New Paradigms in Drug Discovery: How Genomic Data are Being Used to Revolutionize the Drug Discovery and Development Process – A Workshop

Pharma Perspective

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Roche Pharma and Diagnostics

Pharma

Diagnostics

Roche Pharma
Genentech
Chugai

Roche Applied Science
Roche Molecular Diagnostics
Roche Professional Diagnostics
Roche Tissue Diagnostics
Roche Diabetes Care
Biomarker development – why?

Healthy \rightarrow Asymptomatic disease \rightarrow Symptomatic disease \rightarrow Chronic disease/cured

Risk assessment
Predisposition for developing disease

Screening/Diagnosis
Early detection

Prognostic
Predict probable disease course

Predictive
Predict likely response to a drug and/or safety/toxicity

Monitoring
Monitor efficacy/recurrence

Patient stratification/Therapy selection

Right Drugs for the Right Patients at the Right Dose at the Right Time

Escape/resistance mechanisms
• Which drug(s)?

Chronic therapy adaptation if disease recurs

Adapted from Stefan Scherer BRG
Co-development of drugs and diagnostics at GNE / Roche

Drug Development

1. Research
2. Early Dev
3. Phase 1
4. Phase 2
5. Phase 3

Safety, very limited efficacy, rarely Dx information

Drug/Dx Proof of Concept

Drug/Dx Hyp confirmation

REDs

Biomarker Discovery and Clinical Integration

1. Hypothesis generation
2. Technical feasibility & initial testing
3. Test diagnostic hypothesis
4. Test Dx in pivotal trials

Companion Diagnostics Development

CDx IVD development to launch

RDx

Personalized Healthcare for Patients

Adapted from FDA draft concept paper on drug diagnostic co-development, April, 2005.
### PHC Assessment

- **Strong Dx hypothesis**
  - No activity in Dx-

- **Strong Dx hypothesis**
  - Some activity in Dx-

- **No strong Dx hypothesis**
  - Exploratory Stage

### Development Strategy

- **Patient selection through all phases of development**
- **Complex, larger phase IIIs with stratification**
- **Complex phase IIIs**

- **No selection or stratification**
- **Retrospective data exploration**

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**Dx test prior to randomization**

- **Dx+**
  - Placebo
  - Active

- **Dx-**
  - Placebo
  - Active

**Randomize all subjects**

- Placebo
- Active
Key challenges for drug-diagnostic co-development

- Label-enabling trials design and analysis
- Biomarker cutoff selection and refinement
- Multiple biomarkers and multi-marker tests
**Design and Analysis: what is the target population for evaluation?**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Effect in Dx-</th>
<th>Evaluation of Dx- in Ph III</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected</td>
<td>Negative</td>
<td>Exclude or limit patients</td>
<td>Dx+ only</td>
</tr>
<tr>
<td>Stratified</td>
<td>Minimal Benefit</td>
<td>Limited, adaptive stopping, or include all comers?</td>
<td>Dx+ first</td>
</tr>
<tr>
<td>Stratified/All-comers</td>
<td>Positive Benefit</td>
<td>Enroll all Dx- patients</td>
<td>Dx+ or all-comers</td>
</tr>
</tbody>
</table>

**Considerations:**

- Adequate evaluation of Dx- subgroup depends on scenario and clinical context
- Key factors in determining Dx+ vs. all-comers label (Stratified)
  - Clinically meaningful treatment benefit level
  - Magnitude of difference in Dx+ vs. Dx- treatment benefits
  - Risk/benefit evaluation in Dx- patients and unmet need
- If all-comers label pursued in the 3rd scenario, include Dx results in Clinical Studies section of label if clinically meaningful
Biomarker Cutoff Selection and Refinement

Often, no clear best threshold:

Appropriate threshold will depend on:

- clinical benefit/risk
- scientific rationale
- biomarker distributional properties (e.g. bimodal)

Note the population size vs effect size trade-off

Proposed Strategy

Pre-specify Dx+/− threshold prior to Ph III unblinding, and adjust threshold in label based on Ph III results and discussions with HA (assuming positive results based on pre-specified threshold)
Complex Biomarker World Today

- Increasingly complex companion diagnostic
  - Driven by disease biology
- Full clinical validation of each biomarker may not be feasible (ex. infrequent mutations)
- For multiplex biomarker signatures no expectation that individual biomarkers will be predictive
- Alternative clinical and analytical validation should be considered depending on the situation
Matching druggable dependencies with disease subtypes, technically robust biomarkers and pipeline drugs

Adapted from David Shames OBRF presentation, 2012
Everidge (Hedgehog Pathway Inhibitor)—Follow the Tumor Genetics

Disease (BCC) = Diagnostic, hence no companion Dx (nearly all BCCs have mutations in PTCH1 or SMO)
Molecular Classification of Medulloblastoma

- Mutation-based test NOT feasible to identify Hedgehog-driven medulloblastoma
  - Multiple genes involved, no hotspots
  - Non-mutation changes possible (e.g. epigenetic silencing, gene inversion)

Adapted from Kool et al, PLoS ONE 2008
Examining Dx Hypothesis: PBTC-032 Phase II Pediatric Study

Relapsed/Refractory Medulloblastoma

Immunohistochemistry Diagnostic Test (IHC)

Hedgehog Pathway (-)

- Enroll 13 patients
  - Treat with Vismodegib
    - 0/13 responses*
      - STOP
    - 1+/13 responses*
      - Enroll to 20 patients

Hedgehog Pathway (+)

- Enroll 13 patients
  - Treat with Vismodegib
    - 0/13 responses*
      - STOP
    - 1+/13 responses*
      - Enroll to 20 patients

Adapted from Nov 1, 2011 ODAC
PHC: Integrating research and development

- Extensive drug and technology pipeline
- Focus on effective .EDU-.ORG-.COM collaborations
- Cross-functional teams including research and development
- Strategic information gathering to provide robust datasets for better informed efficient drug development

Adapted from David Shames OBRF presentation, 2012
Summary – Biomarkers, clinical development and next generation technologies

- Extensive use of evolving technologies to improve disease molecular classification and biomarker hypothesis generation
  - Effective research-development integration

- Focus on established technologies for companion Dx development
  - Proactive discussions with the regulators to establish acceptable approaches

Beyond companion Dx:

- Formulating strong preclinical hypothesis about effective drug combinations
- Identifying relevant early-on-treatment measures
- Steering Phase I patients to the most appropriate trials – shift in signal-seeking
- Understanding mechanisms of resistance upon progression with the aim of finding most appropriate next treatment
  - Characterizing tumors via circulating tumor cells analysis.
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