Faculty

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

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

• Atezolizumab
• Avelumab
• Durvalumab
• Pembrolizumab
• Nivolumab

CTLA-4: Ipilimumab
Immunotherapy Response

- **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

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>1L inoperable or metastatic melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2L metastatic melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LS metastatic non-small cell lung cancer (NSCLC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance for unresectable, Stage III non-small cell lung cancer (NSCLC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IIIB-IV/1L urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage III urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IV non-small cell lung cancer (NSCLC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage IIIB-IV/2L metastatic melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage III/IV urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage III/IV non-small cell lung cancer (NSCLC)</td>
</tr>
</tbody>
</table>

---

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
Rationale for TMB as a Biomarker in Immunotherapy

TMB Across Tumor Types

TMB Across Tumor Types

High TMB
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 (TCT > TAT)
- 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: > median (~ 200)

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

All tumor types (excluding NSCLC/melanoma)

All tumor types (including NSCLC/melanoma)


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

Immune Checkpoint Response Rates by TMB in Various Tumor Types

Some cancers have better response than would be predicted by TMB

Some cancers have worse response than would be predicted by TMB

Cancer Cell

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
300 genes
48 genes
15 genes

WES (w/ matched normal) (~50Mb) vs. FoundationOne (~1.1 Mb)

Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden
Chakravarti et al. Genome Medicine 2017:11:24
OSI-2017-24
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?

Thank You!