Companion and Complementary Diagnostics: Life After the PD-L1 "Blueprint Initiative"

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Complexities in Personalized Medicine: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies

March 24, 2015

PD-L1 Blueprint Proposal Overview

FDA-AACR-ASCO Public Workshop
24 March 2015

Astra-Zeneca
Bristol-Myers Squibb Company
Dako North America
Merck
Roche / Genentech
Roche Tissue Diagnostics

Situation

- PD-L1 IHC assays are being developed in a “one assay, one drug” paradigm
- Assay scoring and interpretation guidelines are developed to identify responding populations for unique drugs and biologic hypotheses
  - The companion diagnostic development is tied to clinical outcome for drug
- Confidentiality, IP constraints and contractual obligations require that assays are developed within firewalls, even within a single Dx organization

Scope of the Blueprint

- Assess analytical performance of PD-L1 Investigational Use Only (IUO) assay systems from Dako and Ventana
- Study to be designed and executed through collaboration of industry stakeholders with independent third party
- Restricted to tests developed via Pre-Market Approval (PMA) pathway, currently deployed in clinical trials and run on the associated clinical trial platform
- No delay to pivotal studies and patient access to critical new therapies
- Focus on NSCLC
- Deliver a data / information package to inform the medical practice community on PD-L1 IHC testing

AACR 2016

The Blueprint Project: Comparing PD-L1 IHC Diagnostics For Immune Checkpoint Inhibitors

Agenda

Introduction	Fred R. Hirsch
BMS	Steven Averbuch
Merck	Kenneth Emancipator
AstraZeneca	Jill Walker
Genentech / Roche	Andy Williams
Dako / Agilent	Dave Stanforth
Ventana / Roche	Abigail McElhinny
Blueprint Results	Fred R. Hirsch
Community Viewpoint	John Longshore
Panel Discussion	All + Reena Philip (FDA)

Overall Conclusions; Analytical Comparison

- Three assays (22C3, 28-8, SP263) demonstrate similar analytical performance with respect to percentages of tumor cells positive and dynamic range
  - -SP142 consistently labels fewer tumor cells
- All assays label immune cells but there is less precision in analytical performance than with tumor cell labeling
- There is generally higher agreement between observers when assessing TPS than when assessing ICPS

Overall Conclusions; Clinical Diagnostic Comparison

- 36.9% of the cases studied showed discrepant results for PD-L1 expression between the assays
- There is the potential for different diagnostic results according to the key clinical cut-offs if assays and algorithms are mismatched.
- The results of this preliminary study should not alter current guidelines as indicated for each therapeutic-diagnostic validated combination pair.
- **Blueprint team recommodation: Follow the label!**

PD-L1 Assay US Regulatory Approvals (from FDA PMA approval database)

- Dako PD-L1 IHC 22C3 pharmDx (pembrolizumab, Merck)
  - NSCLC, 50% TPS, Companion Dx, October 2015
  - NSCLC, 1% TPS, Companion Dx, September 2016
- Dako PD-L1 IHC 28-8 pharmDx (nivolumab, BMS)
  - Non-sq NSCLC, Complementary Dx, October 2015
  - Add Melanoma, Complementary Dx, January 2016
  - Add SCCHN, UC, Complementary Dx, September 2017
- Ventana PD-L1 (SP142) CDx Assay (atezolizumab, Roche /Genen)
  - UC, Complementary Dx, May 2016
  - Add NSCLC, Complementary Dx, October 2016
- Ventana PD-L1 (SP263) CDx Assay (durvalumab, AstraZeneca)
  - UC, Complementary Dx, May 2017

Recent Comparative Studies on PD-L1 Assays

- Many studies have assessed the analytical comparison of PD-L1 Ab clones using various detection systems manually or on different staining platforms.
  - There is little standardization in these studies for Ab concentration or staining protocol – apples vs. oranges
- Some studies did assess the same four assays as in Blueprint and all reached similar conclusions on analytical comparison
  - Three assays are similar, one is different
- No studies (including Blueprint) have conducted PD-L1 assay comparison studies using clinical trial samples where true clinical assessments could be made between assays and therapeutics.
- Yet most investigations concluded that any of the three concordant assays could be used with any of the three therapeutics
  - **Advocating off label use!**

Notable Clinical Trial Results

- BMS, Nivolumab, CheckMate-026, August 2016
  - First line NSCLC, monotherapy, enrolled TPS$\geq$1%
  - Trial failed to meet primary endpoint (PFS @ TPS$\geq$5%) vs SOC
- Roche, Atezolizumab, Imvigor 211, May 2017
  - Previously-treated UC, monotherapy, confirmatory PhIII to convert accelerated approval to full US approval
  - Trial failed to meet primary endpoint (OS) vs SOC
- AstraZeneca, Durvalumab, Mystic, July 2017
  - First line NSCLC, combination, enrolled TPS$\geq$25%
  - Trial failed to meet primary endpoint (PFS) vs SOC
  - Trial has two additional primary OS endpoints, one for monotherapy and one for combo therapy

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For Your Regulatory Consideration

- Is PD-L1 diagnostic assay harmonization possible? Would patient safety be compromised? Who has the responsibility to educate the medical community on the proper use of these tests?
- Are anti-PDl / PD-L1 therapeutics acting as a class? What explains the surprising failures of confirmatory or first line trials using the same Rx / Dx pairs?
- What happens when confirmatory trials do not confirm the results of trials that resulted in accelerated approvals?
- What is the clinical utility of complementary Dx? What incentives exist for physicians to order them and for manufacturers to market them if they are not required?