CHANGING THE COURSE OF HUMAN HEALTH THROUGH BOLD PURSUITS IN SCIENCE

Precision Medicine at Celgene: considerations for CDx development

September, 2018
Agnes Seyda
Our passion drives us to find cutting-edge, innovative, solutions through integrating diagnostics and therapeutics to extend and improve quality of life for our patients worldwide.

Giving our patients the ability and time to create priceless memories with friends and family.

Celgene - Precision Medicine/CDx
Creating priceless memories for our patients through Precision Medicine
Agenda

Precision Medicine at Celgene
• Risk-base approach to Dx
• Choosing a partner – key considerations

Road to IDHIFA CDx
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- Risk-base approach to Dx
- Choosing a partner – key considerations

Road to IDHIFA CDx
Companion & complementary diagnostic tests will become more critical to patient outcomes

Evolution of drug development

PAST

- Blockbuster
  - Trial & error based drug design
  - “one drug fits all”

PRESENT

- Precision Medicine
  - Target-oriented design
  - “Right drug for right patient group”

FUTURE

- Personalized Medicine
  - Network-oriented design
  - “Right drug for right patient at right time & dose”

Future State:
Increased complexity with a focus on biological pathways and tumor evolution vs. single targets
Integrated evidence development model
Success requires a paradigm shift

Celgene wants to take a “patient centric” approach

Companion diagnostic tests help to fulfill key drug development needs:

- Increasing demand from patients, providers and payers for better, more cost-effective outcomes
- Celgene is focused on more targeted therapeutic solutions
- Concurrent approval of CDx & Therapeutics required in US, Japan & Australia

Right patient Right drug
Right time

Precision Medicine: winning for our patients
Barriers to selection of right test, right therapy

What Technology should I use?

Does Dx fit in workflow of clinical lab?

Are different Dx for the same target transposable?

What are the analytical performance data?

How do I compare assays across different technologies?
Risk Based Approach Needs to be Taken
No One-Stop Answer – Each Opportunity is Unique

Key Considerations:
- Has the biomarker hypothesis been previously validated for intended indication?
- Was the test used to validate hypothesis on same platform for CDx?
- Can a robust and reliable CDx be developed?
- What are the regulatory risks?

Key Considerations:
- Is there already a Dx test on market for biomarker?
- Is there already an LDT that could be leveraged?
- How long would it take to develop a CDx?

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Key Considerations:
- Are there trial designs that could minimize upfront CDx development & de-risk project?
- Are multiple CDx technologies needed?
- Can we leverage an existing panel?

Key Considerations:
- Will platform used sustain us through life cycle of drug?
- Turn-Around Time, Cost, information provided???
- What platforms are our competitors using?
- Regulatory or Reimbursement changes?
A Few of the Potential Types of Partnerships
Pros and Cons to Each - Suggest assessing individual program

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partner with CDx Vendor Early</td>
<td>Partner with Reference Lab Early then CDx Vendor</td>
</tr>
<tr>
<td>• Reduces risk of selecting different sub-population over duration of drug project</td>
<td>• Reduced costs - Service providers like Guardant Health, Genoptix, etc. generate revenue based on services provided</td>
</tr>
<tr>
<td>• Extensive verification, validation &amp; control of mfg. provides greater confidence in data</td>
<td>• Costs not “front-loaded” &amp; are more fee for service model</td>
</tr>
<tr>
<td>• De-risks submission timelines &amp; approval</td>
<td>• Risk that the assay developed by CDx vendor does not measure same population as reference laboratory</td>
</tr>
<tr>
<td>• Reduces risk bridging would be required</td>
<td>• More timeline risk around submission</td>
</tr>
<tr>
<td>• CDx development on avg. costs $5-20MM depending on technology &amp; complexity</td>
<td>• Will need to bridge</td>
</tr>
<tr>
<td>• CDx vendor often front-loads ~50% of costs to get to rCTA to account for opportunity cost if CDx not needed</td>
<td>• If clinical utility of biomarker is not validated or well-established, &amp;/or likelihood of drug success is still unknown</td>
</tr>
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</table>

When Might Consider

- If clinical utility of biomarker is well known & we have good confidence drug will meet clinical endpoints

- If clinical utility of biomarker is not validated or well-established, &/or likelihood of drug success is still unknown
A Few of the Potential Types of Partnerships
Suggest assessing individual program needs

<table>
<thead>
<tr>
<th>Partner with Reference Lab Early – Single Site PMA</th>
<th>Use Existing Approved/Cleared Test &amp; sPMA Approach</th>
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<tbody>
<tr>
<td><strong>PROS</strong></td>
<td><strong>CONS</strong></td>
</tr>
<tr>
<td>• Reduced costs - Service providers like Covance, Guardant Health, Genoptix, etc. generate revenue based on services provided</td>
<td>• Minimizes timeline, cost, regulatory &amp; technical (development risk)</td>
</tr>
<tr>
<td>• Costs not “front-loaded” &amp;; more fee for service model</td>
<td>• Harmonizes testing to a single panel</td>
</tr>
<tr>
<td>• Risk selecting different sub-population reduced</td>
<td>• Increase value for reimbursement</td>
</tr>
<tr>
<td>• Risk bridging needed reduced</td>
<td>Panel/platform may have multiple partners and potentially complex operating model</td>
</tr>
<tr>
<td><strong>CONS</strong></td>
<td><strong>PROS</strong></td>
</tr>
<tr>
<td>• Limits commercial viability – testing has to be centralized to the single site</td>
<td>• If clinical utility of biomarker is not validated or well-established, &amp;/or likelihood of drug success is still unknown</td>
</tr>
<tr>
<td>• More business continuity risk for life cycle management</td>
<td>• Ideal first choice if business, technical and commercial needs can met</td>
</tr>
<tr>
<td>When Might Consider</td>
<td>If commercialization limited to US; volume of testing anticipated to be small (orphan or rare disease), if distributable kit is also planned at later date, and/or technology platform is complex for a commercial kit</td>
</tr>
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</table>
## A Few Key CDx Partner Considerations

<table>
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<tr>
<th>Category</th>
<th>Key Considerations</th>
</tr>
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</table>
| Commercialization Capabilities   | • Channel penetration of Dx platform in regions of the world where we plan to launch & distribute  
• Infrastructure: Sales Force, customer service, complaint mgmt., field service engineers  
• Experience with reimbursement & reimbursed price versus transfer price |
| Quality and Regulatory           | • Obtained FDA approval for Class II & III devices & approval in Japan  
• Has the company been inspected recently by the FDA and/or undergone PAIs or BIMOs?  
• Is the company ISO13485 certified with good design control procedures? |
| Technical                        | • R&D teams capable of developing high quality diagnostic that can accurately and precisely measure our target(s) of interest?  
• Sample requirements (input and, sample type, extraction, first pass rate etc.)  
• Transparency and ease of working relationship  
• Technology – does the company offer novel technology which can improve sensitivity/specificity of the diagnostics |
Innovation has its challenges…. Lots of good potential Dx partners for CDx, but no perfect partner

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<th>Key Considerations</th>
<th>Gene Expression Profiling Vendors</th>
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<td></td>
<td>Vendor 1</td>
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<tr>
<td>Cost for Developing Test</td>
<td></td>
</tr>
<tr>
<td>Cost to Testing Lab</td>
<td>$100-300</td>
</tr>
<tr>
<td>Technical Competence</td>
<td></td>
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<tr>
<td>Sample Requirement</td>
<td>300-600 ng</td>
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<tr>
<td>Market Access (Reimbursement)</td>
<td>Significant experience</td>
</tr>
<tr>
<td>Commercialization</td>
<td></td>
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<tr>
<td>Platform Capable</td>
<td>Yes, but limited # of genes</td>
</tr>
<tr>
<td>Current platform placement</td>
<td></td>
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<tr>
<td>Regulatory Expertise (Japan, EU, Australia, US)</td>
<td></td>
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<tr>
<td>Ease of doing business (BD &amp; legal)</td>
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- **No significant issues anticipated**
- **Unknown, or may be challenges**
- **Significant challenges**
Key Take Aways....
Creating priceless memories for our patients through Precision Medicine

- **Precision Medicine is Here and Now!**
- **Risk-Based approach to Dx development is ideal**
- **Many things should be considered when selecting platforms, partners and generating contracts**
Agenda

Precision Medicine at Celgene
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Road to IDHIFA CDx
**Precision Medicine is Here…. One Example out of 30 Approved Tests**

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<tr>
<th>Benefits</th>
<th>Precision Medicine</th>
<th>Impact</th>
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<tr>
<td>Right Drug, Right Patient, Right Time</td>
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<td>Improved Quality of Life, Avoid Adverse Drug Reactions, Expanding utility of drug candidates, Controlling overall cost of health care</td>
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**Precision Medicine can 1) Accelerate development timelines & approval (reduced costs) 2) Increase Drug Development Success Rate 3) Enable Ability to Price Higher = Potential Increase on Return on Investments**

**Celgene’s First Co-Commercialization with a Companion Diagnostics (CDx)**

- CDx is an RT-PCR based diagnostics developed with Abbott Molecular
  - Rapid, Low Cost, High-Throughput, Sensitive & Robust
- Precision Medicine enabled - Accelerated Development & Launch in targeted population (IDH2 Mutation present)
  - First Patient Dosed to Submission of NDA: Only 3.5 Years
  - Rapid Approval – Submission 30Dec2016 --- Approval 1Aug2017

**Celgene’s Motto:** Creating priceless memories for our patients through Precision Medicine
IDHIFA/CDx story

1. IDHIFA is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

2. The Idhifa NDA was based on the Phase I/II study AG221-C-001, which started out as a Phase I trial in hematological neoplasms and then added a Phase II cohort of IDH2 mutation-positive AML patients.

3. Subjects in the Phase I portion of the study were enrolled based upon IDH2 mutation status in either bone marrow aspirate or blood specimens as determined by local assessment using a variety of LDTs. The study protocol called for retrospective centralized testing to confirm IDH2 mutation status

   - The efficacy of IDHIFA® was evaluated in an open-label, single-arm, multicenter, two-cohort clinical trial (Study AG221-C-001, the only trial) of 199 (out of 346 intended to diagnose) adult patients with relapsed or refractory AML and an IDH2 mutation, who were assigned to receive 100 mg daily dose.
   - Cohort 1 included 101 patients (phase 1 dose escalation and expansion phase) and
   - Cohort 2 (phase 2) included 98 patients.
   - IDH2 mutations were identified by a local laboratory developed test (LDT) and retrospectively confirmed by the Abbott RealTime™ IDH2 assay (170 patient samples), or prospectively identified by the Abbott RealTime™ IDH2 assay.

4. Idhifa benefited from FDA's speed and regulatory flexibility under expedited review programs for serious unmet medical needs. The drug was not designated a breakthrough therapy, but did collect an orphan designation, fast track status and priority review.
## IDHIFA/CDx timeline

<table>
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<tr>
<th>Date</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>6/3/2013</td>
<td>IND #117631 opened</td>
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<tr>
<td>9/20/2013</td>
<td>Phase I Study AG221-C-001 in patients with advanced hematologic malignancies harboring an IDH2 mutation identified or confirmed by the Abbott RealTime IDH2 assay</td>
</tr>
<tr>
<td>6/12/2014</td>
<td>Orphan drug designation granted for acute myelogenous leukemia (AML) with in IDH2 mutation</td>
</tr>
<tr>
<td>7/31/2014</td>
<td>Fast track status granted for AML that harbors an IDH2 mutation</td>
</tr>
<tr>
<td>2/2/2015</td>
<td>Study protocol amended to add Phase II component and added allowance for patients who experience disease progression on study drug to remain on drug if they are benefiting from treatment; also added guidelines for management of differentiation syndrome and QT prolongation</td>
</tr>
<tr>
<td>7/26/2016</td>
<td>Pre-NDA meeting</td>
</tr>
<tr>
<td>12/30/2016</td>
<td>NDA submission, requesting accelerated approval; NDA uses data cut-off of 4/15/2016</td>
</tr>
<tr>
<td>2/28/2017</td>
<td>FDA files NDA for priority review, requests safety and efficacy data with later data cut date of 10/14/2016</td>
</tr>
<tr>
<td>8/1/2017</td>
<td>Approval, along with Abbott RealTime IDH2 companion diagnostic - just five years after IND filing and seven months after NDA submission.</td>
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</table>
Thank you for your time any attention!

Any Questions?