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

March 24, 2015

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

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  - **Nancy Roach**, Fight Colorectal Cancer

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Workshop Structure

- Session 1: Defining the Problem

- Session 2: Comparing the Tests

- Session 3: Clinical Practice/Education

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**Complexities in Personalized Medicine:
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Session 1:
Defining the Problem

Overview Presentation: Reena Philip, FDA

Stakeholder Perspectives:

- **Nancy Roach,** Fight Colorectal Cancer
- **Suzanne Topalian,** Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
- **Debra Leonard,** University of Vermont Medical Center
- **Steve Averbuch,** Bristol-Myers Squibb Company
- **Doug Ward,** Ventana Medical Systems, Inc.
- **Gideon Blumenthal,** OHOP, CDER, FDA
- **Girish Putcha,** Palmetto GBA

Emerging Issues in Companion Diagnostics

FDA Public Workshop

March 24, 2015

Reena Philip, Ph.D.

Director, Division of Molecular Genetics and Pathology
Office of In Vitro Diagnostic Device Evaluation and Safety

Center for Devices and Radiological Health

Personalized Medicine

The success of personalized medicine depends on having accurate, reproducible and clinically useful companion diagnostic tests to identify patients who can benefit from targeted therapies

Companion Diagnostics are those tests that provides information that is <u>essential</u> for the safe and effective use of a corresponding drug or biological product.
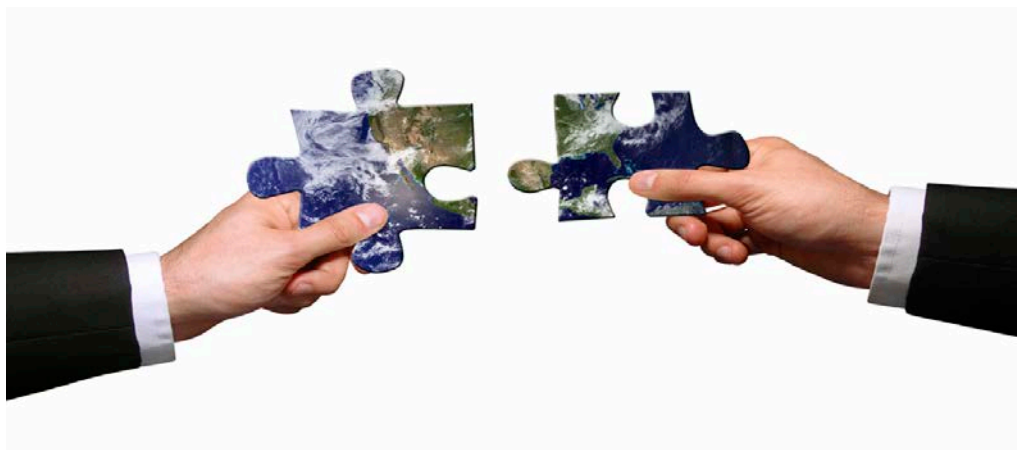
FDA Expectation for Companion Diagnostics

"Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices"

- Guidance finalized August 6, 2014
- Defines companion diagnostic and various scenarios for use
- Describes FDA policies for approval and labeling
- Contemporaneous regulatory approvals of the device and drug

Drug Development Trend

- Dramatic increase in biomarker-targeted drug development programs

  - In the early 1990s, 5% of new drug approvals were for targeted therapies.

  - In 2013, 45% were for targeted therapies.

- Increase in use of tests to detect/measure the biomarkers to identify the ITT population

Why Companion Diagnostics

Companion diagnostics segregate a patient population into two subsets: Marker-positive vs marker-negative - a qualitative result based on an underlying quantitative assessment to which a clinical decision point or cut-off is applied.

The safety and efficacy of the therapeutic product is evaluated in the population that is treated in the clinical trial. This is the subset of patients determined to be "marker-positive" by the test.

Safety and efficacy information about the therapeutic product is frequently not collected in the subset of patients determined to be "marker-negative" by the test.

.

Overview of Companion Diagnostic Validation

- Assay selects target population enrolled in the trial

    - A specific assay is identified for detecting the marker

    - A specific protocol is used with the assay

    - A clinical decision point (cut-off) is selected

    - A specific specimen type is identified for testing

- Analytical validation (e.g., accuracy, reproducibility, specificity, stability) is obtained with attention to the clinical decision point.

- Clinical validation of the device is supported by the results of the drug trial when used to test specimens and identify patients eligible for the trial.

Clinical Validity for Companion Diagnostics:
When the IVD CoDx is not the Clinical Trial Assay

Changing the test (e.g., cut-off) can change the results for a patient specimen, and potentially changes the population from what was selected in the trial.

Requires Bridging Studies:

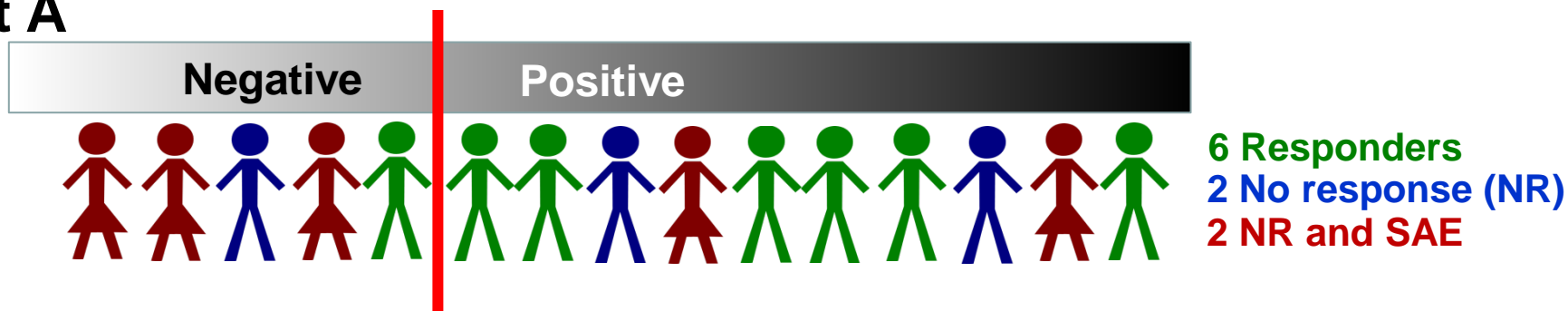Shows the revised test (IVD) supports the Rx safety and efficacy

- Retest specimens (CTA negative and positive) with new/revised test to support the drug's safety and efficacy

- Statistical plan considers discordance, missing samples and impact on drug efficacy.

- Retest population is representative of the intended use population for the device.

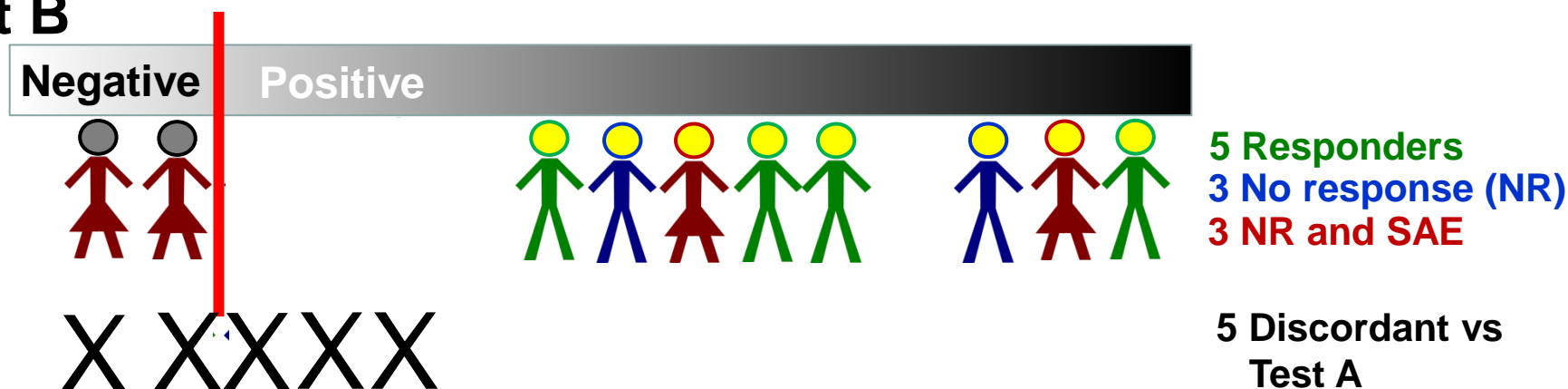# Comparing a Test to an Approved Companion Diagnostic

- A bridging study is not just a method comparison

- Center is developing guidance for follow-on assays

  – Analytical method comparison

  – Procured clinical sample set should be the same as the target population

  – Dilemma in determining impact of discordance

  – Is discordance random or is there bias impacting device performance

Example: Unfavorable Discordance

Test A

Negative | Positive

6 Responders
2 No response (NR)
2 NR and SAE

Test B

Negative | Positive

5 Responders
3 No response (NR)
3 NR and SAE

X X X X X

5 Discordant vs Test A

Current Companion Diagnostic Examples

Many successful companion diagnostic/therapeutic co-approvals

– www.fda.gov/companiondiagnostics

CoDx Complexities - Easy Cases:

- One drug, one disease indication, one test, one allele:

  e.g., Abbott VYSIS ALK Break Apart FISH Probe Kit for Xalkori ® (crizotinib)

- One test, one indication, more than one drug, same alleles

  ➢ E.g., QIAGEN *therascreen* KRAS RGQ PCR Kit– for CRC for two therapeutics Erbitux® (cetuximab) and Vectibix® (panitumumab).

- Originally one drug, one indication:

  ➢ HER2 and Herceptin –breast cancer (Tests - Dako IHC / Vysis PathVysion FISH)

  ➢ Follow on tests demonstrated method comparison, development of CAP guidelines

  ➢ Expanded the indication to gastric cancer

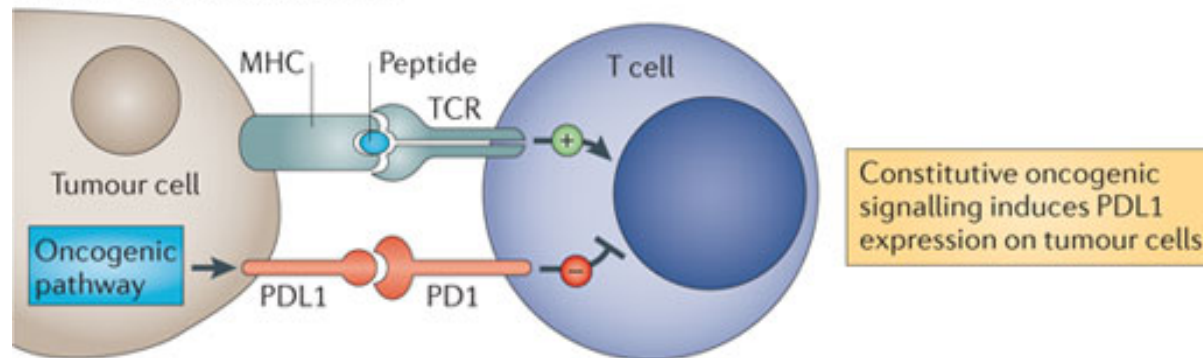 ➢ Other drugs for the same analyte - Perjeta, Kadcyla

CoDx Complexities

One indication, More than one drug, Two tests- Same gene but different allele representation.
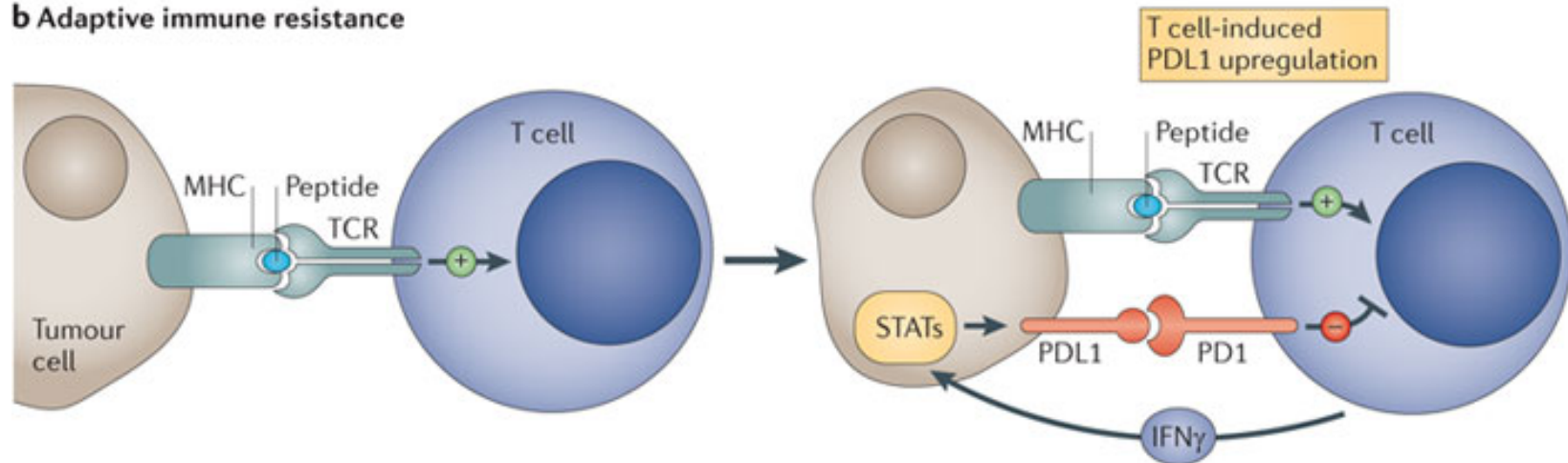
- BRAFV600 mutation:
  - Roche cobas BRAF V600 Mutations Test for Zelboraf® (vemurafenib)
  - BioMérieux THxID BRAF Kit for Tafinlar® (dabrafenib) and Mekinist® (trametinib)

- EGFR Activating Mutations
  - Roche cobas EGFR Mutation Test for Tarceva® (erlotinib)
  - Qiagen *therascreen* EGFR RGQ PCR Kit for Gilotrif® (afatinib)

The Case of PD-L1

Nature Reviews | Cancer

Candidate CoDx Complexities – The Case of PD-L1

- 4-8 drugs in development

- Parallel development programs

- Various trial designs

PD-L1 Pathway Blocking mAbs in Clinical Testing

Source	Target Molecule	
	PD-1	**PD-L1**
Bristol-Myers Squibb	Nivolumab/BMS-936558/ MDX-1106/ ONO-4538 (human IgG4)	BMS-936559/MDX-1105 (human IgG4)
CureTech	Pidilizumab/CT-011 (humanized IgG1)	N/A
EMD Serono	N/A	MSB0010718C (human IgG1)
Genentech/ Roche	N/A	MPDL3280A (Fc-modified human IgG1)
MedImmune/ AstraZeneca	MEDI0680/AMP-514	MEDI4736 (Fc-modified human IgG1)
Merck	Pembrolizumab/MK-3475 (humanized IgG4)	N/A

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Candidate CoDx Complexities – The Case of PD-L1

- 4-8 drugs in development

- Parallel development programs

- Various trial designs

- Multiple anti-PD-L1 immunohistochemistry (IHC) companion diagnostics
  - Different test for each drug

Candidate CoDx Complexities – The Case of PD-L1

- Different IHC antibody clones
- Different staining protocols and platforms
- Different clinical decision points
- Different tumor indications (not all IHC assays will be validated for each tumor type)
- Different assessment methods (Tumor cells, TILs, or both)
- Different scoring methods (% staining, H-score)

PD-L1 IHC Methods in Development

	Hopkins	**BMS**	**Merck**	**Genentech**
mAb clone	5H1	28-8	22C3	SP142
Automated	No	Yes	Yes	Yes
Staining location scored	Membrane	Membrane	Membrane	Membrane
Cell type(s) scored	Tumor cells	Tumor cells	Tumor and/or infiltrating immune cells	Infiltrating immune cells
Positive cutoff	≥ 5%	≥ 5%	≥ 1%	≥1% to ≥10% ("IHC 1-2-3")

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➢ ***Note****: These assays are evolving, pending further clinical correlations*

Example: Therapeutic for NSCLC Patient is Considered

	Drug A (NSCLC)	Drug B (HNSCC and RCC)	Drug C (NSCLC and Melanoma)
Test A (Clone A)	1% of Tumor	?	?
Test B (Clone B)	?	5% of Tumor	?
Test C (Clone C)	?	?	IC > 5%

- Potential for mixing approved drugs and devices (that were not approved together).

- Patient treatment decisions may not be aligned with the approved CoDx testing due to test performance differences.

Issues - The Case of PD-L1

- Performance of each IHC antibody optimized for a particular protocol and platform

- Is the sensitivity and specificity between clones the same?

- Is the reactivity in tumor cells and TILs the same?

- Can laboratories apply one protocol to the same clone for all uses?

- Can laboratories adequately assess concordance with an adequate number of specimens?

Problematic for the following reasons

- High potential for mismatched approved drug/device combination in the clinical setting. Patient treatment may not be based on testing with the matched CoDx.

- FDA approvals are for a specific drug/CoDx combination, so the labeling applies only to that particular combination. Performance across different clinical decision points (cut-offs) may not be established.

- Laboratories are not able to assess the impact of discordance between tests in the absence of clinical outcome data.

- Laboratories are not expected to have more than one assay/platform to detect the same analyte.
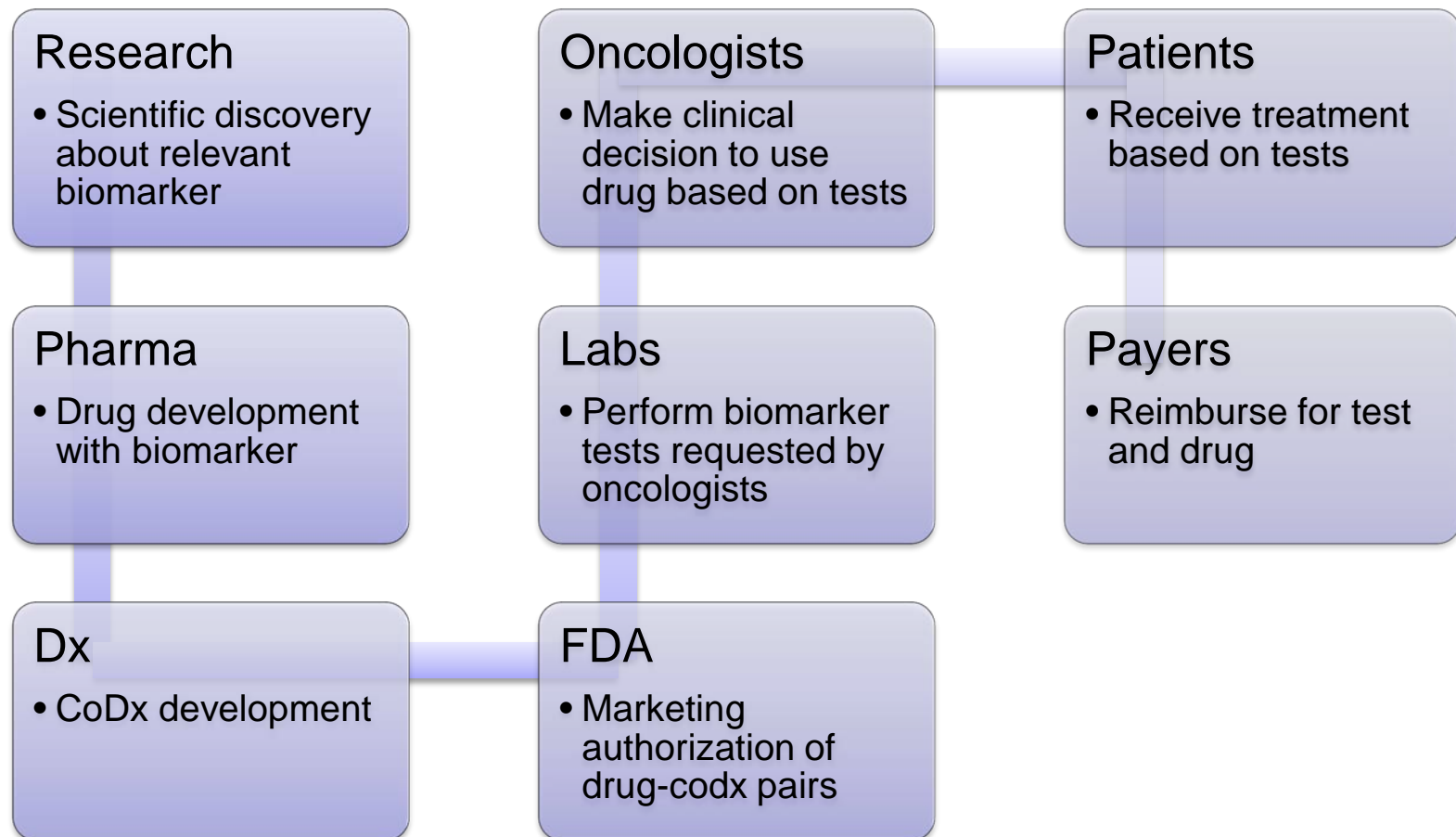
Problems Envisioned

- The Clinician will not know what test the laboratory is running

- The Laboratory will not know what therapeutic the clinician is considering

- It is not cost efficient to run multiple tests

- It is not good use of the patients specimen to run multiple tests

- Payers may not compensate for the test that is not FDA approved for the drug that is used

Purpose of This Workshop

To bring together stakeholders to help determine what is necessary to ensure that:

- Safe and effective companion diagnostics are used in the laboratory

- Clinicians receive the most appropriate information for making patient treatment decisions

- Laboratories are not burdened with multiple tests to detect the same analyte

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

Thank You

Reena.Philip@fda.hhs.gov

Disclosure

- FightCRC accepts unrestricted grants from individuals, foundations and companies, including industry

- My affiliations:

  - NCI: protocol development and review committees; oversight of intramural program; oversight of extramural changes; DSMB

  - FDA: Patient representative program

  - Clinical Trials Transformation Initiative / an FDA-Duke partnership: Executive committee

get behind a cure.

FIGHT COLORECTAL CANCER

Overview

- Describe a consumer perspective

- Provide examples of possible confusion

- Plead for simplicity in a very complex world

Similar

- Require significant scientific expertise to design and manufacture
- Highly regulated and inspected
- Consumer doesn't need to understand the science or regulations
- Consumer generally trusts that the product will work as advertised

Different

- Biology is less reproducible than physics and mechanical engineering
- One driver's ed test lets you drive most cars … but different drugs may require different tests
- Buying a car can be fun.

get behind a cure.

FIGHT
COLORECTAL
CANCER

get behind a cure.

FIGHT COLORECTAL CANCER

Andrew

get behind a cure.

FIGHT
COLORECTAL
CANCER

Trust

get behind a cure.   FIGHT COLORECTAL CANCER

Cautionary Examples

- **Cetuximab**
  - Initially approved in 2004 for EGFR+
  - Changed to KRAS
- **Microsatellite Instability**
  - MSI-high requirement for some PDL trials
  - Different tests have different results

get behind a cure.

FIGHT COLORECTAL CANCER

Patient Confusion

get behind a cure.

FIGHT
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CANCER

Clinician Confusion

Andrew and Alice

Talk doesn't cook rice

get behind a cure.

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Companion diagnostics for immunotherapy: the case of PD-L1 IHC

Suzanne L. Topalian

Johns Hopkins Kimmel Cancer Center

FDA-AACR-ASCO Public Workshop
Complexities in personalized medicine: harmonizing companion diagnostics

March 24, 2015

Disclosures

Consultant for: Five Prime Therapeutics, GSK, Jounce Therapeutics; and (spouse) MedImmune, Merck, Pfizer, and Sanofi

Grant/Research support from: Bristol-Myers Squibb

Stock options (spouse): Jounce Therapeutics

Royalties through institution (spouse): BMS

From the oncologist's perspective: when do we need biomarkers to guide therapy?

- **Unfavorable risk:benefit ratio – rate of potentially serious side effects ≥ potential benefit in the unselected patient population (e.g., ipilimumab in melanoma)**
- **Drug has limited efficacy in the unselected patient population (e.g., anti-PD-1 in colorectal carcinoma)**
- **Biology predicts that *only* "marker positive" patients will respond (e.g., BRAF V600E mutation and vemurafenib)**
- **Treatment sequencing: first-line vs. later line therapy**

➢ *For broadly applicable therapies such as anti-PD1 or anti-PD-L1, these issues may be tumor type-specific*

Intra-tumoral PD-L1 expression and response to PD-1/PD-L1 blockade

	Nivolumab Solid Tumors (Topalian et al. NEJM 2012)	Nivolumab Melanoma (Weber ASCO 2013)	Nivolumab Melanoma (Grosso et al. ASCO 2013)	MPDL3280a Solid Tumors (Herbst et al ASCO 2013)	MPDL3280a Melanoma (Hamid et al ASCO 2013)	MPDL3280a NSCLC (Sorial et al ECC 2013)	Pembrolizumab Melanoma (Daud et al AACR 2014)	Pembrolizumab NSCLC (Gandhi et al AACR 2014)	MPDL3280a Bladder (Powels et al ASCO 2014)	Pembrolizumab Head & Neck (Selwert et al ASCO 2014)	Pembrolizumab Melanoma (Ribas et al ASCO 2014)
n=	42	44	34	94	30	53	113	129	65	55	411
Response Rates											
Unselected	21%	32%	29%	22%	23%	23%	40%	19%	26%	18%	40%
PD-L1 +	36%	67%	44%	39%	27%	46%	49%	37%	43%	46%	49%
PD-L1 −	0%	19%	17%	13%	20%	15%*	13%	11%	11%	11%	13%

Pitfalls for PD-L1 biomarker: multiple cell types in the tumor microenvironment can express PD-L1

→ Melanoma cells

→ Macrophages

→ Lymphocytes

Tumeh, Ribas, et al., Nature 2014

Pitfalls (2): immunologic heterogeneity of anatomically and chronologically distinct tumors

Patient no.	Clinical Resp.	Biopsy site	PD-L1 IHC (%pos. tumor cells)
1	NR	SQ met #1	5-10
		SQ met #2	0
2	NR	Skin primary	20
		LN met	0
3	CR	Skin primary	5
		SQ met	0
		LN met	0
4	NR	Skin primary	5
		LN met #1	0
		LN met #2	5
5	PR	Lung met #1	5
		Lung met #2	50

Variable expression of PD-L1 among melanoma lesions from individual patients receiving anti-PD-1 therapy.

"PD-L1+ tumor": ≥5 % tumor cells with cell surface PD-L1 expression

"PD-L1+ patient": patient in whom *any* tumor is PD-L1+

(adapted from Topalian et al., NEJM 2012)
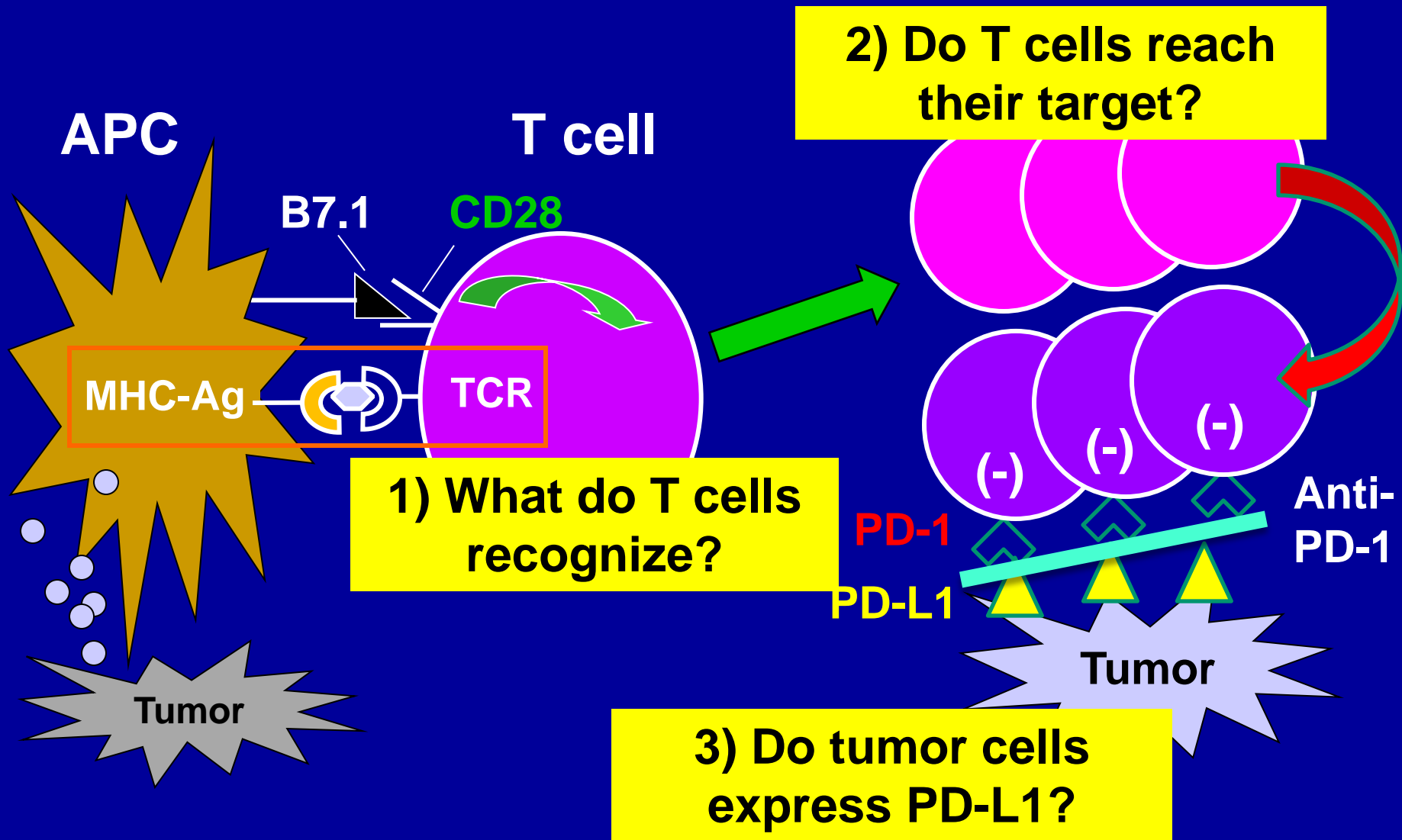
Pitfalls (3): focal PD-L1 expression
"Marker negative" or sampling error??

Invasive primary melanoma, nodular subtype. 10% of tumor cells express PD-L1.

Tumor

Lymphs

Taube et al., Sci Transl Med 2014

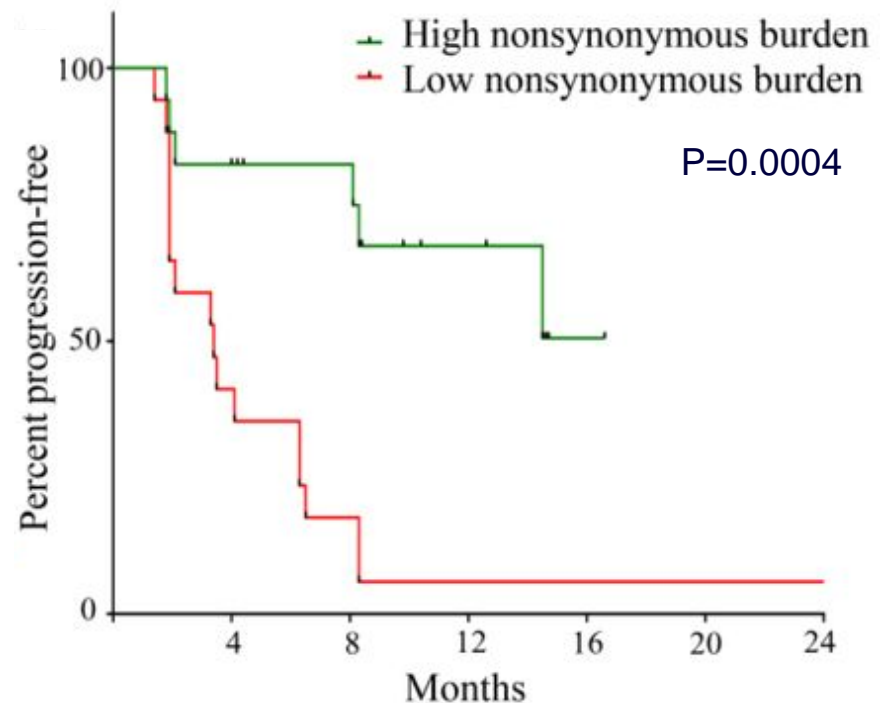The PD-1 pathway plays a major role in suppressing anti-tumor immunity

Preliminary findings: Mutational load in NSCLC correlates with response to anti-PD-1 (pembrolizumab) therapy

Endpoint: "durable clinical benefit"
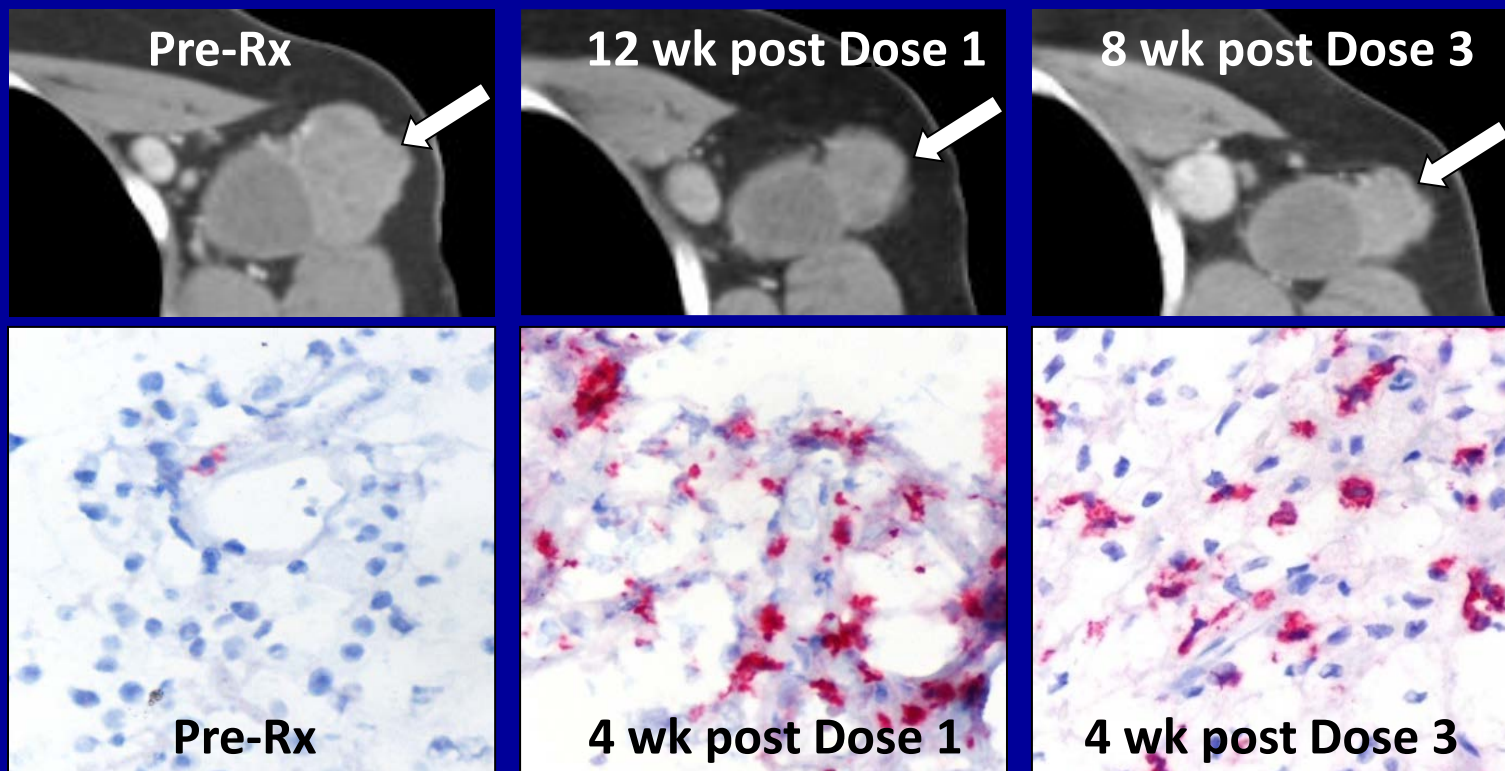
Endpoint: PFS

Rizvi, Chan et al., Science 2015

On-treatment biomarkers: infiltration of CD8+ T cells in melanoma is associated with response to anti-PD-1 (nivolumab)

Intermittent dosing regimen of nivolumab. (Brahmer et al., JCO 2010)

Conclusions

➢ **The immune system is dynamic and complex, posing challenges for biomarker development.**
➢ **Studies correlating biological markers with immunotherapy outcomes are important for establishing drug MOA.**
➢ **_PD-L1 IHC case study_: marker expression by tumor cells and/or infiltrating immune cells is associated with a higher (but not absolute) likelihood of response to PD-1 pathway blockers.**
➢ **Potential utility of PD-L1 IHC:**
  ▪ **Identify cancer types that may be susceptible to PD-1/PD-L1 blockade, for clinical testing**
  ▪ **Enrichment of responsive patients in cancers with very low overall response rates**

Complexities in Personalized Medicine:
A Pathologist's Perspective

Debra G.B. Leonard, M.D., Ph.D.
Chair & Professor, Pathology & Laboratory Medicine
University of Vermont Medical Center

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Issues from Pathologist's Perspective

1. Inadequate tissue for testing

2. IHC test validations

3. Assuring right test for each drug

4. Assuring test results used correctly
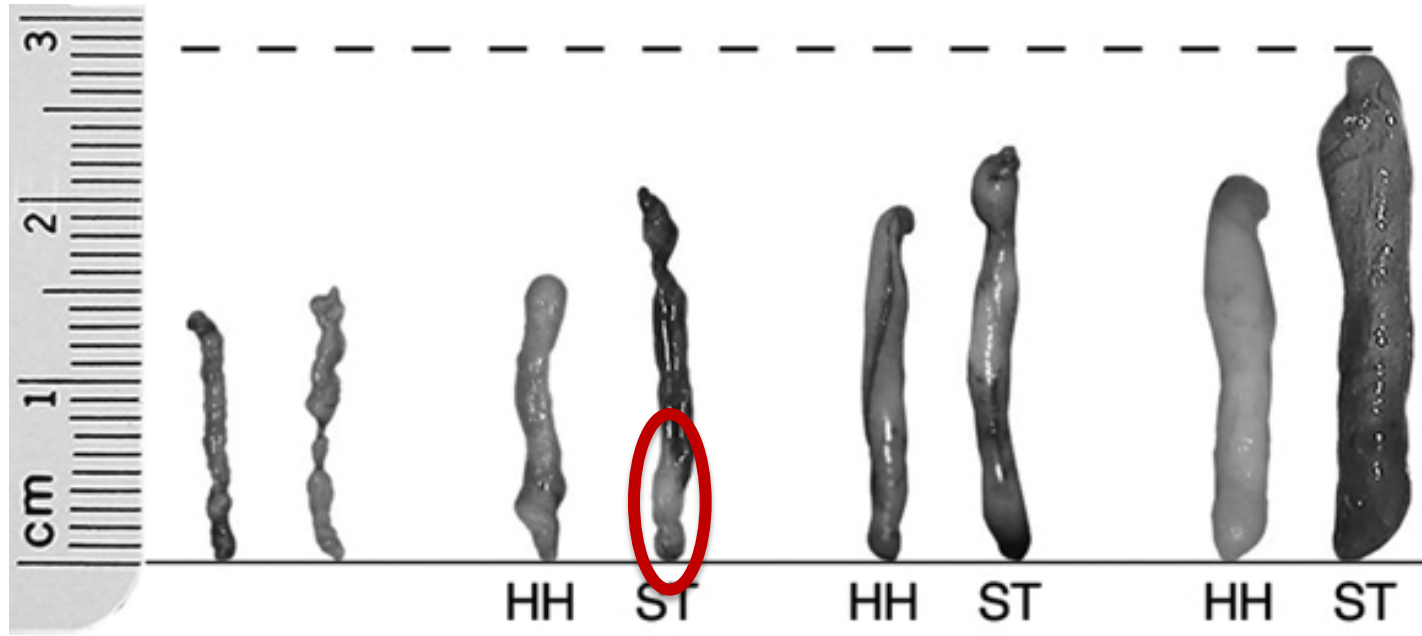
5. Beyond PD-1/PDL-1 to genomics

1. Inadequate Tissue for Testing

- Goal: Optimal tissue for testing (dx, px, tx) with minimal morbidity for patient

Core Needle Biopsy Specimens

18-20 gauge for lung & deep lesions

14 G	14 G	11 G	8 G
HH	ST	HH ST	HH ST

14-gauge conventional core biopsy specimen (12–17 mg)

14-gauge VAB core specimen (35–40 mg)

11-gauge VAB core specimen (83–110 mg)

8-gauge VAB core specimen (250–310 mg)

HH = handheld device. ST = stereotaxic device. VAB – vacuum-assisted biopsy. Photo provided by Johnson & Johnson-Mammotome.

https://www.mja.com.au/journal/2006/184/5/prevention-detection-and-management-breast-cancer

1. Inadequate Tissue for Testing

- Lung biopsies are very small
- Only part of the biopsy may be cancer
- May have few cancer cells due to necrosis, fibrosis or growth pattern of the cancer
- Inflammatory response is variable
- Lung cancers need both IHC & molecular tests
- 4-5 IHCs possible on 18/20-gauge biopsies, but not molecular tests too
- ~50% of biopsies inadequate today

2. IHC Test Validations

- Even FDA-approved tests must be validated for each cancer type by each laboratory (not just LDTs)

- Each IHC validation takes weeks to months

- Need control cancers (10 pos & 10 neg) for each cancer type from archives (search, pull, review)

- Tissue microarray facilitates IHC optimization

- Pathologists & laboratories not paid for test validations

3. Assuring Right Test for Each Drug

- Current Practice: Pathologists order IHC & molecular tests
  - Appropriate for cancer type for diagnosis
  - By protocol with oncologists for care decisions

- Two approaches to PD-1/PDL-1 tests/drugs
  - Know drug being considered by oncologist by case (BAD)
  - Have matrix of IHC tests by drug/cancer type (BETTER)

- If FDA requires test, then antibody, interpretation method & cut-offs required in drug label, plus intended use by cancer type

- CAP include in laboratory accreditation standards

- Pathologist education through CAP, AMP or other organizations

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4. Assuring Test Results Used Correctly

- Current Practice: Pathologists often reluctant to report treatment implications due to push back from oncologists

- Option: Pathologists report test result(s) for specific drug(s), with disclaimer that results not predictive for other PD-1/PDL-1 targeted drugs

- Requires pathologist & oncologist education

- Payers & CAP could influence reporting compliance

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5. Beyond PD-1/ PDL-1 to Genomics

- Many molecular test-drug pairs available or under development

- Inadequate tissue to perform multiple tests for all drugs relevant to each cancer type

- Pathologists can do all molecular tests in one using NGS methods which conserves tissue

- For molecular biomarkers, agree that any test validated to identify the genomic biomarker(s) is acceptable

A Pathologist's Recommendations

1. Promote obtaining adequate tissue for ALL personalized medicine testing

2. FDA require drug label to include all test details, if require testing

3. AACR-ASCO-CAP develop test/drug matrix & reporting guidelines

4. Accreditation standards require reporting compliance with guideline

5. CAP & AACR/ASCO provide pathologist & oncologist education

6. Payers or pharma support test validation expenses

7. Cross-validation done nationally to simplify testing over time (ASCO/CAP)

8. Once a biomarker test approved, FDA require cross-validation for future submissions

9. For molecular biomarkers, agree that any test validated to identify the specific genomic biomarker is acceptable

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Thank You!

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Companion Diagnostics Across a Class of Targeted Therapies:

The PD-1/PD-L1 Case Study

The Biopharmaceutical Perspective

FDA-AACR-ASCO Public Workshop
March 24, 2015

Astra-Zeneca
Bristol-Myers Squibb Company
Merck
Roche / Genentech

Development of PD1/PDL1 Directed Therapy for Patients with Cancer - 1

➢ **Each biopharma company's development of a PD1/PDL1 agent is tailored and informed by clinical experience**

- – Each molecule, while addressing the same pathway, has unique properties

- – The scientific biologic hypotheses are different

- – Each company's development approach is different

- – The patient populations (even within tumor types) under study for market approval are different

Development of PD1/PDL1 Directed Therapy for Patients with Cancer - 2

➢ **The role of "companion" Dx in the context of PD1/PDL1 therapeutic development**

- Each biopharma company has partnered with a Dx company to develop an analytically validated IHC assay measuring PD-L1 expression via the PMA pathway to meet their respective needs

- Purposes of the assay by each company has been informed by clinical experience and may include any or all of the following:

  ▪ Validation (or refutation) for patient selection

  ▪ Patient enrichment as an inclusion criteria

  ▪ Subgroup analysis as a prognostic variable

  ▪ Inform risk-benefit for defined patient populations

Development of PD1/PDL1 Directed Therapy for Patients with Cancer - 3

➤ **The PDL1 Biomarker**

- PD-L1 biology is highly complex

- There are many pre-analytical variables

- IHC precision is inherently limited

- There are many analytical variables

- There are fundamental differences in application of the different assays (e.g. type and timing of biopsy, cell type(s) of interest, scoring method, cut-off, etc.)

Development of PD1/PDL1 Directed Therapy for Patients with Cancer - 4

➢ **Biopharma are committed to delivering the best science and adhere to the highest standards.**

➢ **In this setting, the first step is to help the clinical and testing community understand the comparative analytical performance of each PD-L1 assay under development as in the Proposed Industry Working Blueprint Goal (to be discussed in Session 2):**

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.

Companion Diagnostics Across a Class of Targeted Therapies:

The PD-1/PD-L1 Case Study

The Diagnostic Perspective

FDA-AACR-ASCO Public Workshop
March 24, 2015

Dako
Roche Tissue Diagnostics

Diagnostic Perspective

- Should not slow down approval process for getting potentially impactful drugs to patients

- If approvable, drug and companion diagnostic need to be approved as co-developed today

- Current process driven by unique biologic hypothesis provides safe and effective approach to get innovative drugs to market

Diagnostic Perspective

- Companion Diagnostic IVD Considerations

  - Co-development with pharma
    - 3 to 7 year process
    - Confidential agreements
    - Driven by unique pharma biologic hypothesis
    - Specific intended use population
    - Utilized across number of indications
    - Assay interpretation may be indication specific

Diagnostic Perspective

- Companion Diagnostic IVD Considerations

  - Co-development with pharma molecule
  - Pre-market approval process is appropriate high bar
    - Unique "System" approach
      - Instrument, antibody clone, detection chemistry, interpretation guide
      - Developed together with scoring algorithm and cut-off
      - Analytical Validation of the system
      - Clinical Validation of the system
    - Appropriate Quality System (Design Control)
    - Appropriate Manufacturing Processes/Systems
    - Specific Labeling - Drug/Dx references
    - Adequate processes for commercialization and post-market support (e.g., complaint handling)

Diagnostic Perspective

- Companion Diagnostic IVD Considerations

  - Innovation and cancer biology is complex
  - Desire "Standardized" approach for the lab
  - Training and education on drug and companion diagnostic equally important
  - Post approval studies can help address challenges
  - Appropriate "contamination" – Balance confidential and competition?
  - Simple approach to CDx Class approvals if data warrants?

The looming PD1/PDL1 storm: CDER oncology perspective

Gideon Blumenthal, MD

Clinical Team Leader Lung and Head and Neck Oncology

DOP2-OHOP-CDER-FDA

Pre workshop

Post workshop

March 4, 2015: FDA grants nivolumab regular approval for 2nd line Squamous NSCLC
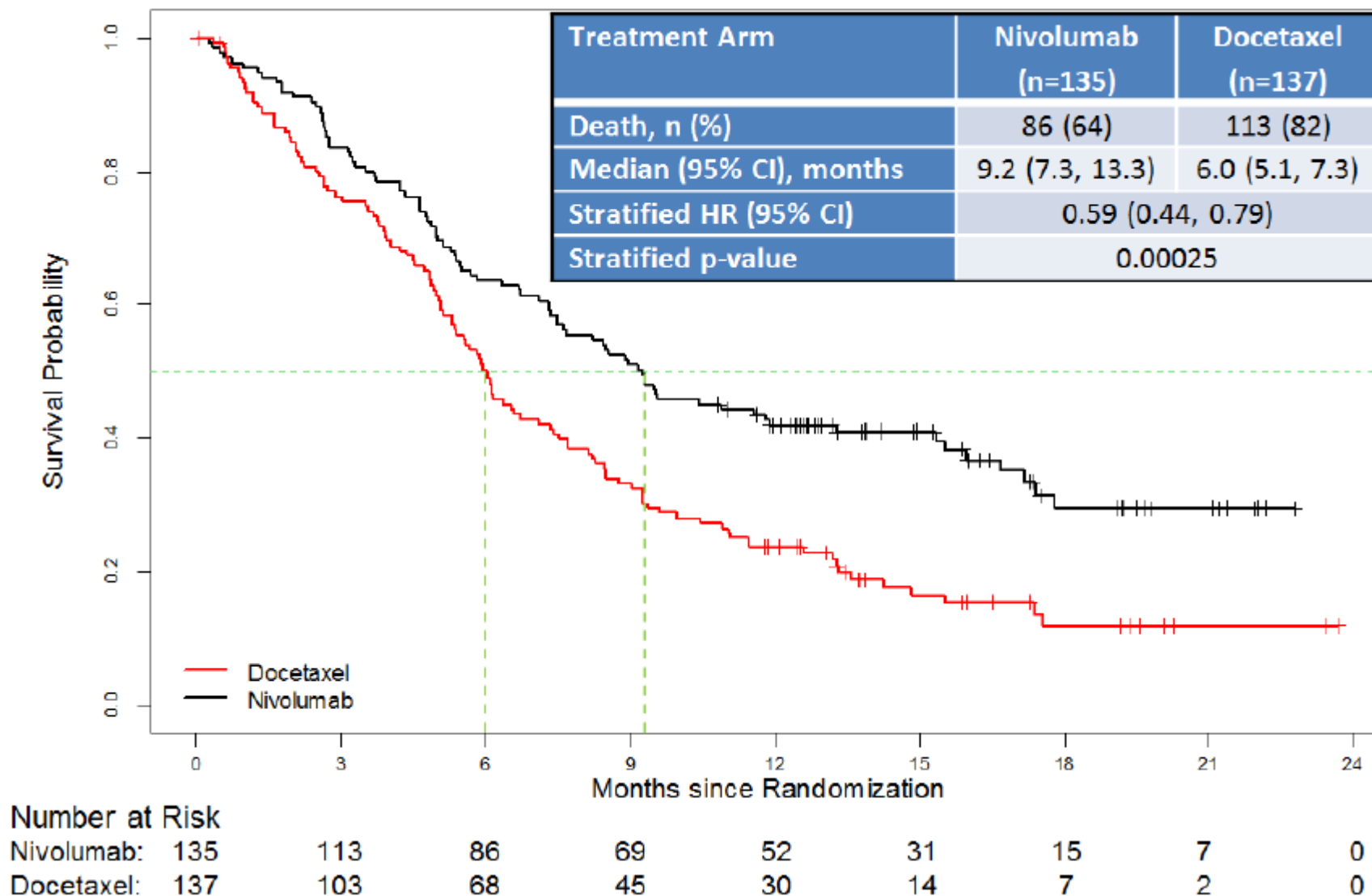
Despite broad approvals in unselected patients, utility PDL1 as a predictive biomarker remains an open question

- All the furthest along PD1/PDL1 inhibitors have ongoing phase 3 trials in various stages of NSCLC with PDL1 enrichment/stratification strategies

- Despite a regular approval in 2nd line SQ NSCLC, accelerated approval still possible for high and durable response rates in biomarker enriched populations (e.g. better than available therapy)

Open Phase 3 trials of PD1 and PDL1 inhibitors in NSCLC

Drug	Target	Phase 3 trial features	Names	
Nivolumab (BMS)	PD1	1st line enriched/ stratified for PDL1, 2nd line not enriched/ stratified	Checkmate	
Pembrolizumab (Merck)	PD1	1st/2nd line enriched, stratified for PDL1	Keynote	
MPDL3280A (Gtech)	PDL1	1st line enriched/ stratified for PDL1, 2nd line stratified PDL1	Oak, Fir, Birch, Poplar	
Medi4736 (Medi)	PDL1	Adjuvant stratified, 3rd line stratified for PDL1	Atlantic, Pacific, Arctic	

PD-L1 IHC in NSCLC (publically available)

Drug	Nivolumab			Pembrolizumab			MPDL3280A			MEDI4736
Assay	28-8			22C3			SP142			SP263
Cells scored	Tumor cell membrane			Tumor cell (and stroma)			Infiltrating immune cells			Tumor cell membrane
Tissue	Archival			Recent			Arch./Recent			Arch./Recent
Setting	1st line	2L ++		1st line	2L ++		2L ++			2L ++
Cut-point	5%	1%	5%	1%	1%	50%	1%	5%	10%	NR
ORR in PD-L1 +	31% N=26	13% N=38	15% N=33	26-47% N=45	19-23% N=177	37% N=41	31% N=26	46% N=13	83% N=6	26% N=47
ORR in PD-L1 -	10% N=21	17% N=30	14% N=35	???	9-13% N=40	11% N=88	20% N=20	18% N=40	18% N=40	10% N=74

NIVO
Topalian, NEJM 2012
Grosso, ASCO 2013, #3016
ASCO 2014, #8112
Rizvi, CSMTO 2014

Pembro
Daud, AACR 2014
Ghandi, AACR 2014
Rizvi, ASCO 2014, #8009
Garon, ESMA 2014

MPDL3280A
Hamid, ASCO 2013, #9010
Herbst, ASCO 2013, #3000
Powderly, ASCO 2013, #3001
Spigel, ASCO 2013, #8008

MEDI4736
Segal, ASCO 2014, #3002
Brahmer, SITC 2014

Key questions moving forward

- Will PDL1 be a necessary predictive/selection biomarker for:
  - Adjuvant? 1st line? 2nd line? Adeno?
  - Combination therapy? Clinical trials?

- How (if at all) will PDL1 assays be used in the clinic?

- Are there better (other) predictive biomarkers than PDL1?

- How will these various PDL1 IHC assays be cross-validated?

Thank you!
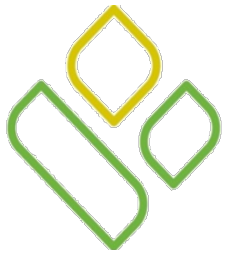
gideon.blumenthal@fda.hhs.gov

FDA-AACR-ASCO Public Workshop:
Complexities in Personalized Medicine
24 March 2015
Girish Putcha, MD, PhD
Director of Laboratory Science

Please note that the opinions expressed herein are my own.

Challenges in Personalized Medicine: A Payer's Perspective

- Coding: For what exactly are we being asked to pay?
  - CPT and/or Z codes (what is the test and/or the lab?) in conjunction with ICD-9/10 diagnosis codes (what is it for?), with any edits are how coverage and payment are effected.
- Coverage: Is this "reasonable and necessary"?
  - For the test
    - "Reasonable" = analytical and clinical validity
    - "Necessary" = "clinical utility" = outcomes
  - For the drug
- Reimbursement: What should we pay?
  - For the test
  - For the drug
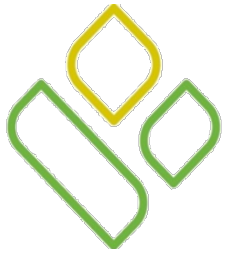
Challenges in Personalized Medicine: A Payer's Perspective

- Should we ensure that the "right" test is performed for the "right" patient (i.e., with the "right" indication), and that the "right" drug is subsequently administered?

- Can we?
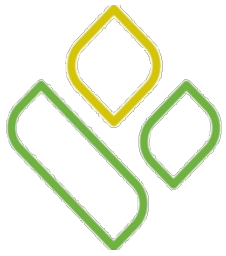
Challenges in Personalized Medicine: A Payer's Perspective

- Coding: Do we need to know the full "chain of custody": What lab? What test? What indication? What drug?

- Coverage:
  - AV: What (ideally) is required to show analytical "comparability"? What is realistic?
  - CV and CU: Can we assume that "comparable" AV = "comparable" CV and CU? Should we? If not, what is required? What is realistic?

- Reimbursement: Should we pay differently (or not at all) if
  - "Wrong" lab?
  - "Wrong" test: "Wrong" CoDx? IVD vs LDT?
  - "Wrong" patient = "wrong" indication (For diagnostic? For drug?)
  - "Wrong" drug
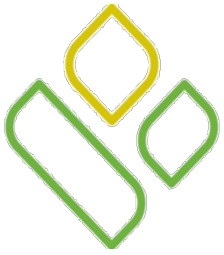
Thank you.

girish.putcha@palmettogba.com

Panel Discussion
Session 1: Defining the Problem

Moderator: Debra Leonard, MD, PhD, University of Vermont Medical Center and College of Medicine

Panelists:

- **Steve Averbuch, MD**, Bristol-Myers Squibb Company
- **Gideon Blumenthal, MD**, CDER, FDA
- **Reena Philip, PhD**, OIR, CDRH, FDA
- **Girish Putcha, MD, PhD**, MolDX, Palmetto GBA LLC
- **Nancy Roach,** Fight Colorectal Cancer
- **Suzanne Topalian, MD**, Johns Hopkins Kimmel Cancer Center
- **Doug Ward**, Ventana Medical Systems, Inc.

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

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 <u>potential</u> 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.

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

High Level Analytical Study Design

- <u>Samples to be tested:</u> no clinical samples from biopharma trials; mix of NSCLC sample types (resections, needle biopsies, etc) and cancer sub-types (squamous, non-squamous) that are representative of target patient populations, assay dynamic ranges, cell types of interest

- <u>Staining of samples:</u> Dx stakeholders (Dako, Ventana) to stain cohort with IUO assays run on clinical trial platforms
  - Minimize logistics, assure expected performance

- <u>Evaluation of samples:</u> stained slides to be evaluated by both Dx company pathologists and independent third party (TBD)
  - Analytical data collection parameters (targets, intensities, frequency of staining, etc) and data analysis plan TBD

- <u>Publication of the results:</u> collaboration between industry stakeholders and third party

Workshop Feedback Invited by Panel

- Comments to the overall proposal?
- Comments to the high level analytical study design?
- What scope of study output and format will add value to the medical community?

Industry Working Group Panel Discussion

Moderator: Debra Rasmussen, Janssen Pharmaceutical

Panelists

- **Steve Averbuch,** Bristol-Myers Squibb Company
- **Kenneth Emancipator,** Merck Research Laboratories
- **Ian McCaffery,** Genentech, Inc.
- **Dave Stanforth,** Agilent Technologies
- **Jill Walker,** AstraZeneca
- **Doug Ward,** Ventana Medical Systems Inc.

FDA

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Making a world of difference in cancer care

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

Panel Discussion Session 2: Comparing the Tests

Moderator: Laura van 't Veer, AACR/ UCSF Helen Diller Family Comprehensive Cancer Center

Panelists:

- **Fred Hirsch,** University of Colorado/ IASLC

- **Elizabeth Hammond,** University of Utah/ CAP

- **Daniel Hayes,** University of Michigan /ASCO

- **Axel Hoos,** GSK/CIC

- **Kenneth Bloom,** GE Healthcare In Vitro Diagnostics

IASLC: PDL-1 CHARACTERIZATION PROJECT ("PCP- Study")

Fred R. Hirsch, MD, PhD

Professor of Medicine and Pathology.

University of Colorado.

CEO; International Association for the Study of Lung Cancer (IASLC)
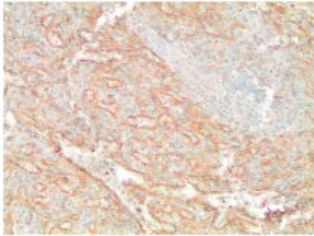
On behalf of IASLC Pathology Committee.

Intra-tumoral PD-L1 expression and response to PD-1/PD-L1 blockade

	Nivolumab Solid Tumors (Topalian et al. NEJM 2012)	Nivolumab Melanoma (Weber ASCO 2013)	Nivolumab Melanoma (Grosso et al. ASCO 2013)	MPDL3280A Solid Tumors (Herbst et al. ASCO 2013)	MPDL3280A Melanoma (Hamid et al. ASCO 2013)	MPDL3280A NSCLC (Soria et al. ECC 2013)	Pembrolizumab Melanoma (Daud et al. AACR 2014)	Pembrolizumab Melanoma (Gandhi et al. AACR 2014)	MPDL3280A Bladder (Powles et al. ASCO 2014)	Pembrolizumab Head & Neck (Seiwert et al. ASCO 2014)	Pembrolizumab Melanoma (Ribas et al. ASCO 2014)
n=	42	44	34	94	30	53	113	129	65	55	411
Response Rates											
Unselected	21%	32%	29%	22%	23%	23%	40%	19%	26%	18%	40%
PD-L1 +	36%	67%	44%	39%	27%	46%	49%	37%	43%	46%	49%
PD-L1 –	0%	19%	17%	13%	20%	13%	13%	11%	11%	11%	13%

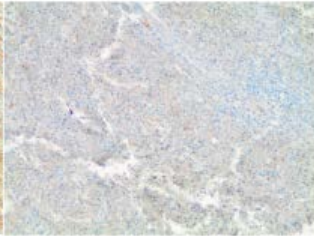*from Callahan: ASCO 2014*

Control in tissue TMA

Cell Signaling   Spring Bioscience

NSCC3 A-7

Cell Signaling   Spring Bioscience

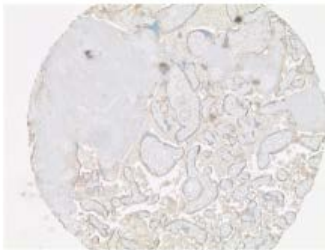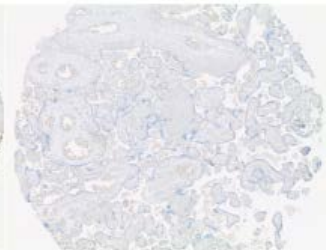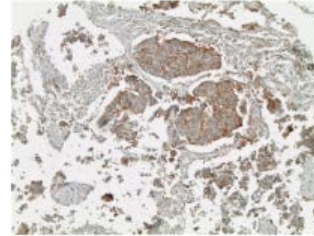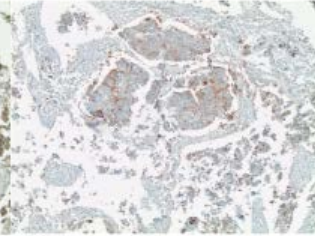Cell Signaling   Spring Bioscience

Cell Signaling   Spring Bioscience

DIFFERENCES IN SPECIFIC AND NON-SPECIFIC STAINING !

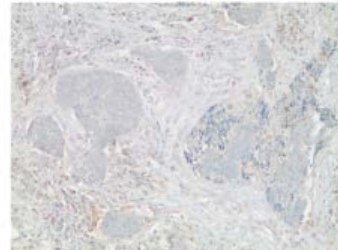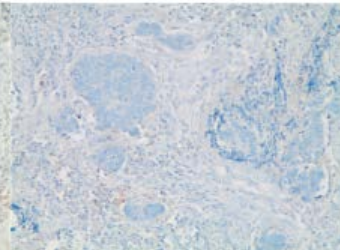# GOALS:

- To achieve a better understanding of the existing IUO PDL-1 assays and their characterization for a global education. (Stage I)

- To produce a **<u>PDL-1 ATLAS</u>** describing the background, feasibility, and comparability of the assays with corresponding illustrations. (Stage II)

- Eventually: To prospectively apply one or more assays to a clinical cohort. (Stage III).

STUDY MECHANISMS

- Establish a "consortium" including representation from IASLC (co-PIs) and representation from each participating industrial partner.

- Steering committee develops protocols and participate in the development of publications coordinated by IASLC.

- Scientific studies will be performed by the IASLC Pathology Panel in collaboration with Dako/Ventana.

IASLC:PDL-1 PROJECT
(proposal to be discussed by steering committee)

- Characterization of different PD-L1 tests applied to same specimens
- Intra- and inter-observer reproducibility (inter-laboratory reproducibility)
- Large specimens vs small specimens vs cytology from same tumors
- Application of the defined predictive scoring algorithms
- Application to different staining platforms
- ATLAS
- Prognostic association based on a well defined cohort ?
- Predictive association : PD1/PDL1 treated pts??

IASLC: PDL-1 PROJECT

- 20 investigators from US, Europe and Asia
- **Study Material:**
- Resected cases (N=100+ cases, further defined after biostatistics consultation)
- Core needle biopsies
- Cytology
- 300-1.000+ NSCLC cases (Prognosis)
- PDL-1/PD-1 Treated Patients ?
- **STAINING:**
- Staining both by DAKO/Ventana resp and local lab after training.
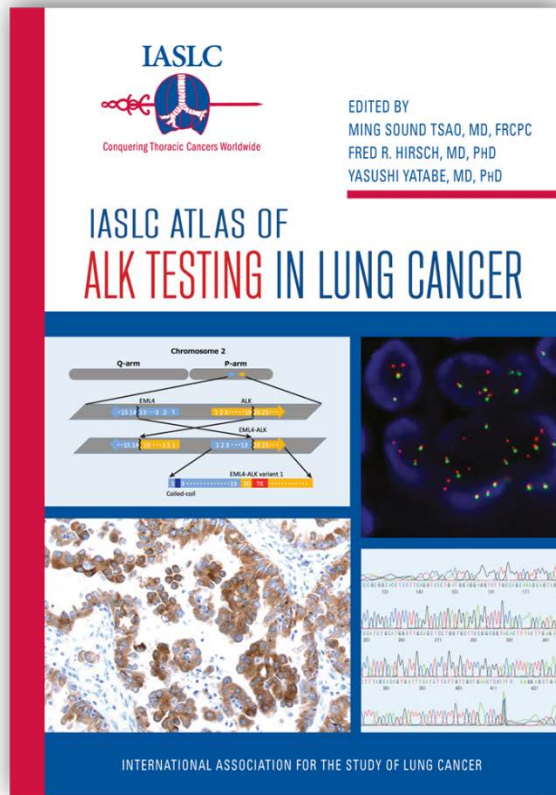
IASLC: PDL-1 Project

Use CDx kits as instructed

- SP142 kit + Ventana platform
- SP263 kit + Ventana platform
- 28-8 kit + Dako (Link 48)
- 22C-3 kit + Dako defined platform

Anticipate what labs might do……….

- Other Staining Platforms:
- Dako/ Ventana
- Leica

PDL- 1 ATLAS SIMILAR TO ALK-ATLAS

TIMELINE

- Stage I+II: 2015 (December 31st.)

- Stage III: ???

IASLC Pathology Panel: Major Accomplishments

2nd Edition of **WHO Classification** of Lung Tumors (1981)	**IASLC/ATS/ERS International multidisciplinary classification** of lung adenocarcinoma. (published in 2011)
3rd Edition of **WHO Histological** typing of lung and pleural tumours (1999)	**CAP/IASLC/AMP guidelines** on EGFR and ALK testing for lung cancer patients. (published in 2013)
WHO Classification of Tumours - Pathology and Genetics, Tumours of the Lung, Pleura, Thymus and Heart (2004)	**IASLC ATLAS of ALK** Testing in lung cancer. (published in 2014)
IASLC/ASCO Workshop on bronchiolo-alveolar carcinoma (2004)	**WHO Classification**: Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart. Fourth Edition (2015)

Elements of Biomarker Testing
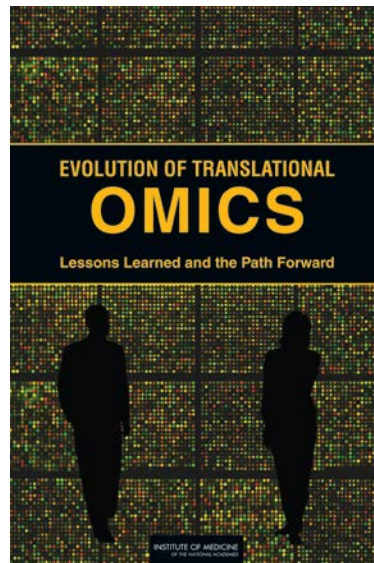
- **Population to be tested***
- **Specimen handling specifics ***
- **Analytic testing ***
  - **Control materials**
  - **Validation of test**
  - **Testing Harmonization**
  - **Analytic performance characteristics**
- **Interpretation criteria***
- **Reporting Requirements***
- **Monitoring Strategy: inspection and proficiency testing**
- **Educational Strategy: lab and pathologist specific**
  - ***Should be evidence based and published widely**

CAP

Overview

Gilbert S. Omenn, MD, PhD
University of Michigan

Evaluation for Clinical Utility and Use

Definitions

- ## Analytical Validity
  - Does the assay accurately and reproducibly measure what you say?

- ## Clinical (or "Biologic") Validity
  - Does the assay actually identify a biologic difference ("pos" vs. "neg") that may or may not be clinically useful?

- ## Clinical Utility
  - Do results of the assay lead to a clinical decision that has been shown with high level of evidence to improve outcomes?

Teutsch S.M., et al. Genet Med. 11:3-14, 2009;
Institute of Medicine. Evolution of translational omics: Lessons learned and the path forward; 2012

Omics-based Biomarker Tests for Cancer

A. Test for Single Analyte

ER Expression

B. Analytical Suite (Panel) of Multiple but Separate Tests for Single Analytes
(Foundation Medicine, Paradigm, others)

| *ER Expression* | *HER2 Amplific'n* | *PIK3CA Mut'n* | *BRAF Mut'n* |

Cancer Abnormality
(DNA, RNA, Protein, Metabolite)

X   X   X   X   X   X   X

C. Algorithm-based Multi-parameter test with Single Score/Result (Signature)

21-gene Recurrence Score

D. Complete Omics Analysis to Detect Individual or Algorithm-based Abnormalities

Complete Next-generation Sequencing of Entire Genome

Undervalue of Tumor BioMarkers: A Vicious Cycle

Marker Utility is Poorly Valued

Poor Reimbursement

Weak Regulatory Environment

Reduced Data Certainty
Higher Scrutiny and Skepticism
Few Recommendations for Clinical Use

Low Funding/Investment for Tumor Marker Research

Lower Academic Prestige

Lower Level of Evidence

Lower Ability and Incentive to Conduct Properly Designed Clinical Studies

Draft Recommended Reforms to Break the Vicious Cycle

- **FDA**
  - **Single Oncology Product Line Review Panel**
  - **Reform or delete Enforcement Discretion of LDTs**
  - **Use Analytical Validity and Clinical Utility for approval**
  - **Insist on Biospecimen bank be established for new drugs and tumor biomarker tests**
- **3rd Party Reimbursement**
  - **Tumor biomarker tests commensurate with value**
- **Tumor Biomarker Test Research**
  - **Raise level of funding = Therapeutic Research**
- **Publication/Journal Editorial**
  - **Adopt and Enforce BRISQ, REMARK, and Registry criteria**
- **Guidelines**
  - **Should be Evidence-Based**

ASCO/CAP Initiatives

- *HER2*
  - Initial (2007)
    - **Established Guidelines/cutoffs**
    - **Established Proficiency Testing**
      - Wolff, et al., J Clin Oncol 25:118-45, 2007
      - Wolff, et al., Arch Pathol Lab Med 131:18-43, 2007
  - Updated (2013-14)
    - **Revised Guidelines/added new information**
      - Wolff, et al., J Clin Oncol 31:3997-4013, 2013
      - Wolff, et al., Arch Pathol Lab Med 138:241-56, 2014
- *ER/PgR*
  - Initial
    - **Established Guidelines/cutoffs**
    - **Established Proficiency Testing**
      - Hammond, et al., Arch Pathol Lab Med 134:e48-72, 2010
      - Hammond, et al., J Clin Oncol 28:2784-95, 2010

Panel Discussion Session 2: Comparing the Tests

Moderator: Laura van 't Veer, AACR/ UCSF Helen Diller Family Comprehensive Cancer Center

Panelists:

- **Fred Hirsch,** University of Colorado/ IASLC
- **Elizabeth Hammond,** University of Utah/ CAP
- **Daniel Hayes,** University of Michigan /ASCO
- **Axel Hoos,** GSK/CIC
- **Kenneth Bloom,** GE Healthcare In Vitro Diagnostics

Panel Discussion Session 3:
Clinical Practice/Education

Moderator: Richard Schilsky, ASCO

Panelists:

- **Edward Kim,** Levine Cancer Institute - Carolinas HealthCare System
- **Stacy Gray,** Harvard Medical School
- **Elizabeth Hammond,** University of Utah/CAP
- **Jane Perlmutter,** Gemini Consulting
- **Michael Kolodziej,** Aetna
- **Daniel Hayes,** University of Michigan/ASCO
- **Jamie Von Roenn,** ASCO

Panel Overview

- Given availability of multiple ways to test for same or similar biomarkers …

- Discuss points of view of stakeholders involved:
  - Community-based clinician
  - Academic-based clinician
  - Pathologist
  - Patient advocate
  - Payer medical director
  - Guidelines panel leader
  - Clinician educator

127

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

KRAS Mutation Testing for Cetuximab (Erbitux)

Indications and Usage Section:

- Single agent, EGFR-expressing mCRC after failure of both irinotecan- and oxaliplatin-based regimens or patients who are intolerant to irinotecan-based regimens. In combination with irinotecan, EGFR-expressing mCRC in patients who are refractory to irinotecan-based chemotherapy.

- Retrospective subset analyses of metastatic or advanced CRC trials have not shown treatment benefit in patients with KRAS mutations in codon 12 or 13. Use of Erbitux not recommended for CRC patients with these mutations.

KRAS testing

- Retrospective analyses done with investigational test
- No KRAS test specified in label

128

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

Testing for Panitumumab (Vectibix)

Indications and Usage:

– EGFR receptor antagonist indicated as a single agent for the treatment of mCRC with disease progression

– Retrospective subset analyses of mCRC trials have not shown a treatment benefit for Vectibix in patients whose tumors had KRAS mutations in codon 12 or 13. Use of Vectibix not recommended for the treatment of colorectal cancer with these mutations

EGFR testing in label

– Detection of EGFR protein expression "necessary for selection of patients." Label references Dako package insert "or other FDA approved kits"

KRAS testing

– Retrospective analyses done with investigational test

– No KRAS test specified in label

129

KRAS Testing

- FDA KRAS companion diagnostic
  – Therascreen KRAS RGQ PCR Kit (IHC)

- McKesson Diagnostics Exchange tests
  – KRAS tests: 56 listed

EGFR Companion Diagnostics

- Cobas® EGFR Mutation Test
  - Erlotinib (Tarceva)
  - Qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations

- Therascreen EGFR RGQ PCR Kit (IHC)
  - Gilotrif (Afatinib)
  - Qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations
  - Safety and efficacy of Gilotrif (Afatinib) have not been established in patients whose tumors have L861Q, G719X, S768I, exon 20 insertions, and T790M mutations, which are also detected by the Therascreen EGFR RGQ PCR Kit. [131]

Initial Questions to Discuss

- What is the intended use of the test?

- How are the results reported/interpreted?

- What action is informed by a positive test or a by a negative test?

- How reliable is the test? What variable can impact the test results?

- How can information about the test be efficiently disseminated (e.g. new approaches to physician education or clinical decision support tools)?

Wrap-up Discussion and Closing Remarks
Workshop Co-chairs

- **Elizabeth Mansfield, PhD**
    - Deputy Director, Personalized Medicine, Office of In Vitro Diagnostics and Radiological Health, CDRH, FDA

- **Richard Schilsky, MD**
    - Chief Medical Officer, ASCO

- **Laura van 't Veer, PhD**
    - Chair, Diagnostics Policy Subcommittee, AACR; Associate Director, Applied Genomics, UCSF Helen Diller Family Comprehensive Cancer Center

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

March 24, 2015