PRECISION MEDICINE: THE DEVELOPMENT CONTINUUM FROM BIOMARKER DISCOVERY TO COMPANION DIAGNOSTICS

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CSO
Covance
Topics

Challenges in Drug Development

Precision Medicine Overview
- Importance of Biomarkers
- Companion Diagnostics

Evolving Trial Designs
- Biomarker Driven Drug Development

Case Studies

Summary
Current Challenges in Drug Development

1. Competitive landscape in specific therapeutic areas
   ▶ Number of companies, approaches and molecules in development

2. Biomarker(s) considerations
   ▶ Intended use of the biomarker(s)
     • Consideration for use as companion or complementary diagnostic
   ▶ Appropriate Cell, Tissue, Genomic biomarkers

3. Appropriate trial design and impact on trial execution
   ▶ Flexible study designs
   ▶ Availability of appropriate patients
Drug Development and Precision Medicine

**ONE-SIZE FITS-ALL MEDICINE**

**STRATIFICATION**

Patients Are Grouped By:
- Disease Subtypes
- Demographics
- Clinical Features
- Biomarkers

**STRATIFIED MEDICINE**

**PERSONALIZATION**

Patient Individual:
- Preferences
- Clinical Features
- Medication History
- Environment
- Behaviors and Habits
- Biomarker

**PRECISION MEDICINE**

Source: Manchester Precision Medicine Institute

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Public
Key Factors in Precision Medicine

BIOMARKERS, DISEASE BIOLOGY AND DATA ANALYTICS

Biomarkers
► Cell, Tissue, Blood-based biomarkers reflective of disease biology and potential drug targets
  • Proteomic, Genomic technologies
► Development of Companion and/or Complementary Diagnostics

Disease Biology
► Disease heterogeneity
► Drug development targets

Data Analytics
► Improved trial protocol design
► Patient recruitment strategy
Precision Medicine-Utility of Biomarkers

CONTINUUM OF DEVELOPMENT FROM DISCOVERY TO CDx

COMPANION/COMPLEMENTARY DIAGNOSTIC

Biomarker Discovery

Exploratory Biomarker

Clinical Trial Assay

Clinical Validation
Biomarker Data Utilization Shifts as Molecule Programs Mature

TARGET ID & VALIDATION
LEAD OPTIMIZATION
CANDIDATE SELECTION
PRE-CLINICAL
PHASE 1
PHASE 2
PHASE 3
CDX

RELATIVE IMPORTANCE

PROOF OF SAFETY
PROOF OF MECHANISM
PROOF OF CONCEPT
PREDICTIVE BIOMARKER

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Biomarker Driven Programs Enhance Success

**Probability of Success with or without Selection Biomarkers**

- **Without Biomarkers**
  - Phase I to Phase II: 83.0%
  - Phase II to Phase III: 46.0%
  - Phase III to NDA/BLA: 66.0%
  - NDA/BLA to Approval: 8.4%

- **With Selection Biomarkers**
  - Phase I to Phase II: 78.0%
  - Phase II to Phase III: 78.0%
  - Phase III to NDA/BLA: 83.0%
  - NDA/BLA to Approval: 28.9%

**Personalized Medicines Top 30% of FDA Approvals for First Time in 2017**

- 2014: 21%
- 2015: 28%
- 2016: 27%
- 2017: 34%

**Biomarkers Are Key Features of Developing New Therapies and Diagnostics**

- Deep knowledge of biology improves success
  - Target/Mechanism/Biomarkers
- Evolution of new treatment modalities
  - Gene and Cell-based therapies
- Patient selection and stratification
  - Biomarkers and Companion diagnostics


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Biomarkers and CDx Strategy to Improve Success

**RIGHT TARGET**
- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

**RIGHT TISSUE**
- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug-drug interactions

**RIGHT SAFETY**
- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity and drug-drug interactions
- Understanding of target liability

**RIGHT PATIENT**
- Identification of the most responsive patient population
- Definition of risk-benefit for a given population

**RIGHT COMMERCIAL POTENTIAL**
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostics and biomarkers

Source: Morgan et. al., Nature Drug Discovery 17:187-181 2018

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## The Evolution of Oncology Clinical Trial Design

<table>
<thead>
<tr>
<th>DESIGN</th>
<th>CYTOTOXIC</th>
<th>TARGETED</th>
<th>IMMUNOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Traditional 3 + 3 dose-escalation design</td>
<td>3 + 3 dose-escalation design with large expansion cohorts in selected populations</td>
<td>Accelerated titration/adaptive design multiple parallel expansion cohorts long-term follow-up + drug re-challenge</td>
</tr>
<tr>
<td></td>
<td>Escalation: 20–30 pts</td>
<td>Expansion: 30–300 pts Molecular enrichment</td>
<td>Escalation: 100–1000 pts Expansion +/- Immune enrichment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DRUG APPROVAL</th>
<th>Based on later phase 2 or 3 trials</th>
<th>Conditional of accelerated approval based on large molecularly selected expansion cohorts</th>
<th>Conditional of accelerated approval based on histology and immune-biomarker selected expansion cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>P2</td>
<td>P3</td>
<td>P1</td>
</tr>
<tr>
<td>P2</td>
<td>P3 (Conditional accelerated approval)</td>
<td>P3</td>
<td>P1 (Conditional accelerated approval)</td>
</tr>
<tr>
<td>P3</td>
<td></td>
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| DRUG DEVELOPMENT TIMEFRAME | 10 YEARS | 5–8 YEARS | <5 YEARS |


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The Case for Companion Diagnostics

**Likelihood of Approval from Phase I**

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Approval Rate</th>
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<tbody>
<tr>
<td>Hematology</td>
<td>23.1%</td>
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<tr>
<td>Internal Medicine</td>
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</tr>
<tr>
<td>Oncology</td>
<td></td>
</tr>
<tr>
<td>Ophthalmology</td>
<td></td>
</tr>
<tr>
<td>Osteology</td>
<td></td>
</tr>
<tr>
<td>Psychiatry</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
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</table>

**One Size Does Not Fit All Patients Can Respond Differently to the Same Medicine**

- Cancer drugs: 75%
- Alzheimer’s drugs: 70%
- Arthritis drugs: 50%
- Diabetes drugs: 43%
- Asthma drugs: 40%
- Antidepressants (SSRIs): 38%


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Two Potential CDx Solutions

**IVD PATHWAY**

**PHARMA**

**CDx**

**CRO**

**Single Site Pathway**

- Enable a faster route for development and commercialization
- Initial launch as FDA-approved PMA IVD contingent on intended use of marker
- Develop/validate test on established IVD platform
- Laboratory service provider also leads the regulatory submission for regulatory clearance
- May subsequently partner with IVD manufacturer for kit development on same platform, allowing testing decentralization
Requirements for CDx Co-Development Partners

Understanding the Pharma and Dx Industry
Choosing a Pharma/Dx Partner
Complex Trial Execution
Managing the Co-Development Process
Regulatory Uncertainty Around Pharma and CDx
Intellectual Property Issues

SUCCESS BEGINS WITH THE RIGHT PARTNERS
Osimertinib Development Timelines

A Discovery phase
- Initiation of drug discovery project
- First synthesis of osimertinib
- Clinical candidate osimertinib
- 2009
- 2010
- 2011
- 2012
- 2013

B Development phase
- AURAx phase II first patient dosed
- First Track designation granted by FDA
- Fast Track designation granted by FDA
- AURAx phase II second patient dosed
- AURAx phase II third patient dosed
- AURAx phase II last patient in
- Breakthrough therapy designation granted by FDA
- FDA approval of osimertinib
- 2013
- 2014
- 2015
- 2016

Rapid transition from Discovery to Development
Incorporation of biomarker(s) into Phase I/II designs
Fast-Track and Breakthrough designations
Accelerated timelines for biomarker/CDx assay development

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Osimertinib Efficacy in T790M Mutation Positive Patients

Patients with EGFR T790M–Positive Status in Both Tumor and Plasma

- **Osimertinib**
- **Platinum–pemetrexed**

<table>
<thead>
<tr>
<th></th>
<th>Median Progression-Free Survival (mo) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>8.2 (6.8–9.7)</td>
</tr>
<tr>
<td>Platinum–pemetrexed</td>
<td>4.2 (4.1–5.1)</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.42 (95% CI, 0.29–0.61)

**No. of Patients**
- Osimertinib: 116
- Platinum–pemetrexed: 56

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
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</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>116</td>
<td>95</td>
<td>63</td>
<td>35</td>
<td>20</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Platinum–pemetrexed</td>
<td>56</td>
<td>39</td>
<td>13</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>


November 13, 2015
Accelerated Approval by FDA
Biomarkers and IO Therapies

- **Cancer cell**
  - Tumor mutation burden
  - Clonal neoantigens
  - Expression of tumor-specific antigens
  - Mutational/expression landscape
  - MMR deficiency

- **Tumor microenvironment**
  - Expression of PD-1/PD-L1
  - IDO expression
  - Angiogenesis
  - Presence of tumor-infiltrating cells
  - Hypoxia

- **Host immune system**
  - Peripheral blood biomarkers
  - Gut microbiome

**Patient’s clinical outcome**
PD-L1 Expression and Response Rates

PD-L1 EXPRESSION IN NSCLC

Companion Diagnostic and/or Complementary Diagnostic assays are in use providing clinical decision making information

Garon et al, NEJM 2015

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Public
Keynote-001 Trial Timelines and Milestones

***Key regulatory milestones***

- **Cohort A**: Advanced solid tumors
- **Cohort B**: Expansion cohort MEL-RCC

### Key study dates and protocol amendments

- **2010**: Initiation of KEYNOTE-001
- **2011**: Cohort A: RCC eliminated, enrollment restricted to MEL; Number of pts with unresponsive MEL increased; Evaluate PD-L1 status and stability/futility at RP2D
- **2012**: Cohort B1: PPPO via dose escalation to MEL; Number of pts with unresponsive MEL increased; Evaluate PD-L1 status and stability/futility at RP2D
- **2013**: Cohort B2: Add pts with MEL; Increase pt #
- **2014**: Accelerated approval for Ipi-R \( \text{aMEL}^{\text{c}} \)
- **2015**: Accelerated approval for PD-L1 NSCLC

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Annals of Oncology 28:1388, 2017

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Response Rates for Keytruda in dMMR Solid Tumors

KEYTRUDA BASKET TRIAL FOR DMMR TUMORS

[Graphs and charts showing response rates for different tumor types]
Biomarker to CDx Development Continuum

**DISCOVERY/EXPLORATORY**
- Fit-for-Purpose Assay Development
- Potential Intended Use
- Appropriate Platform
- Early design and manufacturing planning

**CLINICAL TRIAL ASSAY/IUO**
- Development of CTA under appropriate regulatory considerations
- CTA assay development and Validation
- Design Control
- Clinical Utility

**CDx**
- Analytical Performance and Robustness
- CDx Analytical Validation and Verification
- Assay Manufacturing and Distribution
- Post-marketing Implementation Plan
QUESTIONS?
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