Biomarkers in Clinical Research

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‘The right dose of the right drug to the right patient at the right time

-the promise of personalized medicine
Is personalized medicine finally here?

- Dozens of players emerging in personalized medicine
- Some big pharma companies and payers remain skeptical from the economics perspective
- Real winners will be patients!
Biomarker goals in oncology development?

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**Current state**
- ~95% attrition during clinical development (Kola & Landis, 2004)
- 5% of successful drugs mostly have small overall survival benefits (weeks to months) in unsegmented cancer patients
  - Gleevec in CML may be unique
- Most indications are unsegmented and all patients have identical treatments

**Future state**
- Greatly reduced attrition through use of better preclinical models, PD biomarkers and companion diagnostics
- Successful new drugs will have large overall survival benefits (months to years) in segmented cancer patients
- Many indications will be targeted and defined by companion diagnostics

Treat all patients and have a modest increase in OS

Treat 10% of patients and have significant increase in OS

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Health Authority Perspective

- FDA’s CDER 2006 guidance: micro dosing in limited number of subjects to help identify PK and mechanistic properties of compounds before starting Phase 1 trials (*Exploratory IND’s*).

- Exploratory IND concept may also permit biomarker-enabled studies of efficacy for unprecedented targets with limited number of patients enrolled in Phase 1 studies.
Biomarkers: A new decision making tool in oncology

- Aid target characterization
- Patient selection
- Dose selection and schedule
- Demonstrate whether the drug is having the appropriate target interaction
- Reveal the mechanism and extent of drug action
- Offer information linking a degree of change with a relevant clinical outcome
- Designing rationale combination therapies
Example of PK/PD modeling in dose selection

PK simulation from literature data

Simulated Profile vs Real PK data

Development of PK/PD model

Dosing regimen – based on PK/PD modeling

9mg/kg dose q3W
**Biomarkers terminology**

- **Biomarker**: A characteristic that is objectively measured and evaluated as an indicator of normal biologic process, pathologic process, or pharmacological process for therapeutic observation.

- **Clinical Endpoint**: A characteristic/variable that reflects how a patient feels or functions, or how long a patient survives.

- **Surrogate**: A subset of biomarkers that can potentially substitute clinical end points.
  - serum cholesterol (lipid-lowering agents)
  - Viral load (antiviral agents)
Biomarkers can be……

- Proteins
  - Applicable throughout the drug discovery and development process; longest history as biomarkers
- RNA Expression Profiling
  - Gene arrays used in discovery phase and clinical trials
- SNPs (Single Nucleotide Polymorphisms)
  - Large patient populations required has hindered use but should increase in the future
- Small Molecules:
  - Used the least; may increase with the successful application of metabonomics
Biomarker methodologies

- Minimally invasive imaging
  - PET, MRS, DCE-MRI,

- Invasive molecular endpoints
  - In tissues/blood samples
    - Western blotting, mRNA analysis, RT-PCR,
      - ELISA, MS etc, methylation, FISH

- Immunohistochemistry

- Gene expression microarrays and proteomics, transcriptomics, metabolomics

- Cell search (CTC’s/CEC’s)
# Types of Biomarkers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Function</th>
<th>Test</th>
</tr>
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</table>
| PD/MOA       | ó Determine whether a drug hits the target and has the expected impact on the biological pathway  
ó Evaluate mechanism of action (MOA)  
ó PK/PD correlations and determine dose and schedule | ó Research test used during drug development  
ó Not developed as companion diagnostic |
| Predictive   | ó Identify patients most likely to respond, or are least likely to suffer an adverse event when treated with a drug. | ó Companion diagnostic test (e.g. herceptin, EGFR) |
| Prognostic   | ó Predicts course of disease independent of any specific treatment modality | ó Approved tests (e.g. CellSearch, GeneSearch, Mammaprint, Oncotype Dx) |
| Surrogate    | ó Approved registrational endpoints                                       | ó Commercial diagnostic tests (e.g. LDL, HbA1c, viral load, blood pressure) |
Types of Biomarkers

- **Prognostic**: A marker predictive of disease outcome (PSA, CA-125, CTC’s)

- **Predictive**: A marker associated with treatment (Her2/neu to determine trastuzumab response)

- **Pharmacodynamic (PD)/Mechanism of action (MoA) biomarkers**:
  - A marker that measures effects of drug and may or may not correlate with biological and clinical effects
    - **Proximal** – altered activity/expression of molecular target (decreased phosphorylation of a protein substrate immediately downstream from a target kinase)
    - **Distal** – effects of drug further downstream of its immediate molecular target (Ki-67, apoptosis, molecular imaging changes)
Example of use of PD markers in clinical development

Pre-Treatment

Post-Treatment

Pre-treatment

BCL-2

Bax

pMAPK

Post-treatment
The pharmacological audit trail

Key questions in drug development

- Target expressed and/or pathway active
- Active blood concentration
- Molecular target activity?
- Pathway modulated
- Desired biological effect?
- Disease response?

Key development questions

- Impact on clinical development
  - Patient selection
  - Pharmacological proof of concept
  - Dosing decisions

- Impact of not having biomarkers
BM frameworks–

1. Biomarker in place
   - Pre-clinical: Stratify patient population with biomarker
   - Phase I: Continue to adapt with stratified population
   - Phase II: Ensure availability of companion diagnostic (when necessary)
   - Phase III: Launch drug with biomarker on label and companion diagnostic available (when available)

2. No biomarker in place
   - High response rate:
     - Pre-clinical: Continue with development, BUT take tissue samples
     - Phase I: IF response holds up, continue with development
     - Phase II: IF response falls, return to Rescue OR terminate program
     - Phase III: Launch drug
   - Rescue strategy: re-evaluate samples

3. No biomarker in place
   - Low response rate:
     - STOP: Take tissue samples and look for stratifying biomarker (Rescue strategy)
     - Phase I: Continue ONLY if better response in subpopulation identified via stratifying biomarker OR terminate drug program
     - Phase III: Launch drug with biomarker on label and available diagnostic (companion when available)
How should Biomarkers be integrated in drug development (*Idealized Scenario*)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical/Phase I</td>
<td>Test potential markers</td>
</tr>
<tr>
<td>End Phase II</td>
<td>Select a classifier</td>
</tr>
<tr>
<td>Phase III</td>
<td>Demonstrate clinical utility</td>
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<tr>
<td></td>
<td>Validate the platform and diagnostics (+/- “platform bridging”)</td>
</tr>
<tr>
<td>Post-marketing</td>
<td>Identify safety biomarkers?</td>
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*R. Temple, DIA/FDA/PhRMA Workshop (Oct, 2005)*
Biomarker/diagnostics development

- Identify biomarkers
- Establish prototype biomarker assays
- Preclinical verification studies
- Optimization, method verification/validation
- Clinical validation
- Regulatory submission

(evaluations can be in exploratory mode)

(CLIA/GLP)
Biomarkers in various stages of clinical development

- **Prospective:** Patient selection for pivotal registration trials (i.e., stratification factor)
  - Requires appropriate validated “signature” at onset of study

- **Retrospective:**
  - Safety labeling (e.g. Camptosar)
  - Label restriction (e.g. Vectibix)
  - Hypothesis generation (e.g. Iressa)

**Post-hoc** biomarker analyses have not been a successful “rescue strategy” for failed trials in oncology
## Targeted therapies with predictive biomarkers

<table>
<thead>
<tr>
<th>Selection</th>
<th>No Selection</th>
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<tbody>
<tr>
<td>trastuzumab (HER2+)</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>fulvestrant (ER+)</td>
<td>bortezomib</td>
</tr>
<tr>
<td>tositumomab (CD20+)</td>
<td>erlotinib</td>
</tr>
<tr>
<td>ibrutumomab* (CD20+)</td>
<td>bevacizumab</td>
</tr>
<tr>
<td>imatinib (KIT+)</td>
<td>sorafenib</td>
</tr>
<tr>
<td>cetuximab (EGFR+)</td>
<td>sunitinib</td>
</tr>
<tr>
<td>lapatinib (HER2+)</td>
<td>dasatinib</td>
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</table>
Post approval impact on marketing authorization

- Vectibix(TM) (panitumumab): approved by FDA (and not EMEA) in 2006 for colon cancer
- The efficacy of monotherapy was subsequently shown to be confined to patients with non-mutated (wild-type) KRAS tumors
- In December 2007, the European Medicines Agency (EMEA) granted a conditional marketing authorization for Vectibix as monotherapy for the treatment of patients with EGFr expressing mCRC with non-mutated (wild-type) KRAS genes after failure of standard chemotherapy regimens.
Post-marketing biomarker studies may lead to labeling revision if they raise a safety concern.

Revised Campto(-sar) Label

Clinical Pharmacology section, Pharmacokinetics subsection:
• UGT1A1*28 leads to reduced enzyme activity
• Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele
• Patients who are homozygous for UGT1A1*28 have a higher exposure to SN-38

Warnings section, Patients with Reduced UGT1A1 Activity:
• Individuals homozygous for the UGT1A1*28 allele are at increased risk for neutropenia
• A reduced initial dose should be considered for patients homozygous for the UGT1A1*28 allele
• Heterozygous patients unclear

Dosage and Administration section, Dosage in Patients with Reduced UGT1A1 Activity
• A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele
• However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment

Note: Prophylactic management (G-CSF) would be another option for these high-risk patients.
Biomarkers- is it an expensive distraction?

- Costs associated with biomarker analyses (adds on an average ~$6675 per patient as variable costs)
- A false-positive result will be expensive –given the costs of requisite confirmatory trial
- Misinterpretation or inaccurate use of these results (eg., requirement of EGFR testing for Cetuximab) = poor decision and harm to patients
- Therefore.....
Conclusion

ó ..... BM studies should reliably lead to less expensive drug development and/or clinical benefit to patients

ó They should be well planned out and answer very specific questions and implemented accordingly

ó Is personalized medicine finally arriving?
  – Malorye Allison, Nature Medicine, May 2008

Yes!
UMA PRABHAKAR / MARIAN KELLEY (Eds.)
Validation of Cell-Based Assays in the GLP Setting
A Practical Guide

- Describes the development, optimization and validation of cell-based assays, including procedural documentation required for Good Laboratory Practice
- Provides details of techniques used in the evaluation of immunodeficiency, autoimmune and oncological disorders

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