have established TMB as a predictive biomarker in cancer immunotherapy.

Table 1: Summary of clinical trials which highlight TMB as a cancer predictive biomarker

Trial	Patient (n)	Cancer Type	Drug(s)	TMB Cutoff	Key Outcome	Reference
KEYNOTE-158	M= 108 F= 125	Multiple advanced solid tumors	Pembrolizumab (anti-PD-1)	≥10 mut/Mb	ORR 29% in TMB-H group; FDA approved pembrolizumab for TMB-high solid tumors	Marabelle et al., 2020; Marcus et al., 2021
CheckMate-227	M= 1178 F= 561	Non-Small Cell Lung Cancer (NSCLC) first-line	Nivolumab + Ipilimumab	≥10 mut/Mb	Significantly improved PFS in TMB-high subgroup	Huang et al., 2020 Brahmer et al., 2023
CheckMate-848 (tTMB-H population)	M= 62 F= 73	Advanced/metastatic solid tumors	Nivolumab ± Ipilimumab	≥10 mut/Mb	Evaluated tissue and blood TMB; supported TMB as predictive tool	He et al., 2023; Schenker et al., 2024
CheckMate-848 (bTMB-H population)	M= 56 F= 69	Advanced/metastatic solid tumors	Nivolumab ± Ipilimumab	≥10 mut/Mb	Evaluated tissue and blood TMB; supported TMB as predictive tool	He et al., 2023; Schenker et al., 2024
Pan-cancer meta-analysis (>5,000 pts)	M= 5000 F= 5000	Multiple solid tumors	Various ICIs	High TMB (variable cutoffs)	Improved OS and PFS across histologies; stronger effect in melanoma and NSCLC	Wu et al., 2019; Wang et al., 2022 Kammula et al., 2024
Retrospective pan-cancer study (>8,000 pts, 24 tumor types)	M= 4374 F= 3984	24 solid tumor types	Various ICIs	High TMB	Elevated TMB associated with improved survival; weaker in low-TMB histologies	Gandara et al., 2025

M=Male. F=Female.

Beyond the headline outcomes of these trials, the make-up of their patient populations also bears on how broadly the conclusions can be universal. Table 1 brings together the male and female patient counts reported for each of the same five studies, allowing the gender balance of the underlying evidence base for TMB to be examined directly. Across all five evidence sources, male patients consistently outnumber females or are equal. The imbalance is most striking in CheckMate 227, where men account for roughly two-thirds of recruitment, and is also marked in CheckMate 848, where male patients exceed females in both the tTMB-high and bTMB-high analysis populations. KEYNOTE-158 and the two large pan cancer datasets show a closer male-to-female ratio, but no trial is female-predominant. These bias matters because the strength and direction of the TMB–outcome association are not uniform between sexes, a point taken up in the comparative critique of these trials in Chapter 5.

Chapter 5

Discussion

TMB measures the somatic mutation load of a tumor and hence determines the immunogenicity of a tumor but its predictive power is significantly enhanced by the use of additional biomarkers that describe the tumor microenvironment and the mechanisms of immune suppression (Sankar et al., 2022). PD-L1 and TMB jointly represent two functionally distinct dimensions of tumor-immune interaction: TMB is a reflection of the neoantigen burden whereas PD-L1 is a reflection of the level of active immune suppression (Bi et al., 2024). High TMB and high PD-L1 expression tumors have the greatest response to immune checkpoint inhibitors because both immune engagement criteria have been achieved (Özdoğan et al., 2024). Measuring MSI and TMB at the same time more narrowly defines the group of patients eligible for immunotherapy, since combining the two biomarkers determines a wider range of patients who can respond to immunotherapy as compared to either marker alone (Zhao et al., 2019; Bever and Le, 2018).

Taken individually, each of the five evidence sources summarised in Chapter 4 makes a different contribution to the case for TMB as a predictive biomarker, and each carries its own weaknesses. Reading them side by side helps clarify where their findings reinforce one another and where they diverge.A major strength of KEYNOTE-158 was demonstrating that TMB-H status (≥10 mutations/Mb) is a viable biomarker across a diverse range of over ten different rare tumor types, including anal, biliary, cervical, and endometrial cancers. The objective response rate for TMB-H patients was 29%, compared with only 6% for those with lower TMB (Marabelle et al., 2020). On the limitation side, the same body of work indicates that TMB-H status may not be as strong a predictor of survival in female-predominant cancers such as certain subtypes of cervical or breast cancer as it is in male-predominant cancers like lung or bladder. In some female cohorts

within KEYNOTE-158, TMB-H did not correlate with overall survival as strongly as it did in the male-heavy cohorts (Marabelle et al., 2020).

A major strength of CheckMate 227 was its ability to demonstrate long-term treatment-free survival. In the six-year update, 17% of patients treated with the nivolumab + ipilimumab combination were alive and off treatment, compared with only 7% in the chemotherapy group (Brahmer et al., 2023). Meta-analyses that include CheckMate 227 data indicate, however, that while both sexes benefit, females treated with the nivolumab + ipilimumab combination often achieve smaller survival gains than males. Male patients in particular were significantly more likely to benefit from the addition of the anti-CTLA-4 component, ipilimumab (Conforti et al., 2018).

A major strength of CheckMate 848 was the prospective validation of blood-based TMB. The study showed a high ascertainment rate for bTMB (97.9%) compared with tissue TMB (89.2%), confirming that blood samples can serve as a less invasive and highly reliable alternative for patients whose tissue is inaccessible (He et al., 2023). Its limitation is closely tied to the same combination regimen: meta-analyses of trials evaluating ipilimumab + nivolumab alongside CheckMate 848 suggest that male patients often derive a significantly higher benefit from the addition of anti-CTLA-4 therapy than female patients (Schenker et al., 2024).

In pan-cancer studies comparing survival or treatment response, female patients often exhibit better outcomes overall. Specifically, 42% of oncology trials with sex-based comparisons reported significantly better survival or response in female patients (Kammula et al., 2024). The principal limitation of this evidence base is that females remain underrepresented in many oncology studies due to historical inclusion biases related to hormonal variability and fertility concerns. Males also lack the "protective redundancy" of the X chromosome: certain tumor-suppressor genes that escape

X-inactivation in females are more frequently mutated in male cancers, which may make those tumors more aggressive or less responsive to certain therapies (Kammula et al., 2024).

In retrospective pan-cancer studies including over 8,000 patients and 24 cancer types, among them colorectal, breast, cervical, and lung cancers, the retrospective pan-cancer study provides high statistical power to detect associations that smaller, single-cancer trials would likely miss (Gandara et al., 2025). Supporting literature indicates, though, that while males often have higher incidence rates, females in certain cancer types such as bladder cancer may present with more advanced disease stages and experience worse outcomes even after standardised treatment (Marks et al., 2016).

Chapter 6

Future Direction

As TMB's clinical potential evolves, there are three interrelated areas of development that must be achieved: defining a standardised method of measurement, developing a predictive model using multiple biomarker signatures, and prospective validation in the clinical setting. Beyond this, new immunotherapy approaches are expanding the application of TMB beyond immune checkpoint therapy to other types of therapies.

Integration modeling is the most analytically sound approach to enhancing the clinical application of TMB. TMB quantifies tumor immunogenicity but only in its most basic form, and it is not surprising that its predictive performance is limited when used as a single variable (Havel et al., 2019; Wood et al., 2020). Artificial intelligence and machine learning approaches are well-adapted to the complex multi-omics data needed to develop integrated models, allowing discovery of patterns across data types not detected with traditional statistical methods (Louie et al., 2022; Seyhan and Carini, 2019). The latest developments in TMB research also involve the use of liquid biopsies for dynamic monitoring. Blood-based TMB (bTMB) may be non-invasively measured and monitored at consecutive timepoints during treatment by analyzing circulating tumor DNA (ctDNA) in peripheral blood using next-generation sequencing (Bubnoff, 2017; Cha et al., 2023; Liu et al., 2023). Dynamic bTMB monitoring provides real-time data of tumor mutational evolution that allows identifying the response or resistance to treatment early and promotes the timely adjustment of treatment regimens (Cha et al., 2023; Liu et al., 2023).

Chapter 7

Conclusion

This review tried to evaluate the predictive value of TMB for immunotherapy response across a range of solid tumors, to determine the extent to which TMB's predictive value varies across different histologies, and to determine when and where TMB can be used as a reliable predictor to inform treatment decisions. The analyses reviewed in the chapters above deliver a complex but important message: TMB is a relevant biomarker in certain oncological contexts but requires the level of accuracy, variation and integration of multiple biomarkers that is currently lacking.

The mechanism underlying the predictive value of TMB is clear. In cancers for which the main factor determining immunogenicity is mutational burden (melanoma, non-small cell lung cancer), this pathway leads to robust and clinically meaningful correlations between TMB and enhanced responses to ICI (Galuppini et al., 2019). The US Food and Drug Administration's (FDA) tumor-agnostic approval of pembrolizumab for TMB-high solid tumors, formalised TMB as a regulatory biomarker and opened immunotherapy to patients with rare and otherwise untreatable cancers (Riedl et al., 2023; Weis et al., 2021).

Three areas of progress described in the preceding chapters will lead to the improved use of TMB. First, harmonisation of measurement through the design of uniform panels, validated bioinformatics processing and the setting of histology-specific cutoff values is needed to enable comparisons among institutions. Second, incorporation of TMB into predictive models that take into account additional biomarkers such as PD-L1 expression, MSI, tumor-infiltrating immune cells (TILs) and immune gene expression signatures is needed to capture the full dynamic range of the tumor-immune equilibrium that drives ICI responses. Third, prospective studies in

randomized trials with a focus on TMB in under-serviced populations will be needed to generate evidence to support equitable use (Dafni et al., 2019; Liu et al., 2023).

Recent advances in functional TMB measurement, artificial intelligence-based multi-omics integration, and dynamic monitoring via liquid biopsies are the most promising avenues for further evolution of TMB. With the maturity of these tools and the advancement of standardization, TMB is set to develop from a simple count of mutations into one of the elements of a multi-dimensional precision-based paradigm for immunotherapy selection in the broad spectrum of solid tumors.

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