Biomarker Harmonization toward Histology Independent Drug Development: TMB Case Study

Jeff Allen, PhD
Friends of Cancer Research

TMB Harmonization Project

Background

- Tumor mutational burden (TMB), defined as the number of somatic mutations per megabase of interrogated genomic sequence
- Potential biomarker for the identification of cancer patients most likely to respond to immune checkpoint inhibitors.

Clinical Cut-off Alignment

- As multiple sponsors work independently to optimize TMB measurement for their specific therapy, it is possible that each sponsor may set different cut points for a tissue agnostic TMB assessment
- This is especially problematic for tissue agnostic development because it is redefining the disease based on a biomarker rather than a site of origin or pathologic disease.

Assay Harmonization

- Use of common samples to assess potential variation is measurement and reporting and a common reference standard to facilitate alignment

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Aggregate of publicly available studies that reported TMB and patient response rate to immunotherapy

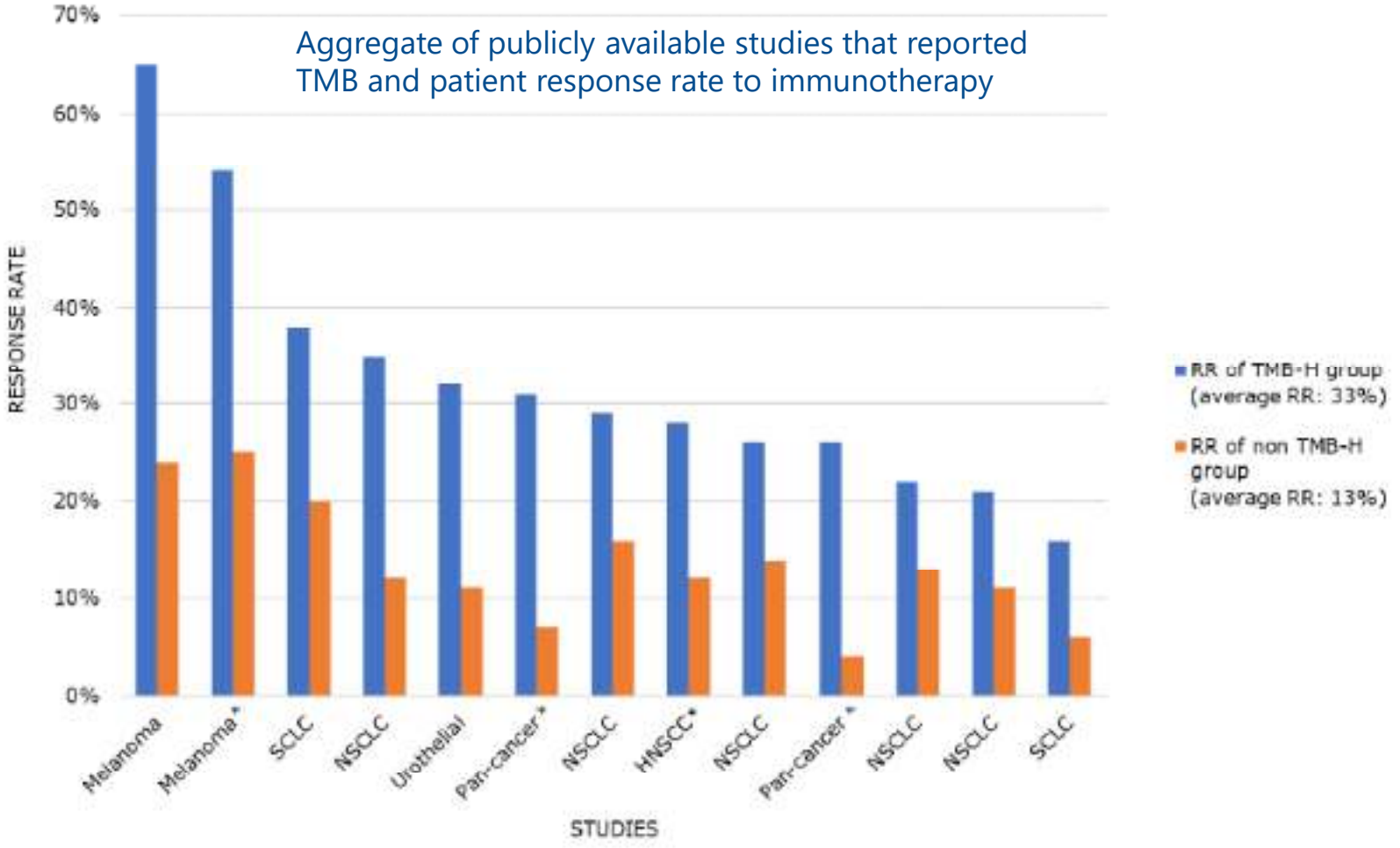


Figure 1: Response Rates for Published Studies Investigating Immunotherapies and Reporting TMB-based Response Rates.
** indicates studies that did not use TMB 10 mut/Mb as the study cut-off*

Pooled analysis of 1732 patient with different cancer types treated with ICI for which TMB had been measured

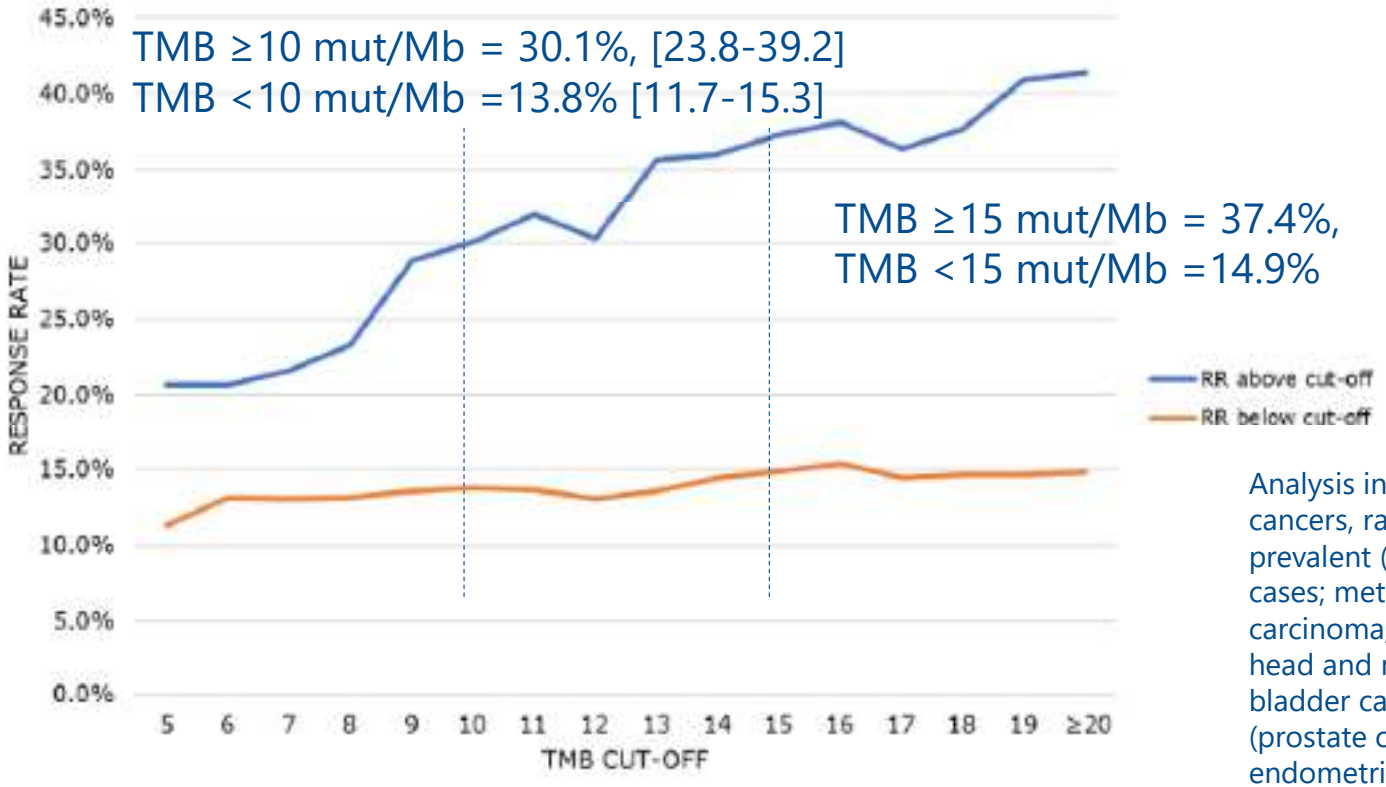


Figure 2. Average Response Rates for Patients Treated with IO Agents - Pooled Cohort

Analysis included15 different cancers, ranging from the most prevalent (lung cancer, 29% of cases; metastatic urothelial carcinoma, 23%; cancer to the head and neck, 10%; and bladder cancer, 9%) to the least (prostate cancer, 1%; endometrial cancer, 1%; salivary gland cancer, 1%; and ovarian cancer, 0.35%)

TMB Assay Alignment

- *Friends* TMB Harmonization Project: 15 labs and test developers establish research partnership to explore variability in measuring and reporting TMB
- In silico component (2018), cell line (2019) and clinical sample (2020) analyses
- Although different assays may differ in the way TMB is estimated, results from the *Friends* TMB Harmonization Project have shown that the empirical variability in TMB values ranging between 10-15 mut/Mb is not as large as what is observed at lower or higher TMB values

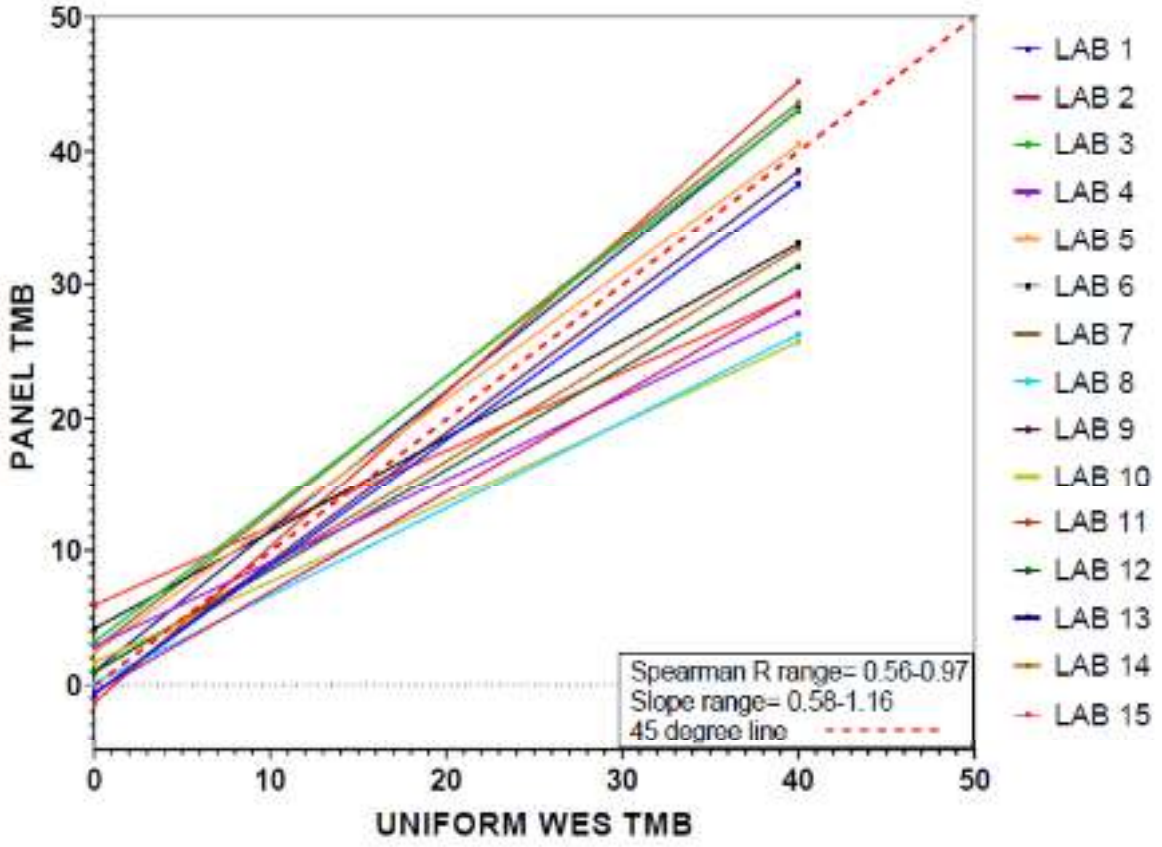
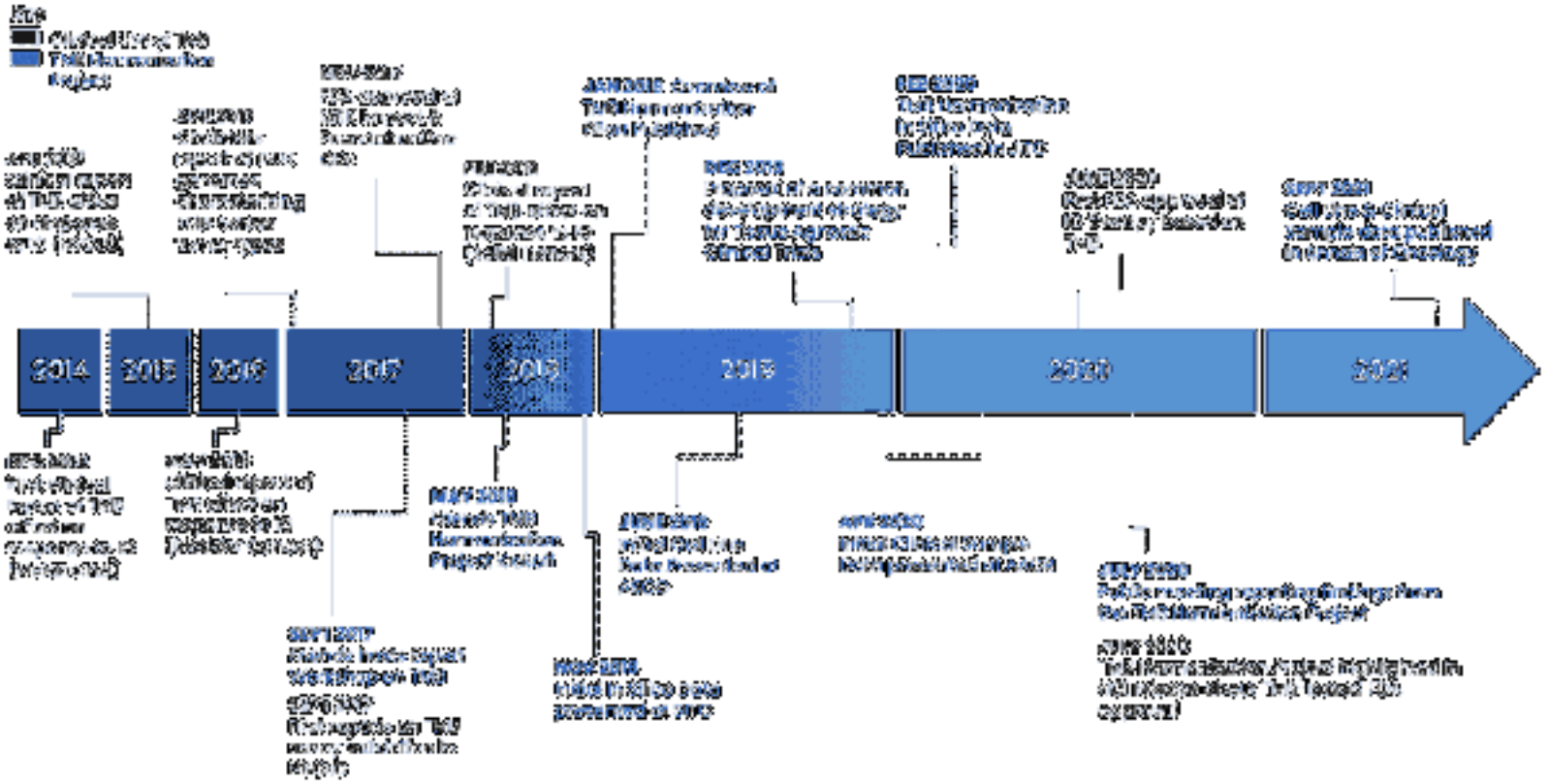


Figure 3. Association between WES-TMB and panel-TMB using human-derived matched tumor-normal cell lines. Results from the Friends of Cancer Research Harmonization Project- Phase 2A: Empirical Phase.

TMB Harmonization Project Timeline



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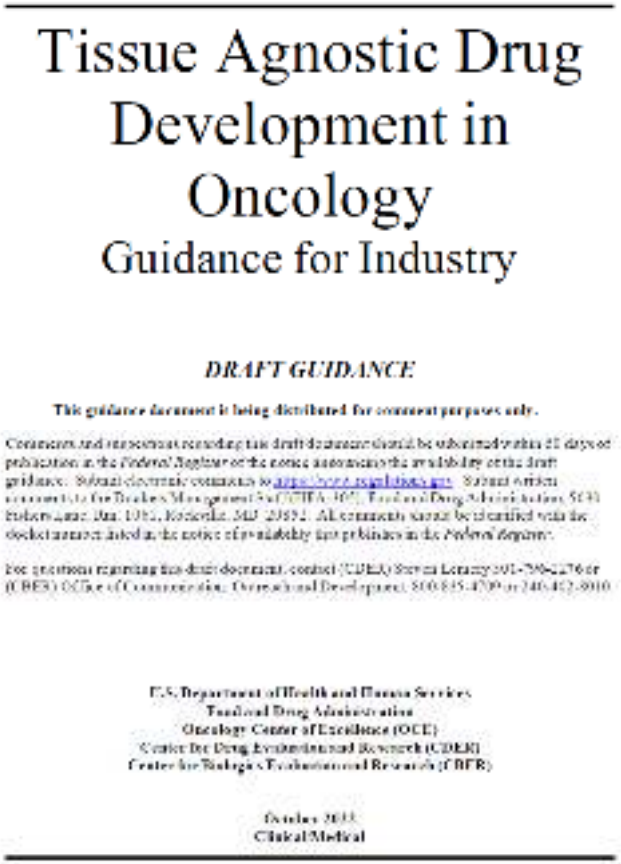
Conclusions

- Tissue agnostic development may be a viable strategy for developing drugs that target specific molecular alterations across multiple cancers
- New regulatory guidance provides scientific considerations for determining if such an approach is appropriate and drug development processes
- To be successful several factors should be aligned in advance – e.g. scope of cancers included, determination of patient population, diagnostic performance



Tissue Agnostic Drug Development in Oncology

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
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Center for Drug Evaluation and Research (CDER)
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TMB Harmonization Project Partners

- ACT Genomics
- AstraZeneca
- Biodesix
- Brigham & Women's Hospital
- Bristol-Myers Squibb
- Caris Life Sciences
- College of American Pathologists
- Columbia University
- EMD Serono, Inc.
- European Organisation for Research and Treatment of Cancer (EORTC)
- Foundation Medicine, Inc.
- Genentech, Inc.
- Genomic Testing Cooperative
- Guardant Health, Inc.
- Hartwig Medical Foundation
- Illumina, Inc.
- Intermountain Precision Genomics
- Johns Hopkins University
- Massachusetts General Hospital
- MD Anderson Cancer Center
- Memorial Sloan Kettering Cancer Center
- Merck & Co., Inc.
- National Cancer Institute (NCI)
- National Institutes of Health (NIH)
- NeoGenomics Laboratories, Inc
- OmniSeq
- Personal Genome Diagnostics (PGDx)
- Pfizer, Inc.
- precisionFDA
- Q2 SOlutions
- QIAGEN, Inc
- Quality in Pathology (QuIP)
- Quest Diagnostics
- Regeneron Pharmaceuticals
- Roche Diagnostics
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- Thermo Fisher Scientific
- Thrive
- University of Heidelberg
- U.S. Food and Drug Administration

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