Personalized Healthcare in Oncology:
Past, Present and Future

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November 16th, 2016
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Disclosures

I am an employee of Ventana Medical Systems, Inc., a member of the Roche Group.

I will not be discussing the off-label use of any pharmaceutical or diagnostic products.
Personalized Healthcare in Oncology

Past

Present

Future
Personalized Healthcare

A front row seat

2001-2005: Novartis Oncology

2005-2008: Ventana Medical Systems, Inc.

2008-present: Roche Diagnostics
Personalized Healthcare in Oncology

Past

Present

Future
Traditional treatment paradigm in oncology

One size fits all

Traditional oncology paradigm
Trial and error / one drug fits all

Responder
Non-responder
One size does not fit all
Cancer drugs effective in only 25% of patients

Percentage of population for whom class of drugs do not work

- Antidepressants: 38%
- Asthma Drugs: 40%
- Diabetes Drugs: 43%
- Arthritis Drugs: 50%
- Cancer Drugs: 75%

Spear B et al. Trends in Molecular Medicine May 2001
Broken drug development model
Increased spending, decreased output

PhRMA 2012 Pharmaceutical Industry Profile
New era of personalized healthcare
Herceptin (1998) and Gleevec (2001)
Personalized healthcare model in oncology

Biomarker-based identification of responders

Traditional oncology paradigm
Trial and error/one drug fits all

Targeted therapy

Companion diagnostics

Responder

Non-responder

Personalized healthcare
“The right drug for the right patient”
Personalized healthcare

Definitions

- Disease risk (E.g. BRCA)
- Prognosis/risk of recurrence (E.g. Oncotype dx)
- Drug response prediction (E.g. Her2)
- Disease monitoring (E.g. Ca125)
- Pharmacogenetics (E.g. Cyp450 genotyping)

A form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.
2005: personalized healthcare paradigm questioned
Short-term fad or long-term sustainable model in oncology?

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Companion Diagnostic</th>
<th>Drug Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>HER2</td>
<td>1998 (metastatic breast cancer)</td>
</tr>
<tr>
<td>Imatinib (Glivec®)</td>
<td>KIT</td>
<td>2001 (CML)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2002 (advanced GIST)</td>
</tr>
<tr>
<td>Erlotinib (Tarceva®)</td>
<td>EGFR mutations</td>
<td>2004 (advanced NSCLC)</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>KRAS mutations (negative predictor)</td>
<td>2004 (advanced colorectal cancer)</td>
</tr>
</tbody>
</table>
Personalized healthcare was not a fad

Steady increase in targeted therapy FDA approvals

Masters et al. JCO 2015 “Clinical Cancer Advances 2015 Annual Report on Progress Against Cancer from ASCO”
## Personalized healthcare widespread adoption

**Explosion in drug:diagnostic co-development**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>#Drugs</th>
<th>Drug(s)</th>
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<tbody>
<tr>
<td>erbB</td>
<td>1</td>
<td>Canertinib</td>
</tr>
<tr>
<td>FGFR</td>
<td>4</td>
<td>AZD-4547 BGJ-398 dovitinib lactate FP-1039</td>
</tr>
<tr>
<td>FLT3</td>
<td>4</td>
<td>KW-2449 lestaurtinib quizartinib dihydrochloride tandutinib</td>
</tr>
<tr>
<td>folate recp</td>
<td>2</td>
<td>EC-145 farletuzumab</td>
</tr>
<tr>
<td>GPC3</td>
<td>1</td>
<td>GC-33</td>
</tr>
<tr>
<td>GPNMB</td>
<td>1</td>
<td>Glembatumumab vedotin</td>
</tr>
<tr>
<td>HER2</td>
<td>8</td>
<td>ARRY-380 CP-724714 ertumaxomab lapatinib mubritinib neratinib pertuzumab TD-M1</td>
</tr>
<tr>
<td>HLA-A2</td>
<td>1</td>
<td>ALT-801</td>
</tr>
<tr>
<td>Met</td>
<td>3</td>
<td>EMD-1214063 onartuzumab SGX-523</td>
</tr>
<tr>
<td>N-cadherin</td>
<td>1</td>
<td>E-caderin</td>
</tr>
<tr>
<td>NPC-1C</td>
<td>1</td>
<td>Ensituximab</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>1</td>
<td>CDX-1401</td>
</tr>
<tr>
<td>PDGFR</td>
<td>2</td>
<td>Crenolanib olaratumab</td>
</tr>
<tr>
<td>PgR</td>
<td>1</td>
<td>Lonaprisan</td>
</tr>
<tr>
<td>Ph+</td>
<td>8</td>
<td>Bosutinib dasatinib DCC-2036 imatinib IY-5511 nilotinib omacetaxine mepesuccinate ponatinib</td>
</tr>
<tr>
<td>PI3K</td>
<td>2</td>
<td>BEZ-235 BKM-120</td>
</tr>
<tr>
<td>RAAG12</td>
<td>1</td>
<td>RAV12</td>
</tr>
<tr>
<td>somatostatin</td>
<td>1</td>
<td>177-Lu-DOTA-oct</td>
</tr>
<tr>
<td>TA-MUC1</td>
<td>1</td>
<td>GT-MAB 2.5-GEX</td>
</tr>
<tr>
<td>TdT</td>
<td>1</td>
<td>Cordycepin</td>
</tr>
<tr>
<td>testosterone</td>
<td>3</td>
<td>Abiraterone acetate degarelix orteronel</td>
</tr>
<tr>
<td>TS</td>
<td>1</td>
<td>Thymectacin</td>
</tr>
</tbody>
</table>

121 oncology drugs with stratification biomarkers in development

Hayashi K et al. Clin Pharm Ther. 2012 Oct 11
Second Wave of Personalized Healthcare
Drug and Diagnostic Combinations Continue

**2011**

**ZELBORAF** (vemurafenib)
Approved in US for people with BRAF V600E mutated metastatic melanoma

**2011**

**XALKORI** (crizotinib)
Approved for patients with locally advanced or metastatic NSCLC that are ALK-positive.

**BRAF test**
- Roche cobas 4800 BRAF V600 Mutation Test
- Identifies patients with BRAF V600E mutations
- BRAF is mutated in approximately ½ of late-stage melanomas

**ALK test**
- Vysis ALK Break-Apart FISH Probe Kit
- Identifies patients with ALK positive NSCLC
- Approx 3% to 5% of NSCLC patients have an ALK-positive tumor
Personalized Healthcare in Oncology

Past

Present

Future
Personalized healthcare benefits

Acceleration of drug development and approval timelines

- BCR-ABL inhibition (imatinib) 1960-2001: 41 yrs
  - Targeted therapy with BCR-ABL inhibition (trastuzumab) 1985-1987: 13 yrs
  - BRAF inhibition (vemurafenib) 2002: 10 yrs
  - ALK inhibition (crizotinib) 2007: 4 yrs

Adapted from Chin L et al. Nature Medicine March 2011
Reduced attrition rates in drug development

Targeted therapy increases success from phase 1 to registration

Phase I-Registration transition probability
all oncology drugs vs. kinase inhibitors

Molecular reclassification of disease
Paradigm shift in how we understand and treat non-small cell lung cancer (NSCLC)

Driver mutations in NSCLC 2000

- Treatment: platinum doublet chemotherapy
- Response rate: 10-20%

Driver mutations in NSCLC Today

- Treatment: Targeted therapies matched to molecular defects (e.g. EGFRmut, ALK, RAS)
- Response rate: 50-70%

Continued paradigm shift in disease classification
From anatomic origin to molecular driver events

Breast  Prostate  Colon  Lung  Brain

PIK3CA  BRAF  HER2  EGFR  KIT
Companion Diagnostics
Diagnostic tests required for drug selection and use

Patient information shown is for illustrative purposes only
Tissue Diagnostics Pre-PHC
Primarily focused on diagnosis

**H&E** + **IHC/ISH**

**Diagnosis**
- Malignant
- Benign
- Morphologic classification
Tissue Diagnostics Post-PHC
Delivering critical treatment guiding information

H&E + IHC/ISH + Molecular Profiling
Identification of Drug Targets, Resistance Mechanisms, Immune Checkpoints and Heterogeneity

Treatment guiding information

Diagnosis
- Malignant
- Benign
- Molecular classification

Prognosis
- Risk of recurrence
- Need for adjuvant chemotherapy

Therapy prediction
- Response
- Resistance
- Rational combo tx
Personalized healthcare challenge #1
Inevitable drug resistance with all targeted therapies

Initial response (1-2 yrs)

Recurrence

Multiple molecular mechanisms of resistance
“Acquired” resistance mechanisms in cancer
Acquisition or selection?

Mechanism appears to be selection of rare pre-existing tumor clones

Translational lung cancer research, Vol 4, No 6 December 2015
Resistance Through Evolution of Genomic Driver Mutations

Molecular ‘Whac-A-Mole’
Personalized healthcare challenge #2

Tumor heterogeneity

Intra-tumoral spatial heterogeneity
Renewed appreciation of tumor heterogeneity
Swanton et al. 2012

Gerlinger, Swanton et al. NEJM 366;10 (2012)
Intra-tumor heterogeneity in renal cell carcinoma
65% of mutations not present in every biopsy

Gerlinger, Swanton et al. NEJM 366;10 (2012)
Branched evolution heterogeneity map
Molecular history of a tumor

Gerlinger, Swanton et al. NEJM 366;10 (2012)
Branched evolution heterogeneity map

Differential mTOR protein expression

Branch length proportional to number of NS mutations from branch point

Gerlinger, Swanton et al. NEJM 366;10 (2012)
Branched evolution in lung cancer
Long vs. short trunks
Intra-tumoral heterogeneity and predicting outcome

Myeloma subclone determining final outcome: <1%

Intra-tumoral heterogeneity
Diversity enables Darwinian evolution and selection

Charles Darwin - July 1837 - 1st sketch of evolutionary tree
Tumor heterogeneity in the news
Threatens PHC approach

Intratumor Heterogeneity Poses Challenge for Cancer “Moonshot” Program

Personalized Medicine Remains the Ultimate Goal

Patricia Fitzpatrick Dimond, Ph.D.

Previous assumptions of tumor homogeneity incorrect
Implications for tumor sampling procedures
Previous assumptions of tumor homogeneity incorrect
Implications for tumor sampling procedures
PHC Challenge #3
Evolving Diagnostics Regulatory Landscape

Is Lab Testing the ‘Wild West’ of Medicine?
Largely unregulated industry comes under FDA scrutiny; lab-developed test providers fight back

FDA Says More Regulation Needed on Lab Tests
Certain laboratory-developed tests, or LDTs, cause patients harm with erroneous results, agency says; congressional hearing

[Image of laboratory and FDA offices]
US FDA Diagnostic Registration Process

- Diagnostic registration:
  - Regulated by FDA Center for Devices and Radiological Health (CDRH)
  - Driven by a risk-based classification of the product
  - Different levels of controls and length/expense of registration process

- Final designation of the product determines how a product is labeled and marketed (i.e. “claims”)

<table>
<thead>
<tr>
<th>Product Class</th>
<th>ASR</th>
<th>RUO</th>
<th>IUO</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>Very limited</td>
<td>Clinical trials</td>
<td>Limited</td>
<td>510K</td>
<td>PMA</td>
<td></td>
</tr>
<tr>
<td>premarketing requirements</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

- Must label “Not for clinical use”
  - Cannot market for clinical applications
- Must label “Investigational Use Only”
  - Cannot market

- In-vitro diagnostics

- Companion Diagnostics
Companion Diagnostic Development
Parallel Development of Drug and Diagnostic
A Tale of Two Diagnostics
In Vitro Diagnostics (IVDs) & Lab Developed Tests (LDTs)

IVD

Lab Developed Tests
1) Commercially Distributed Test Pathway:
   “test kit” manufactured for distribution to multiple labs

2) Lab Developed Test (LDT) Pathway:
   Test designed, manufactured, and used in a single lab

LDT

# A Tale of Two Diagnostics

**In Vitro Diagnostics (IVDs) & Lab Developed Tests (LDTs)**

<table>
<thead>
<tr>
<th>Development, distribution and usage</th>
<th>In Vitro Diagnostic (IVD)</th>
<th>Laboratory-Developed Test (LDT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally developed for wide (e.g. global) distribution and use</td>
<td>Designed, manufactured and used in a single lab (initial intent)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regulatory Authority</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>FDA, but provisions were historically not enforced. Lab quality regulated under CLIA; Draft FDA guidance issued 2014</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Review process</th>
<th>Premarket clearance or approval required</th>
<th>Analytical validation reviewed biennially; often after test already in use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicant validation requirements</td>
<td>Analytic Validity Clinical Validity</td>
<td>Analytic Validity Clinical Validity</td>
</tr>
</tbody>
</table>

IVD Regulation

• Through the 1976 Medical Device Amendments to the FFDCA, FDA has the authority to regulate all in vitro diagnostics (IVDs) as devices, including laboratory tests, regardless of whether they are developed and manufactured by a laboratory or a conventional device manufacturer.

• FDA has generally exercised enforcement discretion (i.e., generally not enforced applicable provisions under the FFDCA and FDA regulations) for Laboratory Developed Tests (LDTs), which FDA defines as:

  an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory.

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm
Public Health Need for Greater Oversight

- Evolution of LDT technology, marketing, and business models has:
  - Increased risk associated with LDTs
  - Created gaps in LDT Oversight

- Consequences
  - Significant adverse health consequences
  - Unnecessary healthcare costs
  - Could undermine progress of personalized medicine, which depends on tests that work

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm
FDA Levels the Diagnostics Playing Field
Warning Letter to 23 & Me, November 2013

Genetic Test Service 23andMe Ordered to Halt Marketing by FDA
Regulators Cite Risk of False Results, Unnecessary Health Procedures

23andMe, Inc. 11/22/13

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Dear Ms. Wojcicki,

The Food and Drug Administration (FDA) is sending you this letter because you are marketing the 23andMe Saliva Collection Kit and Personal Genome Service (PGS) without marketing clearance or approval in violation of the Federal Food, Drug and Cosmetic Act (the FD&C Act).

Stop selling those DNA tests, FDA tells 23andMe
Maggie Fox, NBC News
Nov. 25, 2013 at 10:39 AM ET

Forbes
Matthew Herper, Forbes Staff
I cover science and medicine, and believe this is biology’s century.
+ follow (11,150) 0 follow 0.8k

PHARMA & HEALTHCARE | 11/29/2013 @ 3:15PM | 596,057 views
23andStupid: Is 23andMe Self-Destructing?

23andMe raises questions about at-home genetic testing
By Jacqui separator Wilson, CNN
updated 3:46 PM EDT, Tue November 20, 2013

CNN Health
FDA Draft Guidance
Framework for Regulatory Oversight of LDTs

- October, 2014: draft Guidance: “Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs).”
  - A risk-based approach: Class I, II, III – start with high risk tests and phase in enforcement over time (9 years).

6 months
Notification completed and/or registration, listing, and adverse event reporting

12 months
Pre-market review for initial high risk (class III) devices

24 months
Priority list for remaining high risk (class III) devices with submission starting 12 months later

4 years
FDA releases priority list for moderate risk (class II) devices

5 years
FDA completes phased-in enforcement of premarket review for class III & begins class II phase-in

9 years
Moderate risk LDTs phased-in

Exceptions
- Low-risk LDTs
- Traditional LDTs: manufactured and used by a single health care facility
- Rare diseases (<4,000 patients/year)
- LDTs for unmet needs: no FDA cleared/approved IVD available
Public Health Evidence for FDA Oversight of LDTs
20 Case Studies

- November, 2015 – FDA presented 20 case studies of LDTs that it believes may have caused or could cause harm to patients.

Future Of LDT Oversight Still Uncertain
CAP and AMP Counter-proposals

AACC recently released a position statement on CLIA calling for CMS, not FDA, to be responsible for LDT oversight.

Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP), are advocating an alternate approach to oversight of LDTs that would build on the existing CLIA framework.

FDA is moving ahead with plans to issue a final guidance in 2016, said Eric Pahon, an FDA spokesperson.
Socioeconomic Impact of Inaccurate HER2 IHC Testing of Breast Cancer

FDA-approved IVDs compared with Lab-developed IVDs for HER2

- Study analyzed HER2 testing accuracy (False -/+ rates) using data from the Nordic Immunohistochemistry Quality Control (NordiQC) HER2 IHC program

- Results were used in an economic breast cancer treatment model to estimate direct costs, loss of survival, productivity benefit and quality-adjusted life-years (QALYs).

Socioeconomic Impact of Inaccurate HER2 IHC Testing of Breast Cancer

Study methodology

- Cost calculator/modeling tool
  - Consequences of false-positive/negative HER2 results
  - Patient outcomes based on 232,340 patients with invasive breast cancer in USA 2013
  - Direct medical costs
    - Societal perspective adopted using US costs
  - Life expectancy
    - Survival calculations: NSABP study B31, North Central Cancer Treatment Group trial N9831 studies (EBC), H0648g phase3 study (MBC)
    - Quality of life: Quality- adjusted Life Years (QALYs)
  - Loss of productivity- based on QALYs

Socioeconomic Impact of Inaccurate HER2 IHC Testing of Breast Cancer

Examples of Optimal Staining and False Negatives/Positives

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
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<tbody>
<tr>
<td><img src="image1" alt="Staining" /></td>
<td><img src="image2" alt="Staining" /></td>
<td><img src="image3" alt="Staining" /></td>
<td><img src="image4" alt="Staining" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab 1</th>
<th>HER2 3+ Positive</th>
<th>HER2 2+ Equivocal</th>
<th>HER2 1+ Negative</th>
<th>HER2 0 Negative</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lab 2</th>
<th>False Negative</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lab 3</th>
<th>False Positive</th>
</tr>
</thead>
</table>

Socioeconomic Impact of Inaccurate HER2 IHC Testing
LDTs Associated with Higher False Negative and False Positive Rates with Impact to Recurrence, Survival and QALYs

False Negative and False Positive Rates for IHC testing (NordiQC)

<table>
<thead>
<tr>
<th></th>
<th>LDT HER2 IHC Test</th>
<th>FDA-Approved HER2 IHC Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>False Positive</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Recurrence/progressions due to incorrect test results

<table>
<thead>
<tr>
<th></th>
<th>FDA-Approved IVD</th>
<th>Lab developed IVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>217 yrs</td>
<td></td>
</tr>
<tr>
<td>MBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>109 yrs</td>
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Missed gain in life expectancy

<table>
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<tr>
<th></th>
<th>FDA-Approved IVD</th>
<th>Lab developed IVD</th>
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</thead>
<tbody>
<tr>
<td>EBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>226 yrs</td>
<td></td>
</tr>
<tr>
<td>MBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>273 yrs</td>
<td></td>
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</table>

QALYs lost

<table>
<thead>
<tr>
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<th>FDA-Approved IVD</th>
<th>Lab developed IVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>193 yrs</td>
<td></td>
</tr>
<tr>
<td>MBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 yrs</td>
<td></td>
</tr>
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</table>

# Economic Costs of Inaccurate HER2 IHC Testing

$46M in additional costs associated with LDT

<table>
<thead>
<tr>
<th></th>
<th>Cost US$</th>
<th>FDA-approved IVD</th>
<th>Lab-developed IVD</th>
<th>Additional Cost Associated with LDT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Stage Breast Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct cost/patient</td>
<td>364</td>
<td>1394</td>
<td>1030</td>
<td></td>
</tr>
<tr>
<td><strong>Total direct costs</strong></td>
<td>14,447,666</td>
<td>55,377,720</td>
<td><strong>40,930,054</strong></td>
<td></td>
</tr>
<tr>
<td>Cost of lost productivity/patient</td>
<td>83</td>
<td>190</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td><strong>Total cost of lost productivity</strong></td>
<td>3,301,263</td>
<td>7,546,231</td>
<td><strong>4,244,968</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Metastatic Breast Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct cost/patient</td>
<td>176</td>
<td>1228</td>
<td>1052</td>
<td></td>
</tr>
<tr>
<td><strong>Total direct costs</strong></td>
<td>859,446</td>
<td>5,992,471</td>
<td><strong>5,133,025</strong></td>
<td></td>
</tr>
<tr>
<td>Cost of lost productivity/patient</td>
<td>52</td>
<td>120</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td><strong>Total cost of lost productivity</strong></td>
<td>255,594</td>
<td>586,221</td>
<td><strong>330,627</strong></td>
<td></td>
</tr>
</tbody>
</table>

Economic Costs of Inaccurate HER2 IHC Testing

IVDs more expensive initially but usage results in net savings to healthcare system

• More expensive initial outlay for approved vs. laboratory-developed IVD tests (LDTs)
  – $45 vs $10 assumed in current study

• Additional direct costs resulting from false-positive and false-negative test results are significantly higher for LDTs

• “Use of approved rather than laboratory-developed IVD tests could result in a savings of approximately $46 million.”
  – “Every $1 saved by labs by using cheaper reagents could potentially result in approximately $6 additional costs to the healthcare system”
  – Overall cost of using a LDT is 2.5x greater than using an approved IVD

FDA Regulation of Next-Generation Sequencing (NGS) February 25th, 2016 Public Workshop

Outline

- Background
- Scope
- Hypothetical Case
- Workshop Discussion Topics
  - Potential general intended use
  - Pre-analytical and quality metric approaches
  - Analytical validation, bioinformatics, and post-approval assay modifications
  - Clinical and follow-on companion diagnostic claims

http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM488271.pdf
Challenges for NGS-based Oncology Panels

- What genes and associated variants should be included in the panel? How to qualify a gene/variant for inclusion?
- Limitation on reporting? Pre-defined reporting vs. de novo reporting
- Unit of validation: specimen source, analyte type, specific gene variants, specific exons, variant categories, genomic landscape?
- What is the most difficult unit(s) to validate?
- Somatic vs. germline: based on allelic frequency? Compared to matched blood?

http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM488271.pdf
FDA Regulation of Next-Generation Sequencing (NGS) February 25th, 2016 Public Workshop

Hypothetical Case:
Elements of a 10-gene NGS-based Oncology Panel

- FDA is considering entire test system validation
  - From specimen collection, sample preparation down to the individual steps in the sequencing pipeline, and to the generation of result report
- Validation studies should be designed to demonstrate the performance characteristics of the device within the context of the intended use population

http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM488271.pdf
FDA Regulation of Next-Generation Sequencing (NGS) - February 25th, 2016 Public Workshop

- Potential intended use statement with table listing variants with established use as companion diagnostics.

http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM488271.pdf
FDA Regulation of Next-Generation Sequencing (NGS) Public Workshop

February 25th, 2016

- Potential analytical results table for variants where safe and effective use has not been established for selecting therapy

http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM488271.pdf
• Adaptive approach to regulating NGS-based tests is part of the FDA’s engagement in the Precision Medicine Initiative (PMI)

• For rare hereditary diseases (not somatic tumor testing), and addresses the potential for using FDA-recognized standards to demonstrate analytical validity

• Approach where test developers may rely on clinical evidence from FDA-recognized public genome databases to support clinical claims

PHC Challenge #4: Diagnostics are Undervalued

Diagnostic tests inform 60% of clinical decisions, but make up <2% of healthcare spend

The Value Of Diagnostics

Diagnostics are:
<2% Total Worldwide Healthcare Spend

Diagnostics Influence:
>60% of Critical Decision Making

Source: DxInsights White Paper January 2012
Personalized Healthcare – Payer Perspective

Payer’s Concerns

• Cost of testing many individuals to identify the few who could benefit

• Uncertainty regarding clinical- and cost-effectiveness – particularly linkage of diagnostic tests to health outcomes

• Coding issues: Code stacking versus test-specific codes reflective of value
### PHC Coding Challenges and Opportunities

#### Code stacking vs. test-specific codes

**BCR/ABL-t(9;22) by RT PCR (Quantitative)**

**Indication for use:** Gleevec monitoring for CML (leukemia)

<table>
<thead>
<tr>
<th>2011 CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83891 (2)</td>
<td>Extraction of highly purified nucleic acid</td>
</tr>
<tr>
<td>83892 (2)</td>
<td>Enzymatic digestion</td>
</tr>
<tr>
<td>83896 (4)</td>
<td>Nucleic acid probe(s)</td>
</tr>
<tr>
<td>83902 (2)</td>
<td>Mutation scanning by physical properties</td>
</tr>
<tr>
<td>83912</td>
<td>Interpretation and report</td>
</tr>
</tbody>
</table>

**UGT1A1 Testing for Colorectal Cancer**

**Indication for use:** Irinotecan monitoring for colorectal cancer

<table>
<thead>
<tr>
<th>2011 CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83891</td>
<td>Extraction of highly purified nucleic acid</td>
</tr>
<tr>
<td>83892 (7)</td>
<td>Enzymatic digestion</td>
</tr>
<tr>
<td>83896 (12)</td>
<td>Nucleic acid probe(s)</td>
</tr>
<tr>
<td>83903 (4)</td>
<td>Mutation scanning by physical properties</td>
</tr>
<tr>
<td>83908 (4)</td>
<td>Signal amplification of patient nucleic acid</td>
</tr>
<tr>
<td>83912</td>
<td>Interpretation and report</td>
</tr>
</tbody>
</table>

**2012 CPT CPT 81206 BRC/ABL MAJOR/MINOR/OTHER BREAKPOINTS**


The conversion of stack CPT codes to specific codes will improve ability to track utilization, enable decision support tools, and enforce coverage policy.
Coverage of Companion Diagnostics

Reimbursement landscape must evolve to keep pace with the increasingly complex PHC/CDx environment

<table>
<thead>
<tr>
<th>Reimbursement</th>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Medicare reimbursement of companion diagnostics is reported to be <strong>limited</strong> and <strong>highly variable</strong>¹</td>
<td>• Most complex molecular tests have <strong>no specific CPT codes</strong>²</td>
</tr>
<tr>
<td>– Drugs may be reimbursed while their CDx is not</td>
<td>• Traditional “<strong>stacked coding</strong>” does not describe actual assay</td>
</tr>
<tr>
<td>– Documentation of CDx prior to prescribing is rarely required</td>
<td>• <strong>MolDx system</strong>: Instituted in 2011 by Palmetto, a Medicare Part B contractor, to identify and establish coverage and reimbursement for molecular diagnostic tests³</td>
</tr>
<tr>
<td>• <strong>Value-based reimbursement</strong> has been proposed to incentivize development and use of tests that improve patient outcomes</td>
<td></td>
</tr>
</tbody>
</table>

Palmetto GBA Molecular Diagnostic Program (MoLDX)

Test-specific Z-Code identifiers

- Clinical Laboratory Fee Schedule pricing methodology does not account for the unique characteristics of molecular diagnostic tests (MDTs) and LDTs.

- Palmetto GBA’s MoLDX Program strives to create a consistent approach to coverage and pricing decisions for MDTs and LDTs.

- MoLDX Program requires laboratories to obtain a test-specific identifier – i.e., a Z-Code Identifier – that is unique to the laboratory’s specific test.

- When reported in conjunction with the appropriate CPT/HCPCS code, the Z-Code Identifier allows payers to determine the exact test that has been performed, facilitating the process of making pricing and/or coverage determinations.

Patient Selection Strategy is Key in PHC Era
CDx Cut-Offs Impact Payor and Regulatory Acceptance

Companion Diagnostic Cut-Off

Increasing patient population
Increasing probability of regulatory approval and payor coverage

Even if health authorities approve an all-comer label payors may restrict to Dx-selected population
Patient Selection Strategy is Key in PHC Era

The New York Times

Immunotherapy Drug Opdivo Fails Clinical Trial to Expand Use

Timothy Anderson, an analyst at Sanford C. Bernstein & Company, said that Bristol-Myers might have "pushed the envelope too far in designing its trial." Hoping to broaden the population eligible for treatment, it set the cutoff value for PD-L1 levels too low.

“They likely made it too broad, meaning they enrolled patients with too little PD-L1 expression, and this soured the overall analysis,” he wrote in a note Friday. Merck, he said, studied a narrower population.
Reimbursement and Regulatory Policy Imperatives
Re-balancing the value equation & bringing certainty

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Proposed Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reimbursement currently based on activity, not value</td>
<td>Create new reimbursement system that rewards value</td>
</tr>
<tr>
<td>Lack of harmonization of standards for demonstrating clinical utility</td>
<td>Create clear, unified clinical utility proof standards to capture enhanced value</td>
</tr>
<tr>
<td>Uncertainty regarding regulatory oversight for lab developed tests</td>
<td>Create certainty through timely regulatory framework and transparent implementation</td>
</tr>
<tr>
<td>Lack of published outcomes and health econ data regarding impact of Dx</td>
<td>Cross industry research groups</td>
</tr>
<tr>
<td>Not enough resources or new regulatory expertise relating to diagnostics</td>
<td>Create a new FDA Center for Advanced Diagnostics Evaluation and Review (CADER)</td>
</tr>
</tbody>
</table>
The future of personalized healthcare
Match driver mutations to targeted therapy drugs

Cancer Driver A
Drug A

Cancer Driver B
Drug B

Cancer Driver C
Drug C

Cancer Driver D
Drug D
Immunotherapy in the headlines
Science breakthrough of the year 2013
Immunotherapy in the mass media
New York Times

Harnessing the Immune System to Fight Cancer

New drugs and methods of altering a patient's own immune cells are helping some cancer patients — but not all — even when standard treatments fail.

By DENESE GRADY  JULY 30, 2016

Metastatic Melanoma Response to Ipilimumab

Before Ipilimumab
04/22/11

After Ipilimumab
08/05/11

Case by Antoni Ribas, MD, PhD.
http://www.slideshare.net/roblyngold/community-oncology-clinical-debates-advanced-melanoma
Unique Kinetics of Response in Patients Treated With Ipilimumab

Screening

Week 12: Swelling and Progression

Week 12: Improved

Week 16: Continued Improvement

Week 72: Complete Remission

Week 108: Complete Remission

Images courtesy of Jedd D. Wolchok, MD.  http://www.slideshare.net/roblyngold/community-oncology-clinical-debates-advanced-melanoma
Immunotherapy in the mass media

New York Times

Immunotherapy Clinical Effect
Jason Greenstein, lymphoma patient

Shrinking a Tumor
After years of chemotherapy and radiation treatment, Jason Greenstein tried an immunotherapy drug called nivolumab. Within weeks his Hodgkin's lymphoma tumors had disappeared.

Theoretical immunotherapy advantages
Adaptability, Broad Activity, Combinations

- Immune adaptability and memory offers potential for long-term survival
- Targeting the immune system, not the tumor, offers potential for activity across multiple tumor types
- Unique MOA offers opportunity for combination

Potential to Improve Clinical Outcome
The cancer-immunity cycle
How the immune system fights cancer

1. Release of tumor antigens
2. Presentation of tumor antigens to T cells
3. Priming and activation of the T cell response
4. Trafficking of activated T cells (cytotoxic T lymphocytes [CTLs]) to the tumor microenvironment
5. Infiltration of CTLs into tumors
6. Recognition and binding of CTLs to cancer cells
7. Killing of cancer cells

Chen DS, Mellman I. Immunity. 2013
Regulation of T cell activation
Balancing activating and inhibitory signals

Activating interactions

Inhibitory interactions

Net balance of immune activity and regulation determines tumor fate

**Anticancer immune response vs. immunosuppressive cells**

**Anti-tumor immunity**
- CTLs
- Th1
- pTh17
- NK cells
- DCs
- Type I IFN
- Chemokines

**Intratumoral immunosuppression**
- TGF-β
- Treg
- IL-10
- Th2 cells
- IDO
- MDSCs
- PGE2
- TAMs (M2)
- CTLA-4
- Some B cells
- PD-1/PD-L1
- IL-4/IL-13

Net effect: tumor control
Net effect: tumor growth

Immune checkpoints
Central and peripheral regulatory mechanisms

Adapted from Kyi C and Postow M. FEBS Letters 2014; 588:368-376
Targeting immune checkpoints
Inhibit the inhibitory regulatory mechanisms

Adapted from Kyi C and Postow M. FEBS Letters 2014; 588:368-376
## Immunotherapy FDA Approvals
### Checkpoint Inhibitors in Multiple Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Tumor(s)</th>
<th>Approval History</th>
<th>Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yervoy (ipilimumab)</strong></td>
<td>CTLA-4</td>
<td>Melanoma</td>
<td>March 25, 2011: unresectable or metastatic melanoma. Oct 28 2015: adjuvant therapy for stage III melanoma</td>
<td>None</td>
</tr>
<tr>
<td><strong>Opdivo (nivolumab) + Yervoy (ipilimumab)</strong></td>
<td>PD-1 + CTLA-4</td>
<td>Melanoma</td>
<td>Oct 1, 2015: BRAF V600E wt unresectable or metastatic melanoma</td>
<td>None</td>
</tr>
<tr>
<td><strong>Tecentriq (atezolizumab)</strong></td>
<td>PD-L1</td>
<td>Bladder, Lung</td>
<td>May 18, 2016: Locally advanced/metastatic urothelial carcinoma 2nd line Oct 18, 2016: Metastatic NSCLC w/progression after platinum-based chemotherapy and EGFR/ALK targeted therapy (for tumors with EGFR/ALK gene abnormalities).</td>
<td>Complementary Diagnostic VENTANA PD-L1 (SP142) Assay (Bladder, NSCLC)</td>
</tr>
</tbody>
</table>
Companion vs. Complementary Diagnostics

Essential vs. Guiding information

**Companion Diagnostic**

- **FDA definition:**
  - "in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product."

- **PD-L1 drug and diagnostic example:**

  **Drug Label: KEYTRUDA® (pembrolizumab)**
  
  "KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of..." 
  
  "...patients with metastatic NSCLC whose tumors have high PD-L1 expression ([Tumor Proportion Score (TPS) ≥50%]) as determined by an FDA-approved test..."

  **Dx Label: Dako PD-L1 IHC 22C3 pharmDx**
  
  "PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab)"

**Complementary Diagnostic**

- The term "complementary diagnostic" was introduced in June 2015 by Elizabeth Mansfield, Deputy Director for Personalized Medicine at FDA, but has yet to be officially defined.
  - A complementary test isn't required for the safe and effective use of a drug; it can be used to guide treatment strategies and identify patients likely to derive the most benefit from a drug.

- **PD-L1 drug and diagnostic example:**

  **Drug Label: TECENTRIQ (atezolizumab)**
  
  "TECENTRIQ is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy."

  "No reference to diagnostic"

  **Dx Label: VENTANA PD-L1 (SP142) Assay**
  
  "PD-L1 expression in ≥ 50% TC or ≥ 10% IC determined by VENTANA PD-L1 (SP142) Assay in NSCLC tissue may be associated with enhanced overall survival from TECENTRIQ (atezolizumab)."

  "PD-L1 expression in ≥ 5% IC determined by VENTANA PD-L1 (SP142) Assay in urothelial carcinoma tissue is associated with increased objective response rate (ORR) in a non-randomized study of TECENTRIQ® (atezolizumab)."
Kaplan-Meier Survival Curves

Interpretation

• Graphical way to compare survival of two patient groups

• Overall survival vs. progression-free survival

• All subjects within the group begin the analysis at the same point

• All are surviving until one of two things happen:
  - 1) patient dies or progresses
  - 2) patient is censored (e.g. subject drops out, is lost to follow-up, or required data is not available.)
**Immunotherapy clinical efficacy**

**Ipilimumab FDA phase III registration study data**

![Graph showing improved survival with Ipilimumab in patients with metastatic melanoma.](image)

- **Ipilimumab alone**
- **Gp100 alone**
- **Ipi + Gp100 (peptide vaccine)**

Durable responses (4+yrs) in 20% of patients

Hodi et al. NEJM 2010
Non-small-cell Lung Cancer Survival on Chemotherapy

Median survival 8 months

Median survival: C/C+G: 8.1 months
C/C+T: 8.2 months
P = .8

Strata:
- C/C+G: cisplatin/carboplatin plus gemcitabine
- C/C+T: cisplatin/carboplatin plus a taxane

Does Type of Tumor Histology Impact Survival among Patients with Stage IIIB/IV Non-Small Cell Lung Cancer Treated with First-Line Doublet Chemotherapy? Chemotherapy Research and Practice vol. 2010
20% 10-year survival in advanced melanoma

Pooled analysis of 1,861 patients treated with ipilimumab

Schadendorf et al. J CO 2015
PD-L1 Dampens Immune Response by Deactivating T cells

- PD-L1 is normally expressed by a subset of macrophages
- PD-L1 can be induced as part of a physiological process to down-modulate ongoing host immune responses in peripheral tissue
- PD-L1 can be induced on activated lymphocytes (T, B and NK), endothelial cells and other non-malignant cell types
- Tumor cells and associated stromal cells can also express PD-L1, turning off T effector cells

Park et al. Blood. 2010
Nivolumab 2nd Line Squamous NSCLC Checkmate 017 trial
Nivolumab 2nd Line Squamous NSCLC
Checkmate 017 trial

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

- Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arin Frongers, M.D., Libor Havel, M.D., Martin Stein, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudeslet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lesni, M.D., Ph.D., and David R. Spigel, M.D.

- Duration of Response
  - Nivolumab
  - Docetaxel

- Patients with Ongoing Response
  - 63% (17 of 27 patients with response)
  - 33% (4 of 12 patients with response)
Immunotherapy in metastatic bladder cancer
Atezolizumab PD-L1 inhibition

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial


<table>
<thead>
<tr>
<th>Group</th>
<th>Median overall survival, months (95% CI)</th>
<th>12-month overall survival, % of patients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC2/3 (n=100)</td>
<td>11.4 (9.0–not estimable)</td>
<td>48% (38–58)</td>
</tr>
<tr>
<td>IC1 (n=107)</td>
<td>6.7 (5.1–8.8)</td>
<td>30% (20–39)</td>
</tr>
<tr>
<td>IC0 (n=103)</td>
<td>6.5 (4.4–8.3)</td>
<td>29% (20–39)</td>
</tr>
</tbody>
</table>

Overall survival (%) vs Months
Immunotherapy in lung cancer
Pembrolizumab PD-1 Inhibition – KEYNOTE-024 1st Line NSCLC Trial
Atezolizumab 2nd Line Non-small-cell Cancer
POPLAR phase 2 trial

PD-L1 Immunohistochemistry

Staining can be observed in tumor cells, immune cells or both

Tumor cells (TCs)

Immune cells (ICs)

Tumor and immune cells (TCs and ICs)
Response rate by PD-L1 status

Higher response rate in PD-L1-positive population

Non-sq.=non-squamous; sq.=squamous

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

Higher response rate in PD-L1-positive population

<table>
<thead>
<tr>
<th></th>
<th>Topalian et al. NEJM 2012</th>
<th>Nivolumab Melanoma</th>
<th>Nivolumab Solid Tumors</th>
<th>Wolchok et al. ASCO 2013</th>
<th>MPDL3280A Solid Tumors</th>
<th>MPDL3280A Melanoma</th>
<th>Herbst et al. ASCO 2013</th>
<th>MPDL3280A NSCLC</th>
<th>Pembrolizumab Melanoma</th>
<th>Pembrolizumab NSCLC</th>
<th>MPDL3280A Bladder</th>
<th>Pembrolizumab Head &amp; Neck</th>
<th>Nivolumab PD-L1 NSCLC</th>
<th>Pembrolizumab NSCLC</th>
<th>N=</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>42</td>
<td>44</td>
<td>34</td>
<td>94</td>
<td>30</td>
<td>53</td>
<td>113</td>
<td>129</td>
<td>64</td>
<td>55</td>
<td>411</td>
<td>Adapted from Margaret Callahan, ASCO 2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unselected</td>
<td>21%</td>
<td>32%</td>
<td>29%</td>
<td>22%</td>
<td>23%</td>
<td>23%</td>
<td>40%</td>
<td>19%</td>
<td>26%</td>
<td>18%</td>
<td>40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 +</td>
<td>36%</td>
<td>67%</td>
<td>44%</td>
<td>39%</td>
<td>27%</td>
<td>46%</td>
<td>49%</td>
<td>37%</td>
<td>43%</td>
<td>46%</td>
<td>49%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 -</td>
<td>0%</td>
<td>19%</td>
<td>17%</td>
<td>13%</td>
<td>20%</td>
<td>15%</td>
<td>13%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td>13%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Margaret Callahan, ASCO 2014
Cancers can evade immune destruction
Presence, type and activity of immune cells are key
The tumor immunity continuum
Immune oasis vs. immune desert

<table>
<thead>
<tr>
<th>Inflamed</th>
<th>Non-inflamed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing immunity</td>
<td>Excluded infiltrate</td>
</tr>
</tbody>
</table>

- TILs
- CD8 T cells/IFNγ
- PD-L1
- Mutational Load
- Angiogenesis
- Reactive stroma
- MDSCs
- Proliferating Tumors/Low Class I

Respond favorably to checkpoint inhibition
Convert to inflamed phenotype with combinations

Mutational burden hypothesis
Higher mutational load increases probability of immunogenic neo-antigens

The prevalence of somatic mutations across human cancer types.

- Altered proteins contain new epitopes for immune recognition, providing a common denominator for immunotherapy

Role of targeted therapy in the era of immunotherapy
Additive, synergistic, or independent?

Immunotherapy meets targeted therapy: will this team end the war against cancer?

Daniela Morales-Espinosa, Silvia García-Román, Cristina Teixido, Niki Karachalios, Rafael Rosell

Clinical trials combining tyrosine kinase inhibitors and immunotherapy

Review
Combining targeted therapy with immunotherapy. Can 1 + 1 equal more than 2?
Combining immunotherapy with other therapies
Which combinations for which patients?

- TCE BiSpe mAbs
- IDOi
- Herpes oncolytic virus
- Vaccinia oncolytic virus
- TLR ago
- STING ago
- RIG ago
- TKI
- Radiotherapy
- Chemotherapy
- αCD137
- αOX40
- αKIR
- αGITR
- αPD-1/αPD-L1

αCTLA4
### Combination immuno-therapies in NSCLC

Enhanced efficacy with increasing levels of PD-L1 expression

<table>
<thead>
<tr>
<th>PD-L1 expression</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>43</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>23</td>
</tr>
<tr>
<td>≥1%</td>
<td>18</td>
</tr>
<tr>
<td>≥5%</td>
<td>14</td>
</tr>
<tr>
<td>≥10%</td>
<td>57</td>
</tr>
<tr>
<td>≥25%</td>
<td>28</td>
</tr>
<tr>
<td>≥50%</td>
<td>32</td>
</tr>
<tr>
<td>≥75%</td>
<td>26</td>
</tr>
</tbody>
</table>

**Graph:**

- **Opdivo 3 Q2W + Yervoy 1 Q6/12W (pooled)**
- **Opdivo 3 Q2W**

---

Hellmann et al. Presented at ASCO 2016
Immunotherapy in oncology

Challenges

- Increase proportion of durable responders
- Predict response to specific immune checkpoint drugs
- Understand role of immune agents in context of targeted therapies and traditional chemotherapy
- Manage toxicity

Mellman et al. Nature 2011
Immunotherapy side effects

Autoimmune toxicity c/w mechanism of action

Mellman et al. Nature 2011
Personalized Healthcare in Oncology

Past

Present

Future
How can we continue to improve survival rates?

Illustrative KM curve for overall survival

- Targeted Therapy
- Chemotherapy

Pre-1990s
Chemotherapy

1990s+
Targeted Agents
Immunotherapy represents one of the most significant advances in the treatment of cancer.
Immunotherapy represents one of the most significant advances in the treatment of cancer.

Illustrative KM curve for overall survival

Pre-1990s
Chemotherapy

1990s+
Targeted Agents

2010+
First “Next Gen” Immunotherapy

2015+
Personalized Immunotherapy

2015+
Combination Immunotherapy
Cancer immunotherapy
Additional pillar of cancer care

Personalized healthcare next
Comprehensive tumor profiling drives therapy combinations
Questions and answers
Doing now what patients need next
MMR status and pembrolizumab response
Mismatch-repair deficiency correlates with improved response and survival

The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Table 2. Objective Responses According to RECIST Criteria.

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Mismatch Repair–Deficient Colorectal Cancer (N=10)</th>
<th>Mismatch Repair–Proficient Colorectal Cancer (N=18)</th>
<th>Mismatch Repair–Deficient Noncolorectal Cancer (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (14)*</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>4 (57)†</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
<td>5 (50)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (10)</td>
<td>11 (61)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%)</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
</tbody>
</table>

Objective response rate (95% CI) — %
40 (12–74) 0 (0–19) 71 (29–96)

Disease control rate (95% CI) — %
90 (55–100) 11 (1–35) 71 (29–96)

Median duration of response — wk
Not reached NA† Not reached

Median time to response (range) — wk
28 (13–35) NA† 12 (10–13)

MMR status and pembrolizumab response
Mismatch-repair deficiency correlates with improved response and survival
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