Challenges in developing Companion Diagnostic (CDx): alignment with stakeholders is key of success.
Agenda

- Challenges of Biomarker assay transition to a CDx product
- What do we do as pharma
- Where are we today
- CDx development Pathways
  - Xalkori CDx Approval
- Summary
“A bad test is every bit as bad as a bad drug.” (FDA Quote)

Wrong biomarker

- Wasted Drug development effort
- Lost treatment opportunity

Poor analytical performance

- Obscures drug’s effect
- Wrong patients treated
The determination of whether or not a biomarker is a companion diagnostic is based on the risk/benefit profile in each subgroup and is considered on a case-by-case basis. 

The Agency does not have a pre-specified level of evidence that is required.
A diagnostic product is a complex system of reagents, instruments, software, algorithms and procedures, all of which comprise the final regulated product.
<table>
<thead>
<tr>
<th>Function</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Business Development</td>
<td>CDx contracting requires unique skills and knowledge. Multiple partners are a frequent possibility.</td>
</tr>
<tr>
<td>Clinical</td>
<td>To accommodate the Dx validation.</td>
</tr>
<tr>
<td>Translational</td>
<td>Provide technical input into assay design and assess results.</td>
</tr>
<tr>
<td>Medical</td>
<td>Input on design goals and assess product design.</td>
</tr>
<tr>
<td>Regulatory</td>
<td>Support CDx submission strategy development, incorporates into drug submissions.</td>
</tr>
<tr>
<td>Commercial</td>
<td>Input on design goals, launch planning.</td>
</tr>
<tr>
<td>Reimbursement and market access</td>
<td>Understand the market and leverage what has been done Alignment with Commercial and medical affair required prior to launch.</td>
</tr>
</tbody>
</table>
How do we Manage Team Expectations?

Design CDx strategy based on clinical needs.
  • Share risk assessment and mitigation plan. Help the clinical team to understand the challenges.

Engage them in the development process.
  • So they understand the schedule, risks, and challenges.

Communicate status widely and frequently.
  • Tailor the message to the audience- not everyone wants to know the details, nor does everyone want just a summary.

Prepare the team for changes.
  • Partner strategy, development program, regulatory strategy and Dx market will undoubtedly evolve for a while.
Global strategy: other regions Dx requirements are evolving and may require additional development work.

The Intended Use drives the strategy. Clinical strategy is linked to the regulatory plan.

- Patient cohort selection
- Alignment with drug trial(s)
- Consider the requirement for an IDE if patient selection will occur during the clinical trials.

Pre-IDE meeting(s) with CDRH and other HA are a good tool.

- Coordinated between Rx and Dx partners.
- Combined CDER/CDRH meetings are valuable.
Launch planning needs to be accounted for:

Commercial plan is not always straightforward.

- Product distribution – ensuring supply chain at launch.
- Instrument base and providing access to testing.
  - Worldwide considerations
  - Turn-around time
- Training programs for sales, physicians, support staff, etc..
- Customer support, including reporting between companies of product issues.
- Technical support in the field.
- *Existing LDT’s evaluation/impact on standardizing the Dx product.*
Where are we today

Pharma fully understands the requirement of CDx development.

• Unmet medical need and highly competitive space in Oncology is challenged by
  • Same BM multiple drugs
  • Evaluating the risks of existing test.
  • Can pharma work together?
• The outcome of the phase1/2 pivotal trial in relation to Biomarker not well understood.
  • HA requirements are not well understood early on.
  • Requiring on time a test that meet HA requirements.
  • Large investment required up front.
• Early communication with Health Authorities are established.
  • FDA willing to support pharmas early on and the diagnostic approval space is evolving. (LDT’s, complementary diagnostic test..etc)
• Different RA requirements among regions.
Where are we today cont’d

- Technology evolving..
  - Will NGS be the future? How we become part of this process early on? Can we work together?
- A gap between RA requirements and reimbursement process.
  - The LDT’s/homebrew assays
  - Present challenges to standardize a approval test globally
  - Addition investment by Pharma on evaluating the existing assays (LDT’s) and leveraging their use when possible.
- Coding and reimbursement processes across regions continue to be a challenge.
Pathway 1: Best Scenario for CDx Development

**minimum risk**

Use commercial assay and validate the cut off in phase III

*No bridging is Required!!*

BUT, higher cost and longer timeline

Example: Xalkori (Alk) and Zelboraf (Braf)
Pathway 2: Maybe the today’s Pharma solution

**Moderate risk**

Tailored for rapid CDx development process, in parallel with early filing trials. Reality…

**Develop a Clinical trial assay under Design Control**

Early collaboration with diagnostics companies to develop Formulation Lock Assay (FLA) or called hybrid. FLA is the final design (analytically) of commercial assay as a result

**Bridging may not be required.**

Higher price than CTA!!! A lot less than final commercial assay BUT faster transition if CDx required.
Pathway 3: Early Filing/phase III Trials with no CDx Development

**Higher risk**

Develop clinical trial assay (CTA) at CRO. Analyze clinical trial cohort using data generated by CTA. If CDx assay is required by Regulatory Authorities then a bridging of CTA and CDx assay is necessary!!! It may delay launching of the drug!!

Example of Bridging: Herceptin (Her2) and Erbitux (Kras)
Risks Associated with Pathway 3

Development
- CTA does not identify correct Intend To Treat (ITT) Population
- CTA is linked to clinical outcome, CDx is linked to CTA cut off to identify correct treatment population
  – no direct link of CDx to outcome

  Bridging study may fail!!

Regulatory
If the bridge fails, the FDA may request extension of the trial to validate the utility of the test which ultimately will delay the drug approval unless you qualify for a breakthrough approval (True only for FDA)
Risks associated with Bridging

Health Authorities require minimum of 90% concordance of the CTA and CDx commercial assay.

✓ Do we have the freedom to use the archived samples?
  • Include in the Informed consent that the samples will be used for CDx development
  • Ethical issues among regions, should be taken in consideration

✓ Do we know sample stability?
  • Trials vary in length from 3-5 years, sample stability a major concern.
  • Preferable blocks instead of slides (IHC case)

✓ Have the clinical team standardized the protocol for samples/tissue collection?
  • Early plan for sample collection and stability studies is key

✓ How do we mitigate the risk for not having samples for all patients?
  • Prepare a detailed statistical analysis plan and discuss as early as possible with HA.
XALKORI® (crizotinib) Capsules, oral, indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) (ALK)-positive as detected by an FDA-approved test

- Around 1-7% of patients express the ALK gene and this mutation is normally associated with non-smokers.

CDx: Abbott Molecular Vysis CDx (FISH)

CDx assay was used to generate phase III data

CDx and Rx approved concurrently on August 26, 2011

Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in non-small cell lung cancers (NSCLC) tissue specimens to aid in identifying those patients eligible for treatment with XALKORI® (crizotinib)
Food and Drug Administration extended the approval of Xalkori (Crizotinib) to treat people with advanced (metastatic) non-small cell lung cancer (NSCLC) whose tumors have an ROS-1 gene alteration. March 2016

- Breakthrough approval with post marketing commitment to deliver Ros 1 test 18 months after drug approval.
- Bridging still may be a risk
Every CDx development situation is unique. Follow the science and be creative.

- Clarify the BM intended use.
- Select the right pathway that fits your clinical strategy the best.
- Evaluate and select the right partner capable to develop, file and commercialize a successful IVD product.
- Early discussions with Regulatory are necessary.
- Early alignment with stakeholders on CDx strategy is key to success.
Acknowledgements

David Stanforth, Senior Director, Companion Diagnostics

Kenji Nakamaru, Senior Director, Biomarker and Companion Diagnostics

Masato Murakami, VP, Global Biomarker and Companion Diagnostics

Arnaud Lesegretain, VP, Oncology R&D, Head of AML Franchise

Russell Weiner, Executive Director, Head of Bioanalytical, Biomarker and Companion Diagnostics
THANK YOU