PD-L1 IUO Assay Characterization

On behalf of the Blueprint Team:

Bristol-Myers Squibb
Merck
AstraZeneca
Roche
Dako/Agilent
Ventana/Roche Tissue Diagnostics
AACR
IASLC Foundation

Current state of IVD 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

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 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

Challenges

Running a different test for each drug is impractical

- Limited tumor tissue
- Turnaround time

Using one test for all drugs is equally impractical

- Platform systems are different for tests
- Each test has different performance characteristics
- Scoring and interpretation guidelines are unique
- Each drug may have different clinical response based on biologic, chemistry and MOA differences

Potential for harm to patients if:

FDA-approved IVDs and drugs are cross-matched by end users in the absence of FDA reviewed and approved claims of clinical and analytical concordance.

- Public workshop " **Complexities in Personalized Medicine: Harmonizing Companion Diagnostics across a class of Targeted Therapies**" held on March 24, 2015

  - Highlight the issue using PD-L1 as a case study
  - build awareness of the issue
  - foster a public examination of the problem
  - and offer potential solutions.

Blueprint Project

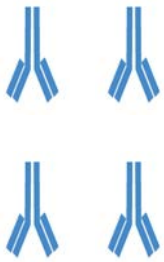
GOAL: “To agree and deliver, via cross industry collaboration, a package of information/ data upon which analytic comparison of the various diagnostic assays may be conducted, potentially paving the way for post-market standardization and/or practice guideline development, as appropriate.”

Scope of the Project

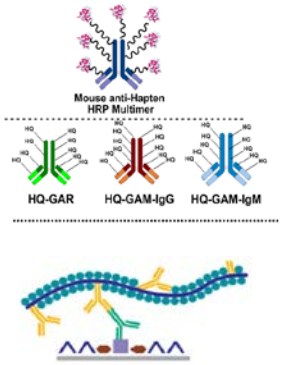
- Assess **analytical performance** of PD-L1 assay systems from **Dako and Ventana**
- Study to be designed and executed through **collaboration** of industry stakeholders with **independent third party (Fred Hirsch, IASLC)**
- Restricted to tests developed and/or approved via **Pre-Market Approval** (PMA) pathway
- Restricted to tests **run on the associated platform**
- **No delay** to ongoing 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

Companion Diagnostic Assay Systems

The system, not just the antibody, ensures accurate selection of patients

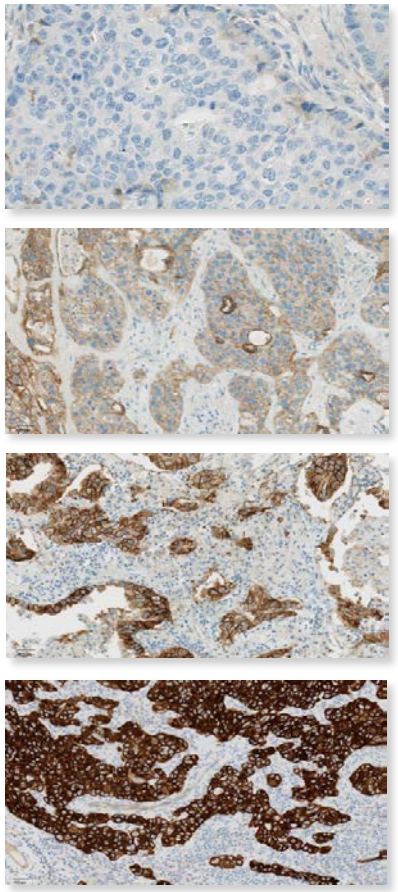


Primary Antibodies

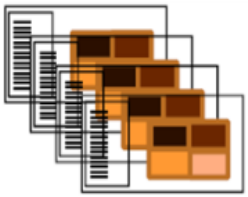


Sensitive Detection Chemistries

Slide Staining Platforms



Patient sample results within dynamic range of the assay: Scoring Algorithm Development based on clinical outcome



recommended control materials

Interpretation Guides (Training on Scoring Algorithm)

Analytically Validated Assays Used in Clinical Studies to Test Hypotheses Related to PD-L1 Status (NSCLC)

Agent	Nivolumab	Pembrolizumab	Durvalumab	Atezolizumab
Diagnostic Platform	Dako (now approved)		Ventana (currently IUO)	
IUO Antibody	28-8	22C3	SP 263	SP 142
Cut-off(s) tested	1%, 5% or 10% (TC[1])	TC[1] ≥50% (and 1% any stroma)	≥ 25% TC[1]	TC[1] or IC[2] 1%, 5%,10%

1) TC = tumor cell staining.
2) IC = infiltrating immune cell staining

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 based on data from pilot phase study

Phase 1 Study: Feasibility

To assess the 4 IUO assays on the same cases and gather initial data on their staining patterns and intensities to inform 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: vendor sourced 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 IASLC experts on scoring criteria

Two F2F meetings to discuss data and align on publication strategy (Oct and Nov, 2015).
Data analysis and manuscript drafting ongoing.

Blueprint Proposal

Aim is to Characterize Relative Performance of 4 IUO Assays

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

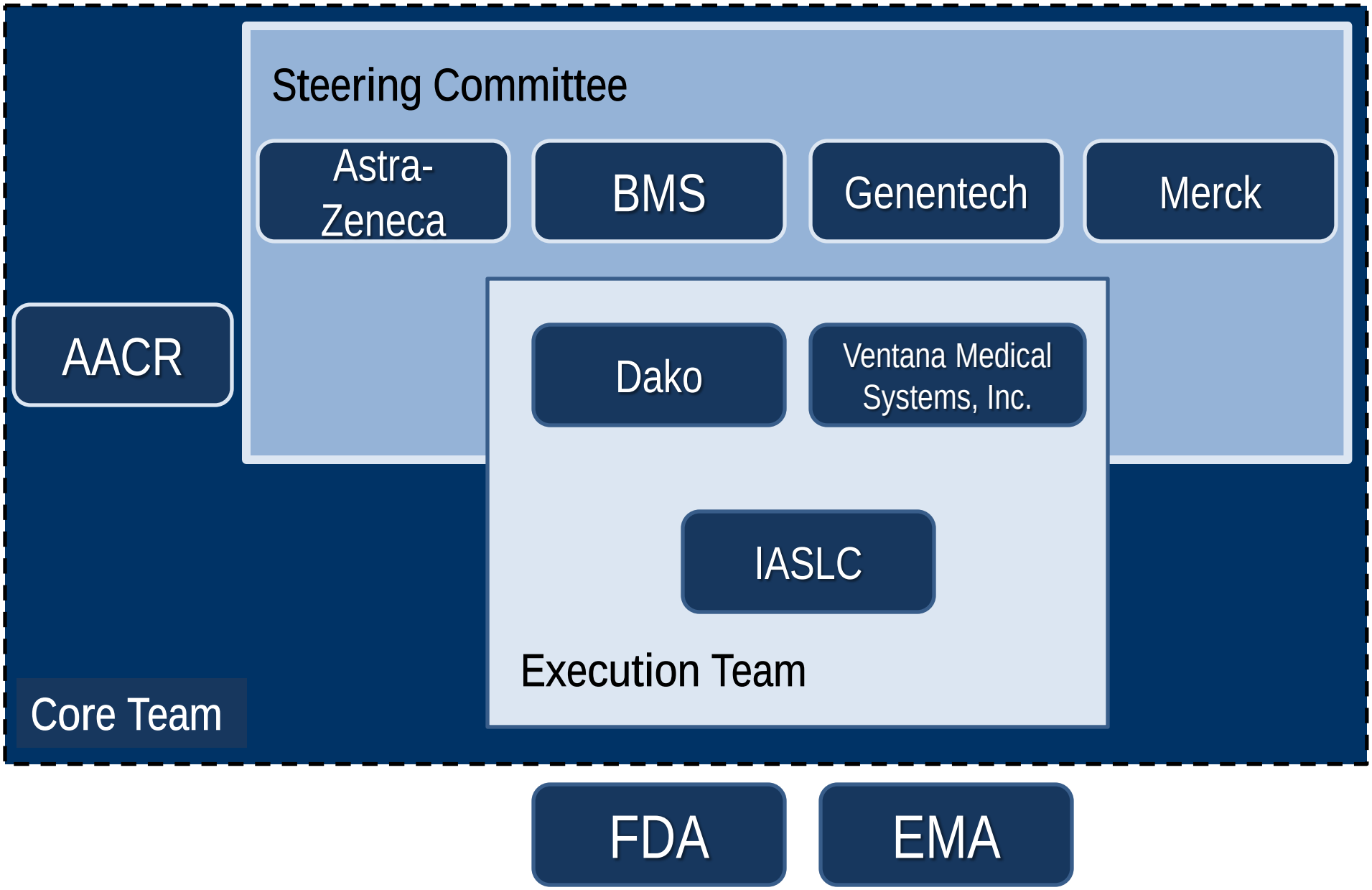
Focus on NSCLC

Primary goal is to characterize the 4 assays under controlled conditions using IUO/approved assays and Pathologists trained to accurately read stained slides for each assay

Pathologists from IASLC have been engaged to provide independent interpretation

Subsequent experiments to be informed from this analysis

BLUEPRINT TEAM



Roles and Responsibilities

AACR	• Facilitate conversations and project updates
Pharma Companies	• Funding • Steering Committee
IVD Companies	• Technical expertise • Steering committee • Execution team
IASLC	• Independent pathology expertise • Execution team
FDA and EMA	• Public health advocates • Neutral observer

Summary

- Blueprint is a collaborative initiative to evaluate 4 IUO assays

- A rigorous study design being implemented with a 2 phased approach

- Blueprint will be transparent with its findings

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
- Fred Hirsch, IASLC
- Pamela Bradley, Reena Phillip, FDA
- Jorge Martinalbo, EMA