Biomarkers in Cancer Immunotherapy Current Regulatory Landscape

National Academies Workshop
"Addressing Resistance in the Development of Cancer Immune Modulator Therapeutics"
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Outline

- Current Immuno-oncology (IO) biomarkers
- IO Companion and Complementary Diagnostics
- IO biomarker challenges
- Tissue Agnostic drug development
- ctDNA for IO based therapies

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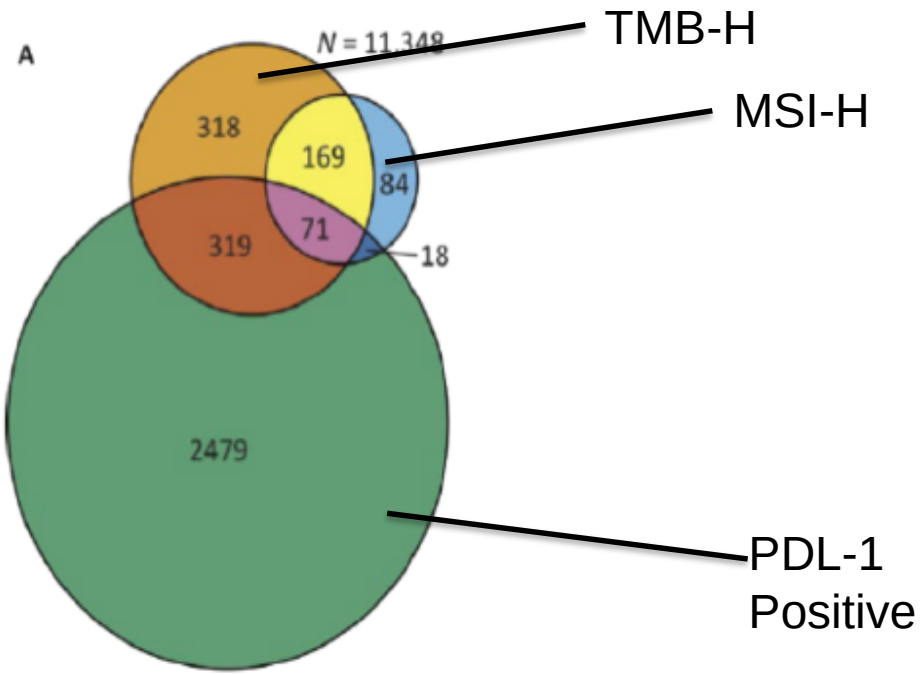
Selecting Responders to cancer immunotherapy

- PD-L1 Expression (Immunohistochemistry): Many therapeutic indications approved for this biomarker.
- Microsatellite Instability-high (MSI-H) or mismatch repair deficient (dMMR) : This was the first tumor agnostic indication: indication for a treatment was defined based on a biomarker and not the cancer type. Two drugs approved.
- Tumor Mutational Burden: Novel biomarker approved for tumor agnostic: to select patients with solid tumors who may benefit from immunotherapy (pembrolizumab), based on a biomarker, which reflects the number of mutations per megabase (mut/Mb) of the genome.

Relationship Between PD-L1, TMB-H, and MSI-H



Vanderwalde et al., *Cancer Medicine* **2018; 7(3):746–756**

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Companion Dx and Complementary Dx

- Companion Diagnostics (CDx): Tests that provide information that is essential for the safe and effective use of a corresponding therapeutic product.

- Complementary Diagnostics: (Draft definition): Tests that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk / benefit assessments for individual patients, but are not pre-requisites for receiving the drug (i.e., are not companion diagnostics).

- Companion vs Complementary: decision based on both the design and outcomes of clinical trials.

- List of cleared/approved CDx: *www.fda.gov/companiondiagnostics*

Companion Dx and Complementary Dx Indications for use

- Companion vs Complementary: Device Indications are different.

- Companion Diagnostics (CDx): (Mostly "**selection**" claim)
  - Example: PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA (pembrolizumab).

- Complementary Diagnostics: (**All comer trials**)
  - Example: PD-L1 expression in 50% TC or 10% IC as detected by Ventana PD-L1 (sp142) assay in NSCLC may be associated with enhanced overall survival from TECENTRIQ (atezolizumab).

PD-L1 *Invitro Diagnostic* (IVD) Assays Approvals

- PD-L1 IHC 22-C3 pharmDx : Agilent/ Dako: 7 CDx
- PD-L1 IHC 28-8 pharmDx: Agilent/ Dako: 1 CDx (NSCLC) and 3 Complementary Dx (nsNSCLC, SCCHN, UC)
- PD-L1 (SP263): Ventana/ Roche Diagnostics: 1 CDx (NSCLC)
- PD-L1 (SP142): Ventana/ Roche Diagnostics: 3 CDx (Urothelial, TNBC, NSCLC)

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PD-L1 IHC 22C3 pharmDx – Intended Use – example (Different scoring and cut-offs)

Tumor Indication	PD-L1 Expression Level	Therapy
NSCLC	TPS ≥ 1%	KEYTRUDA®*
Gastric or GEJ Adenocarcinoma	CPS ≥ 1	
ESCC	CPS ≥ 10	
Cervical Cancer	CPS ≥ 1	
Urothelial Carcinoma	CPS ≥ 10	
HNSCC	CPS ≥ 1	
TNBC	CPS ≥ 10	
NSCLC	TPS ≥ 50%	LIBTAYO®**

*See the KEYTRUDA® product label for specific clinical circumstances guiding PD-L1 testing.
**See the LIBTAYO® product label for specific clinical circumstances guiding PD-L1 testing.

https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150013S020B.pdf

PD-L1 assays (Different scoring)

- **Tumor cell staining only** - TPS (Tumor proportion score)
  NSCLC – Dako 22 C3, Dako 28-8 and Ventana SP 263

- **Tumor cell staining and immune cell** (lymphocytes, macrophages) staining - CPS (**combined positive score**): Gastric or GEJ adenocarcinoma, ESCC, cervical cancer, urothelial carcinoma, HNSCC, TNBC – Dako 22C3

- **Immune cell staining only** (Lymphocytes, macrophages, dendritic cells, and granulocytes) (IC)– TNBC, urothelial – SP142

March 2015 FDA-AACR-ASCO Public Workshop

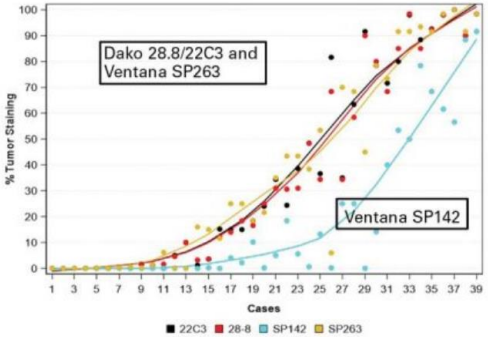
Complexities in Personalized Medicine:

Harmonizing Companion Diagnostics Across a Class of Targeted Therapies

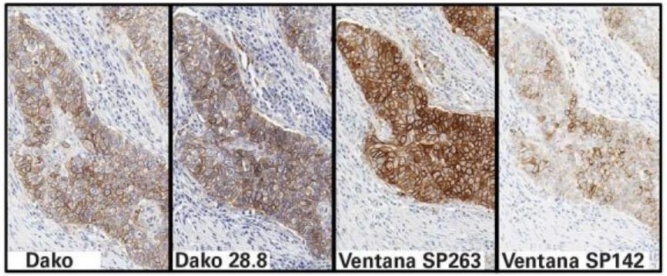
March 24, 2015

Blueprint PD-L1 IHC Comparability Project

A multi stakeholder harmonization effort for PD-L1 CDx comparability to align performance across different antibodies, staining platforms and clinical cutoffs.



Each dot represents the mean score of three pathologists



Conclusion: 1: Three assays showed similar staining characteristics for PD-L1 staining on tumor cells, but Ventana SP142 comparatively showed fewer tumor cells stained.

Hirsch et al, J Thorac Oncol 2017; 12(2):208-222
Tsao et al, J Thorac Oncol 2018; 13(9) 1302-1311

Continuing challenges with PD-L1 assays

- Lack of standardization – Different PD-L1 assays have variable definition of “PD-L1 expression”
- Various cut-offs for “PD-L1 positive/high” making it hard to compare the drug efficacy of the different therapeutics
- Different scores applied (tumor cells, immune cells, composite score, etc.)
- PD-L1 not predictive in all tumor types, lines of therapy
- New information about value of biomarker emerges between phase 2 and phase 3 trials.

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MSI-High/dMMR in Immuno-oncology

- Immunotherapy shown to be effective in treating patients whose tumors have defective MMR (Le DT et al. N Engl J Med. 2015;372(26):2509-20).
- May 23, 2017: Keytruda was granted an accelerated approval for the treatment of patients who have unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) **solid tumors** that have progressed after prior treatment and who have no satisfactory alternative treatment options.
- **This was a novel approval: a disease was defined based on a biomarker and not the cancer type**
  - Development of a companion diagnostic was part of a postmarket commitment. F1CDx received CDx approval on Feb 18, 2022 (P170019/S029)

  August 17, 2021: Accelerated approval granted to Jemperli for dMMR advanced solid tumors: P210001 VENTANA MMR RxDx Panel co-approval

Tumor Mutational Burden (TMB) in Immuno-oncology

- Novel biomarker
- June 16, 2020: Keytruda was granted an accelerated approval or the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] **solid tumors**, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
  - FDA also approved the FoundationOneCDx assay (**P170019/S016)** as a companion diagnostic
  - TMB is measured by counting all synonymous and non-synonymous substitution and indel variants present at 5% allele frequency or greater and filtering out potential germline variants according to published databases. The resulting mutation number is then divided by the coding region.

Sources of Variability in TMB measurement

- TMB measures can have significant variability, based on:
  - Pre-analytic variables: Extraction/tumor purity
  - Analytic: How many kb of sequence captured, WES vs. targeted panel affects the accuracy of the panel
  - Bioinformatics: Impact of different algorithms

- To address the variability in measurement of TMB, efforts by the Friends of Cancer Research to help harmonize TMB measurement among device manufacturers. (Vega et al ., Annals of Oncology, Volume 32, Issue 12, December 2021, Pages 1626-1636).

TMB continuing challenges

- Tissue TMB
  - Alternative cutoff?
  - Should certain tumors have different cutoff?
- Blood TMB
  - Is blood TMB really reflective of tissue TMB levels or is it another analyte? (some evidence in the literature indicating that blood TMB does not correlate with tissue TMB).
  - Comparator method to determine analytical accuracy (No currently accepted method for measuring blood TMB accuracy)
  - Limit of detection metric (computational Tumor Purity was used for tissue)

Tissue Agnostic drug development Challenges

- Logistical challenges
- Incidence of biomarker across tumor types
- Enrollment challenges
- Peds population/formulations
- Companion Diagnostic validation
- Tissue Agnostic vs. Specific Tumor Type development

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ctDNA for IO based therapies

- Another promising promising biomarker to guide treatment decision-making for IO
- ctDNA as a marker of MRD: Ongoing trials to determine whether ctDNA positive patients will benefit from (neo)adjuvant anti-PD(L)1-based therapy
- Changes in ctDNA levels after initiation of immunotherapy may predict treatment response (FOCR ctMonitor project analyzing ctDNA from lung cancer immune checkpoint inhibitor clinical trials)
- Could be used to evaluate mechanisms of treatment resistance, for deciding when to switch therapies
- May be useful to differentiate between pseudoprogression versus true progression
- May also be used to assess for genetic determinants of response to IO

ctDNA assays: Challenges

- Different methods used for MRD detection including tumor-informed methods, tumor-naïve methods, or a smaller panel of candidate genes
- Need for standardized protocol for collection, storage, handling ((temperature, and specified number of freeze/thaw cycles), shipment for consistent ctDNA measurement
- Need for standardized protocol for the schedule of measurement of ctDNA, and the different scheduled assessments in clinical benefit endpoints
- Need for harmonization of “Units of measurement for assays” that may vary across assays including outputs such as variant allele frequency (VAF) and mean tumor molecules per milliliter (mtm/mL)

Thank you

Oncology Center of Excellence/ Office of Oncologic Drugs

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