Bio/pharma collaboration in the pre-competitive space

PD-L1 Assay Characterization

A Case Study

Steve Averbuch, MD
Bristol Myers-Squibb

On behalf of the PD-L1 Blueprint Team:

- Bristol-Myers Squibb
- Merck
- AstraZeneca
- Roche
- Dako/Agilent
- Ventana/Roche Tissue Diagnostics
- IASLC (Int. Assoc. for the Study of Lung Cancer)
Current state of IVD Rx-Dx co-development

• Independent and unique test development programs for each therapeutic product
• Multiple drug-companion/complementary diagnostic pairs entering the market in parallel
• Complex challenge for testing and decision-making in the clinic
• Potential harm to patients if inappropriate tests are used to make treatment decisions
Role of PD-1 Pathway in Suppressing Anti-tumor Immunity and MOA of anti-PD-1/PD-L1 inhibitors

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

Tumor cell

IFNγR

IFNγ

Dendritic cell

CD28

B7

PD-L1

PD-L2

PD-1

PD-1 Receptor Blocking Ab

PD-L1 Receptor Blocking Ab
PD-L1 assays

- 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
  - Companion/Complementary diagnostic development is tied to clinical outcome of the drug

- Confidentiality, IP constraints and contractual obligations require that assays be developed within firewalls, even within a single Dx organization
4 Assays Have Been Analytically Validated and Used in Clinical Studies to Test Hypotheses Related to PD-L1 Status (NSCLC)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Nivolumab BMS</th>
<th>Pembrolizumab Merck</th>
<th>Durvalumab AZ</th>
<th>Atezolizumab Roche/Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Platform</td>
<td>Dako (now approved)</td>
<td></td>
<td>Ventana (currently IUO )</td>
<td></td>
</tr>
<tr>
<td>IUO Antibody</td>
<td>28-8</td>
<td>22C3</td>
<td>SP 263</td>
<td>SP 142</td>
</tr>
<tr>
<td>Cut-off(s) tested</td>
<td>1%, 5% or 10% (TC&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>1% or 50% TC&lt;sup&gt;1&lt;/sup&gt;</td>
<td>≥ 25% TC&lt;sup&gt;1&lt;/sup&gt;</td>
<td>TC&lt;sup&gt;1&lt;/sup&gt; or IC&lt;sup&gt;2&lt;/sup&gt; 1%, 5%,10%</td>
</tr>
</tbody>
</table>

1) TC = tumor cell staining.
2) IC = infiltrating immune cell staining
Validated Diagnostic Assay Systems

The system, (i.e. antibody, reagents, platform, pathologist) not just the antibody, ensures correct assessment of biomarker for clinical application.

- Primary Antibodies
- Sensitive Detection Chemistries
- Slide Staining Platforms
- Recommended control materials
- Interpretation Guides (Training on Scoring Algorithm)

Patient sample results within dynamic range of the assay: Scoring Algorithm Development based on clinical outcome.
PD1/PD-L1 Program Development:

*Each biopharma company’s agent and assay development is different and may introduce complexity for patient management*

- The scientific/diagnostic hypotheses and patient populations under study for market approval are different (even within tumor types)
- Each biopharma company has partnered with a Dx company to independently develop an analytically validated IHC assay measuring PD-L1 expression
- Relationships between efficacy endpoints and PD-L1 expression are different across sponsors and assays in randomized studies with respect to type and timing of biopsy, cell type(s) of interest, scoring method, cut-off, etc.
- This may result in at least 4 approved CDx assays ostensibly measuring the same biomarker but are tailored to inform treatment decisions with a specific drug
Perception in the Community that These Assays are Highly Discordant

Kerr et al, J Thorac Oncol July, 2015

- Proposes a multi-center international standardization effort to address significant concerns around testing complexity arising upon approval of more than one drug with a diagnostic
Challenges:

Running a different test for each drug is impractical
- Limited tumor tissue
- Turnaround time

Using one test for every drug is equally impractical
- All tests will not run on all platforms
- Each test has different performance characteristics
- Scoring and interpretation guidelines are not harmonized
- Each drug may have different clinical response based on biologic, chemistry and MOA differences

There is the potential for harm to patients if:
FDA-approved IVD’s and drugs are cross-matched by end users in the absence of FDA reviewed and approved claims of clinical and analytical concordance.
Complexities in Personalized Medicine: Harmonizing Companion Diagnostics across a class of Targeted Therapies

*FDA-AACR-ASCO Public Workshop 24 March 2015*

- Highlight the issue using PD-L1 as a case study
- Build awareness of the issue
- Foster a public examination of the problem
- Offer potential solutions.
PD-L1 BLUEPRINT EXTENDED TEAM

Steering Committee
- Astra-Zeneca
- BMS
- Genentech
- Merck

Execution Team
- Dako
- Ventana Medical Systems, Inc.
- IASLC

Core Team
- AACR

Agencies
- FDA
- EMA
GOAL:

“To agree and deliver, via cross industry collaboration, a package of information/data upon which analytic comparison of the various diagnostic assays may be conducted, potentially paving the way for post-market standardization and/or practice guideline development, as appropriate.”
PD-L1 Blueprint Project Scope

- 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 platform**

- **No delay** to pivotal studies and **patient access** to critical new therapies

- Focus on **NSCLC**

- Deliver a data package to **inform the medical community** on PD-L1 IHC testing
## PD-L1 Blueprint Project Roles and Responsibilities

<table>
<thead>
<tr>
<th>Organization</th>
<th>Roles and Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACR</td>
<td>• Facilitates conversations and project updates</td>
</tr>
<tr>
<td>Pharma Companies</td>
<td>• Steering Committee&lt;br&gt;• Funding</td>
</tr>
<tr>
<td>IVD Companies</td>
<td>• Steering Committee&lt;br&gt;• Technical expertise&lt;br&gt;CDx assay development and data generation</td>
</tr>
<tr>
<td>IASLC</td>
<td>• Steering Committee&lt;br&gt;• Pathology expertise&lt;br&gt;• Neutral observer</td>
</tr>
<tr>
<td>Regulatory</td>
<td>• Public health advocates&lt;br&gt;• Neutral observer</td>
</tr>
</tbody>
</table>
Blueprint Proposal
Initial Aim is to Characterise Relative Performance of 4 IUO Assays

Ultimate goal is to help the clinical and testing community understand the comparative analytical performance of each IUO grade PD-L1 assay that is under development

Initial focus on NSCLC

Primary goal is to characterize the 4 assays under controlled conditions, using IUO versions of the assays and Pathologists that have been trained to accurately read stained slides for each assay

Pathologists from external organizations will be engaged to provide independent interpretation

Subsequent experiments may be informed from this analysis
Blueprint Study:
2 phased study to gain sufficient data and rigor

Phase 1 study:
• Feasibility on small cohort stained at Dako and Ventana

Phase 2 study:
• Larger, statistically powered study that will be designed from the phase 1 “information gathering”
Phase 1 Study: Feasibility

To assess the 4 IUO assays on the same cases and gather initial data on their staining patterns and intensities in order to a robust design for Phase 2.

**Design**: Each Dako and Ventana IUO team identified vendor-sourced NSCLC cases representative of the dynamic range of each assay (total N ~40: NOT CLINICAL SAMPLES)

Ventana and Dako exchanged consecutive unstained sections from each of the cases.

Ventana stained the cases with their 2 IUO assays:
Dako stained the cases with their 2 IUO assays
(Ensures controlled conditions)

Ventana and Dako pathologists and biostatisticians collaborated with Fred Hirsch on what scoring criteria to capture.

Ventana and Dako currently exchanging stained slides for evaluation. F2F data review and slide review including IASLC pathologists in Nov 2015.
Summary

- Blueprint is a *successful* pre-competitive collaboration to evaluate assays for PDL1 diagnostic important for patient management

- A 2 phase rigorous study design is being implemented to achieve a common goal

- Blueprint will be transparent with the findings (Phase 1 data projected for AACR, 2016)
Thank you

- Abigail McElhinny, Ventana
- Dave Stanforth, Dako
- Steve Averbuch, James Novotny, BMS
- Eric Rubin, Ken Emancipator, Merck
- Ian McCaffery, Andy Williams, Genentech
- Jill Walker, AZ
- Rasika Kalamegham, AACR
- Fred Hirsch, IASLC
- Pamela Bradley, Reena Phillip, FDA
- Jorge Martinalbo, EMA