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Development of PD-L1 Diagnostics

09 October 2015

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Discussion Topics

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- Development of Class 1 vs. Class 3 assays
- Changing clinical program paradigm – accelerated approval scenario creates challenges
- PD-L1 testing in the market – PD-L1 Blueprint

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Development of Class 1 vs. Class 3 Assays

IVD Class 1 Assay vs. CDx Class 3 Assay
Background

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- **Dx's (IVD Class I)**
  - Confirms a diagnosis (diagnosis all ready set by H&E and SS)
  - Qualitative test ("yes or no to the presence of the biomarker")
  - Minor sensitivity variations between lots will be accepted, because the overall test-outcome will not change

"YES"
("Yes – it's a carcinoma")

"YES"
("Yes – it's a carcinoma")

"YES"
("Yes – it's a carcinoma")

"NO"
("It's NOT a carcinoma, but a different tumor type"

- **CDx's (IVD Class III)**
  - Decides if the patient will benefit from a specific drug attached to the test
  - Quantitative by nature (only those patients which express a certain amount of the biomarker are eligible for drug treatment)
  - Assay lots must display same sensitivity all time at all locations

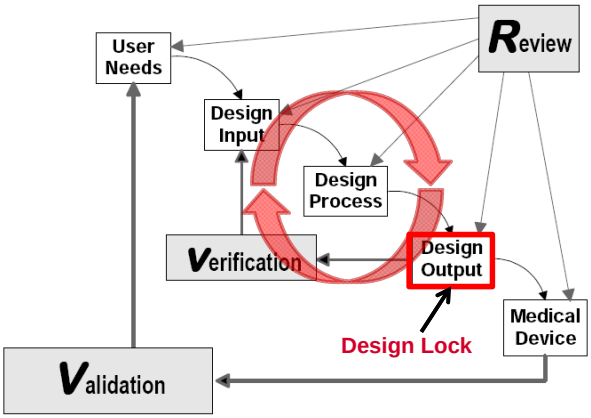
"+400"
Positive (above cut-off)
Eligible for drug X treatment

"+300"
Borderline (around cut-off)
Re-test

"+200"
Negative (below cut-off)
Not eligible for drug X treatment

"0"
Negative (below cut-off)
Not eligible for drug X treatment

Development of a CDx assay
Background



The following performance characteristics are extensively tested against design specs (verification) and Intended Use (validation):

- Sensitivity
- Specificity
- Precision
- Robustness
- Multi-site Reproducibility
- Stability: reagents and tissues
- **Testing is performed with emphasis on samples close to the clinical decision point**

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Accelerated Approval Paradigm and Challenges for Dx Development

Accelerated PD-L1 Drug Approval

Co-development Alignment Challenges

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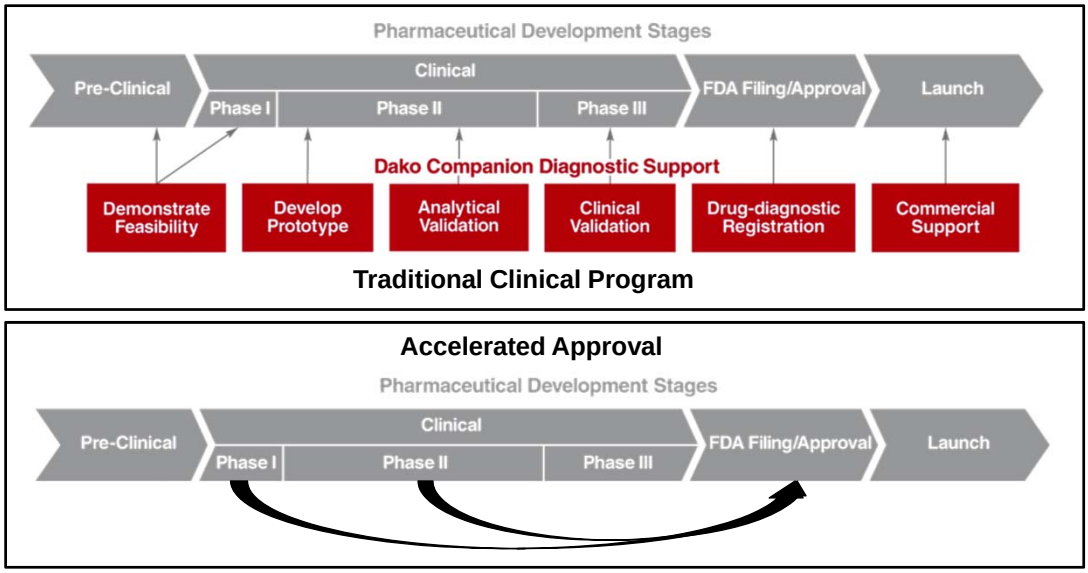

Accelerated PD-L1 Drug Approval

Co-development Alignment Challenges

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- Clinical decision point (i.e. assay cutoff) not known in Phase 1
  - Require validation of multiple cutoffs (enrollment cutoff, secondary cutoff)
  - Divided trial cohort (assay training set, clinical validation set) may be required to establish and clinically validate the cutoff
  - External multi-site reproducibility study with multiple cutoffs
- Phase 1 trial enrolled with prototype assay
  - Bridging study required
  - Samples exist as cut sections – blocks not available
  - Real time cut section stability becomes a critical parameter
- PMA must be prepared on compressed schedule

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PD-L1 Testing Complexity in the Market Blueprint Initiative

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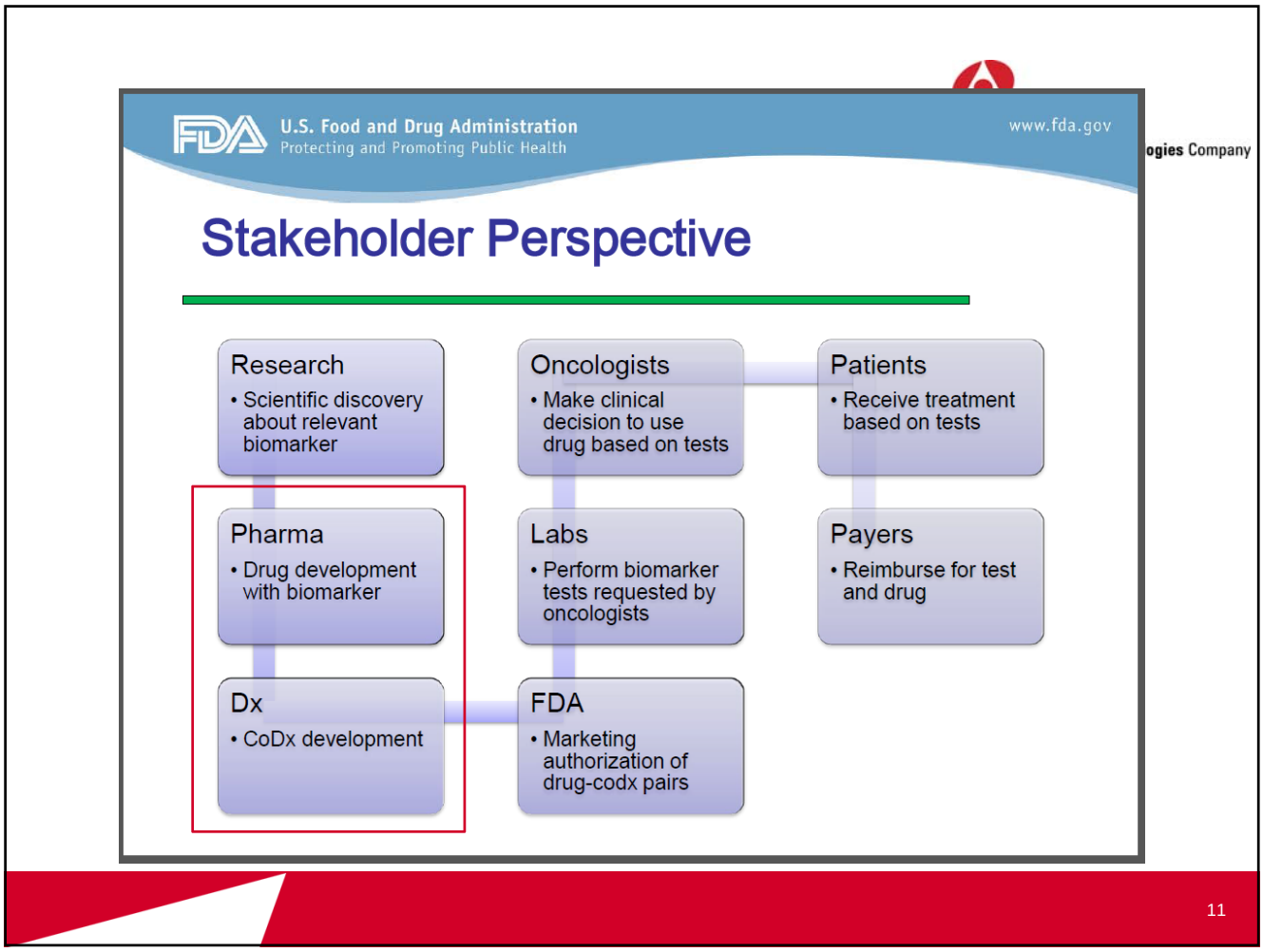
FDA

AACR
American Association for Cancer Research
FINDING CURES TOGETHER™

ASCO
American Society of Clinical Oncology
Making a world of difference in cancer care

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

March 24, 2015


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
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Stakeholder Perspective
Research
• Scientific discovery about relevant biomarker
Oncologists
• Make clinical decision to use drug based on tests
Patients
• Receive treatment based on tests
Pharma
• Drug development with biomarker
Labs
• Perform biomarker tests requested by oncologists
Payers
• Reimburse for test and drug
Dx
• CoDx development
FDA
• Marketing authorization of drug-codx pairs
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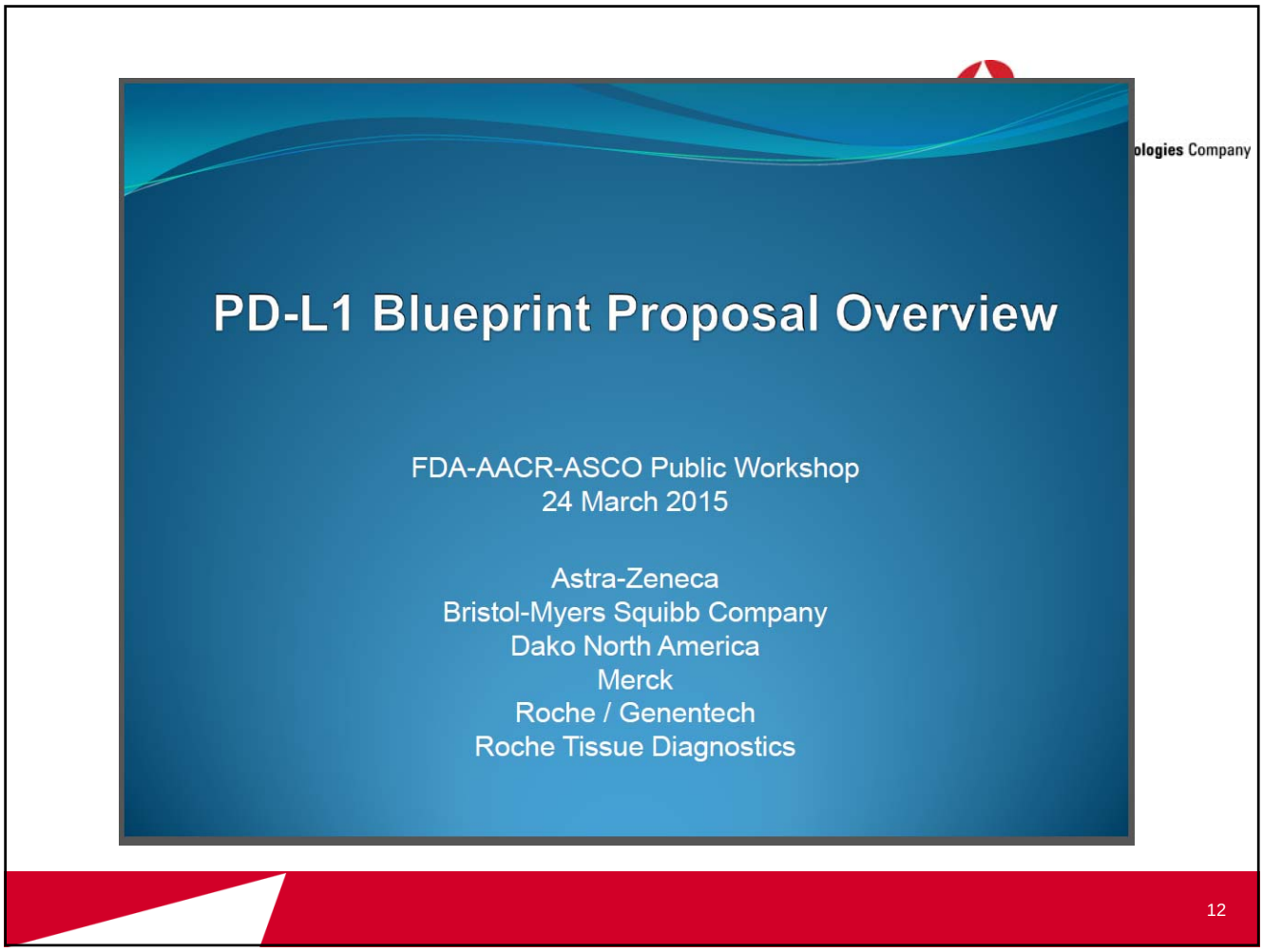
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PD-L1 Blueprint Proposal Overview
FDA-AACR-ASCO Public Workshop
24 March 2015
Astra-Zeneca
Bristol-Myers Squibb Company
Dako North America
Merck
Roche / Genentech
Roche Tissue Diagnostics
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Complications

- Running a different test for every drug is impractical
- 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.

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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

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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"

18 September 2015, CRI-CIMT-EATI-AACR Joint Immunotherapy Conference, NYC

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 Fred Hirsch will be mid-Oct.

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