STRONGERTOGETHER

ASCP Scientific Updates: Tumor Mutational Burden

September 2018

Faculty

Lauren L. Ritterhouse, MD, PhD
University of Chicago
Division of Genomic and Molecular Pathology

STRONGERTOGETHER

Notice of Faculty Disclosure

In accordance with ACCME guidelines, any individual in a position to influence and/or control the content of this AMP/ASCP CME activity has disclosed all relevant financial relationships within the past 12 months with commercial interests that provide products and/or services related to the content of this CME activity.

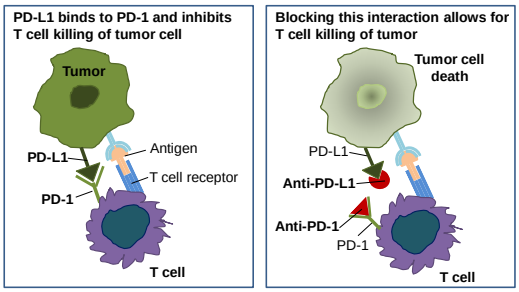
The individual below has disclosed the following financial relationship(s) with commercial interest(s):

- Lauren L. Ritterhouse, MD, PhD: None

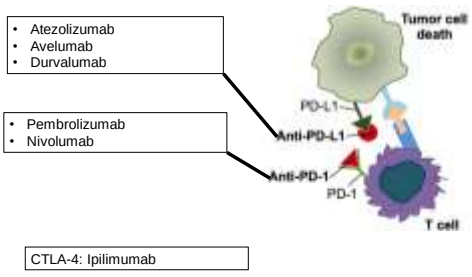
Overview

- Immune checkpoint inhibitors
  - Overview and mechanism of action
  - Biomarkers
- Tumor mutational burden (TMB)
  - Defined
  - Across tumor types
  - Different mutational signatures
- Evidence for TMB as a biomarker in immuno-oncology
- Methods for TMB determination

Immune Checkpoint Inhibitors: Mechanism of Action



Immune Checkpoint Blockade Drugs



Immunotherapy Response

Nature **532**, 162-164 (April 2016)

Targeted therapy
- Patients with specific molecular features respond well
- Less durable responses
- *Biomarker* → specific genomic alterations

Immune checkpoint inhibitors
- Only a subset of patients will respond
- More durable responses
- *Biomarkers* → PD-L1, MSI-H, Others??

Immune Checkpoint Inhibitors with Biomarkers in Indication

Name	Target	Indications
Pembrolizumab (Keytruda®)[1]	**PD-1**	• 1L inoperable or metastatic melanoma • 2L metastatic non-small cell lung cancer with **PD-L1 expression** • 1L metastatic non-squamous non-small cell lung cancer • 1L metastatic non-small cell lung cancer with **high PD-L1 expression** • 1L recurrent or metastatic head and neck squamous cell carcinoma • 4L refractory classical Hodgkin lymphoma • 3L refractory primary mediastinal B-cell lymphoma (PMBCL) • Locally advanced or metastatic urothelial carcinoma • **Microsatellite instability-high (MSI-H) or mismatch-repair deficient (dMMR) cancers** • Recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma • Recurrent or metastatic cervical cancer
Durvalumab (Imfinzi®)[2]	**PD-L1**	• 1L/2L locally advanced or metastatic urothelial carcinoma • Maintenance for unresectable, Stage III non-small cell lung cancer (NSCLC)
nivolumab (Opdivo®)[3]	**PD-1**	• Adj./1L inoperable or metastatic meanoma • Adj. treatment of melanoma • 2L metastatic non-small cell lung cancer • 1L advanced, intermediate or poor risk renal cell carcinoma • 2L advanced renal cell carcinoma • 3L/4L classical Hodgkin lymphoma • 1L recurrent or metastatic head and neck squamous cell carcinoma • 1L/2L locally advanced or metastatic urothelial carcinoma • **Microsatellite instability-high (MSI-H) or mismatch-repair deficient (dMMR) metastatic colorectal cancer** • 2L Heptocellular carcinoma
Ipilimumab (Yervoy®)[4]	**CTLA4**	• 1L inoperable or metastatic melanoma • Adjuvant treatment of stage IIIa cutaneous melanoma • 1L advanced, intermediate or poor risk renal cell carcinoma
Atezolizumab (Tecentriq®)[5]	**PD-L1**	• 1L/2L locally advanced or metastatic urothelial carcinoma • 2/L metastatic non-small cell lung cancer
Avelumab (Bavencio®)[6]	**PD-L1**	• 1L metastatic Merkel cell carcinoma (MCC) • 1L/2L locally advanced or metastatic urothelial carcinoma

First FDA Approval Agnostic of Cancer Site

- Pembrolizumab
- Adult/pediatric patients with unresectable/metastatic solid tumors that have progressed following prior treatments
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)

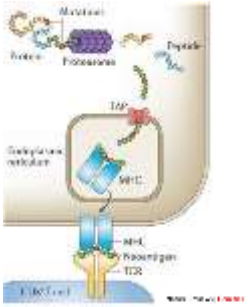
Tumor Mutational Burden (TMB)

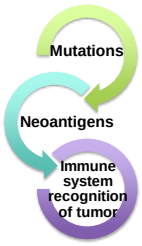
- Measurement of the number of mutations that exists within a tumor
- Specifically, the number of mutations within the coding region of a tumor genome (exome)
  - Generally thought of as the burden of non-synonymous mutations in an exome
  - Often reported as the number of mutations/Mb
  - Can also be determined from a targeted panel
- *However*, there is a current lack of standardization regarding TMB
  - Various labs/groups may calculate it differently and include different kinds of mutations

Tumor Mutational Burden (TMB)

TMB as a biomarker for response to immunotherapy

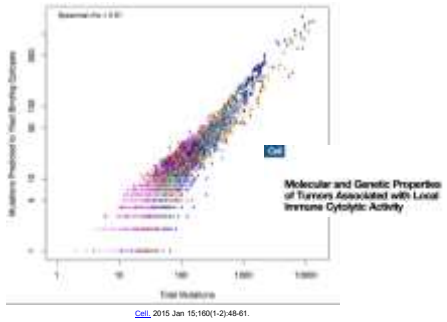
Rationale for TMB/MSI-H as a Biomarker in Immunotherapy





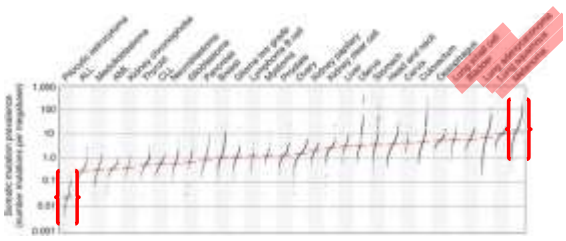
Nature Reviews Genetics **volume17**, pages441–458 (2016)

Rationale for TMB as a Biomarker in Immunotherapy



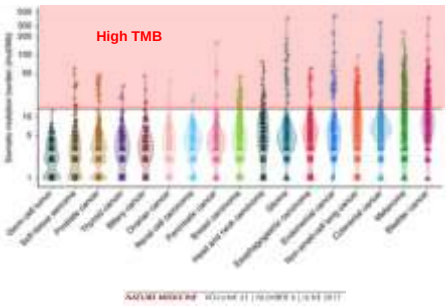
Cell. 2015 Jan 15;160(1-2):48-61.

TMB Across Tumor Types



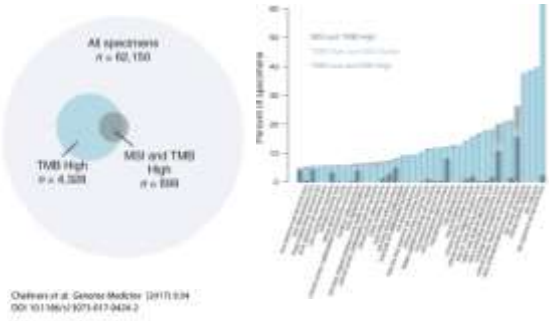
Nature Biotechnology **34**,1019–1024 (2016)

TMB Across Tumor Types



Nat Med. 2017 Jun;23(6):703-713.

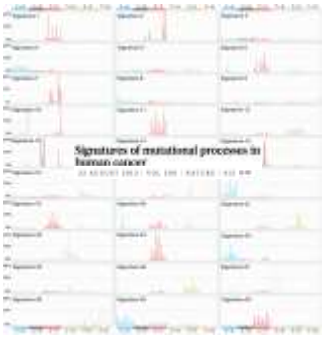
TMB and MSI Overlap



Mutational Signatures

Characteristic combinations of mutation types arising from specific mutagenesis processes:

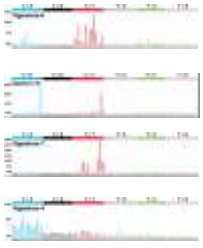
- DNA replication infidelity
- Exogenous/ endogenous genotoxins
- Defective DNA repair pathways



Mutational Signatures

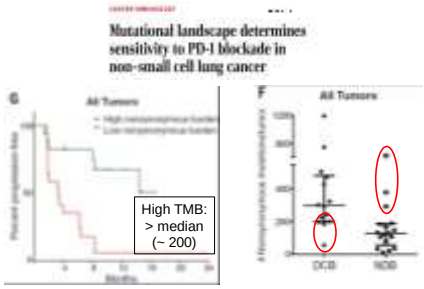
Signatures that can be associated with high TMB:

- Mismatch repair deficiency
  - High numbers of **small insertions and deletions** at mononucleotide repeats
- *POLE* mutations
  - **C>A mutations** at TpCpT context (T**C**T > T**A**T)
- Ultraviolet light exposure
  - Large numbers of **CC>TT dinucleotide mutations** at dipyrimidines
- Smoking exposure
  - Transcriptional strand bias for C>A mutations as well as **CC>AA dinucleotide** substitutions



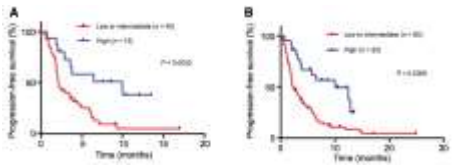
https://cancer.sanger.ac.uk/cosmic/signatures

High TMB Associated with Response to PD-1 Blockade



Rizvi et al. Science. 2015 Apr 3; 348(6230): 124–128

High TMB Associated with Response to PD-1/PD-L1 Blockade

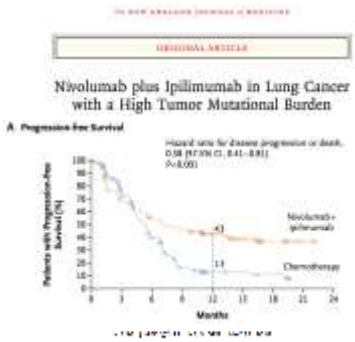


All tumor types (excluding NSCLC/melanoma)

All tumor types (including NSCLC/melanoma)

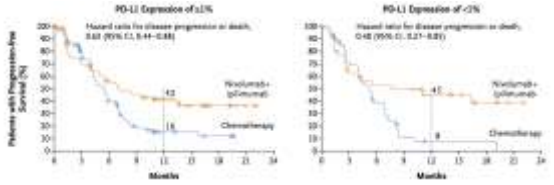
Mol Cancer Ther. 2017 Nov;16(11):2598-2608.

High TMB Associated with Response to CTLA-4 plus PD-1 Blockade

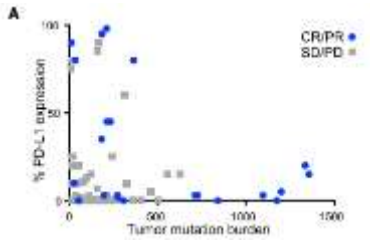


CheckMate 227

High TMB Associated with Response Regardless of PD-L1 Expression

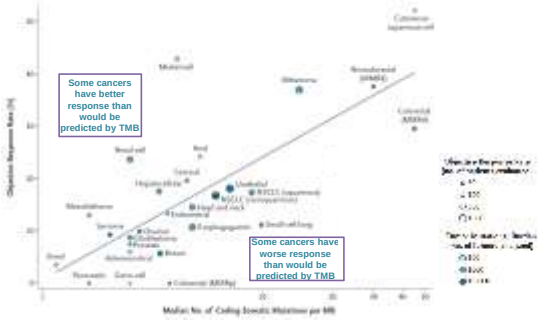


PD-L1 and TMB as Independent Biomarkers



Cancer Cell
Article

Immune Checkpoint Response Rates by TMB in Various Tumor Types



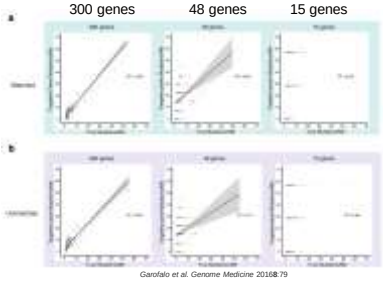
N Engl J Med 2017; 377:2500-2501

TMB Methodologies: Whole Exome Sequencing

Matched tumor/normal whole exome sequencing

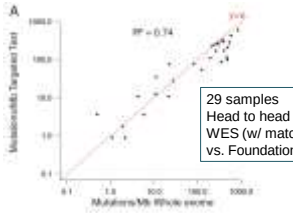
'Gold standard' for TMB calculation → show correlation with this method

TMB Methodologies: Targeted Cancer Panels



Garofalo et al. Genome Medicine 2016;8:79

TMB Methodologies: Targeted Cancer Panels

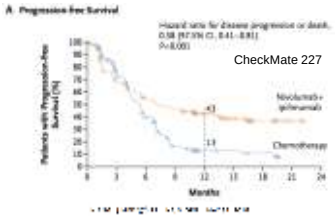


29 samples
Head to head sequencing
WES (w/ matched normal) (~50Mb)
vs. FoundationOne (~1.1 Mb)

Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden

Chalmers et al. Genome Medicine (2017) 9:34
DOI 10.1186/s13073-017-0424-2

TMB Methodologies: Targeted Cancer Panels



Some clinical trials are incorporating TMB as a biomarker from tumor only targeted cancer panels

Tumor Mutational Burden: Remaining Questions

- What is TMB-High?
  - >200 mutations/exome
  - > Median for that particular cohort
  - >20 mutations/Mb, >10 mutations/Mb
  - Should it be dependent on tumor type?
- What size targeted panel is suitable for TMB calling?
- How should germline variants be filtered?
- What kinds of variants should be included in TMB calculation?
- How should labs validate their targeted panels for TMB testing?