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Comment on 'Tumor mutational burden and survival on immune checkpoint inhibition in >8000 patients across 24 cancer types'

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The study by Gandara *et al*[1] provides a landmark analysis of tumor mutational burden (TMB) as a predictive biomarker for immune checkpoint inhibitor (ICI) efficacy across 24 cancer types. By leveraging a large real-world dataset (>8000 patients) and standardized TMB measurement via the Food and Drug Administration (FDA)-approved FoundationOneCDx assay, the authors demonstrate that elevated TMB (≥10 mut/Mb) correlates with improved real-world overall survival in patients receiving ICI monotherapy. However, while this work significantly advances the field, several critical limitations warrant attention to refine the clinical applicability of TMB and guide future research.

LACK OF HARMONIZATION IN TMB MEASUREMENT ACROSS PLATFORMS

The study relies on a single TMB assay (FoundationOneCDx), which limits the generalizability of the findings. While the FDA-approved assay ensures analytical rigor, the broader clinical adoption of TMB is hindered by inter-laboratory variability in panel size, bioinformatic pipelines, and germline variant filtering. For example, Nassar *et al* demonstrated that TMB algorithms relying on public germline databases (eg, gnomAD) underperform in non-European populations due to ancestral bias.[2] Although the authors note that FoundationOne uses a proprietary ancestry-balanced database, they do not provide comparative data on TMB performance across diverse genetic backgrounds. Future studies should further validate TMB thresholds in multi-ethnic cohorts and align with harmonization efforts such as the Friends of Cancer Research TMB Harmonization Project, which emphasizes minimum panel size (>667 kb) and standardized filtering.[3]

UNEXPLORED MECHANISMS BEHIND MICROSATELLITE STABLE (MSS) COLORECTAL CANCER (CRC) EXCEPTION

The MSS CRC subgroup uniquely fails to show a survival benefit for TMB ≥10 (HR 1.02; 95% CI: 0.72 to 1.44). This anomaly contradicts the pan-tumor trend and suggests CRC-specific resistance mechanisms. The study does not explore potential confounders, such as *POLE/POLD1* mutations (significantly associated with ultra-mutated MSS CRC) or immunosuppressive features of the CRC tumor microenvironment [eg, Transforming Growth Factor-β (TGF-β) dominance[4]]. A granular analysis stratifying MSS CRC by mutational signatures (eg, UV exposure) or immune cell composition (eg, T-reg infiltration) could clarify this discrepancy. Single-cell RNA sequencing or spatial profiling would be critical to dissect localized immune evasion in CRC.

THRESHOLD AMBIGUITY IN ICI-CHEMOTHERAPY COMBINATIONS

The exploratory analysis of ICI-chemotherapy combinations (n=4369) identifies TMB ≥20 as the only predictive threshold (HR 0.65; p<0.001). However, this finding lacks biological rationale or clinical validation. The authors hypothesize that chemotherapy may dilute TMB-driven immunogenicity but omit mechanistic data [eg, neoantigen clonality, Human leukocyte antigen (HLA) diversity] to support this. Furthermore, the threshold of 20 mut/Mb conflicts with prior studies suggesting tissue-specific TMB cutoffs.[5] Prospective trials comparing ICI-chemotherapy versus chemotherapy

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alone across TMB strata are needed to establish context-specific thresholds.

RETROSPECTIVE DESIGN AND IMMORTAL TIME BIAS

Despite risk-set adjustment for delayed cohort entry, residual immortal time bias may inflate survival estimates. Patients entering the database post-comprehensive genomic profiling report (median follow-up: 31.7 months) likely represent a survivor cohort with slower disease progression. A prospective registry tracking TMB from diagnosis would mitigate this bias. Additionally, the lack of treatment randomization limits causal inference; unmeasured confounders (eg, comorbidities, socioeconomic access to ICI) may skew results.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. Multi-platform TMB validation: Compare FoundationOneCDx with whole-exome sequencing and other FDA-cleared assays (eg, MSK-IMPACT) in diverse populations.
2. Mechanistic CRC studies: Integrate mutational signature analysis and spatial transcriptomics to elucidate TMB resistance in MSS CRC.
3. Threshold-driven trials: Design phase III trials (eg, TMB≥20 vs TMB 10–20) for ICI-chemotherapy combinations.
4. Composite biomarker models: Incorporate HLA diversity, neoantigen quality, and immune contexture into TMB-based algorithms.

In conclusion, Gandara *et al* work solidifies TMB ≥10 as a pragmatic biomarker for ICI monotherapy but underscores the complexity of translating TMB into precision oncology. Addressing platform variability, tissue-specific exceptions, and biomarker interplay will be pivotal to optimize TMB's clinical utility in the future.

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