Integrating Predictive Biomarkers and Classifiers into Oncology Clinical Development Programs

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Predictive Biomarkers are Sometimes Essential for Any Approval At All

- Detailed simulation: Herceptin® would not have succeeded if studied in general population
- Iressa® failed in early lung cancer because predictive biomarker of epidermal growth factor receptor (EGFR) mutations was not appreciated
- Vectibix®: K-ras mutation status required for approval in colorectal cancer
Sometimes the Need for a Predictive Biomarker Sneaks Up on You

• Erbitux®: K-ras mutation status will likely soon be required for colorectal cancer, altering Imclone’s market
Sometimes a Biomarker Doesn’t Work, or Isn’t Needed

• EGFR expression does not predict response to Erbitux® in colorectal cancer
• Biomarker subsets were not required for sorafenib approval in renal cell cancer
  – But cost per QALY may suggest some biomarker work will be needed for these scenarios in the future
When Biomarkers Work, They Will…

- Generate products with real value, obvious to payors
- Result in smaller, cheaper Phase 3 studies:
  - Effective biomarker targeting means greater benefit
  - Needed Phase 3 study size gets 4 times smaller if the benefit doubles
- Reduce chance of failed Phase 3 studies, the largest contributor to poor ROI.
  - Herceptin® would have failed Phase 3 without predictive biomarker
When Biomarkers Don’t Work, They Will…

• Add cost
• Add complexity
• Add time
A Cross Functional Consensus

• Several years of cross functional discussion
• New clinical trial designs developed based on discussions
• Summarized in:
Objectives

• Increase utilization of biomarkers in oncology clinical development plans
• Provide broad guidelines for incorporation of biomarkers into clinical development plans
• Maximize efficiency of development of personalized medicines (greatest throughput per resource unit expended)
• Manage risk across oncology portfolio by series of adaptive, data-driven decisions
• Create biomarker driven strategies which address regulatory, commercial, and clinical execution issues
• Achieve cross-functional consensus on clinical strategies in biomarker driven environment
Proposed Strategic Principles

- Adaptive decision making
- Continuous integration of biomarker and clinical information
- Validation of clinical benefit ID hypothesis against qualified clinical endpoints
- Strategies designed to maximize objective functions such as utility per resource unit expended
Optimizing efficiency of clinical trials: example

• Efficiency optimized Phase 2 (P2) study*:
  – power and alpha chosen to maximize objective function of correctly identified effective drug per resource unit expended in P2/P3 development.
  – Results in smaller, more efficient RANDOMIZED studies, making biomarker work feasible.


*Chen, Cong and Beckman, Robert A. Maximizing Return on Socioeconomic Investment in Phase II Proof-of-Concept Trials, *Clinical Cancer Research*, Published online before print, February 13, 2014.
Drug Active

Large POC Trial Outcome

Yes (0.3)

False negative (0.2)

Benefit = 0; Cost = 160 = Cost of traditional POC trial

True positive (0.8)

Benefit = 1; Cost = 760 = Cost of traditional POC trial plus cost of Phase III trial

No (0.7)

False positive (0.1)

Benefit = 0; Cost = 760 = Cost of traditional POC trial plus cost of Phase III trial

True negative (0.9)

Benefit = 0; Cost = 160 = Cost of traditional POC trial

One large POC trial will be executed
Risk adjusted benefit = 0.24; Risk adjusted cost 346 patients; Efficiency = 6.9 X 10^-4
Drug Active

Small POC Trial Outcome

Yes (0.3)

False negative (0.4)

Benefit = 0; Cost = 80 = Cost of small POC trial

True positive (0.6)

Benefit = 1; Cost = 680 = Cost of small POC trial plus cost of Phase III trial

No (0.7)

False positive (0.1)

Benefit = 0; Cost = 680 = Cost of small POC trial plus cost of Phase III trial

True negative (0.9)

Benefit = 0; Cost = 80 = Cost of small POC trial

Two small POC trials will be executed
Risk adjusted benefit = 0.18 X 2; Risk adjusted cost = 460 patients; Efficiency 7.8X10^{-4}
Departing from Tradition and the Type III Error

- Traditional Type I and II error describe the false positive and negative rates
- Type III error describes the opportunity cost of not investigating valid hypotheses due to budgetary limitations
- Under a fixed budget, smaller than traditional randomized Phase 2 studies are optimal
Biomarker (BM) enriched P2 study:
- Designed to optimally test BM hypothesis by enrolling 50% BM+.
- Trial powered for independent analysis of BM+ and BM- subsets.
- Study has 4 groups: BM+ experimental, BM+ control, BM- experimental, BM- control
- Size using Chen-Beckman method applied to BM+ and BM- subsets

2D decision rule (Clark): see next slide
2D Decision rule for MK-0646 triple negative breast cancer (Clark)
Example of adaptive study design (II)
The Biomarker adapted P3 study

• BM Adaptive P3*
  – Study proceeds in full population.
  – Use data from P3 up to interim analysis and maturing data from P2 to:
    • Optimally focus analysis (“allocate alpha”) between full and sub-population
    • Maximize utility per cost function, such as power per study size, or expected ROI
  – Greater ROI than either traditional or biomarker driven P3

Phase 2 Influencing Phase 3 Adaptation: The Phase 2+ Method
Summary

- Predictive biomarkers will be increasingly essential to deliver competitive patient value
- Proposed guidelines for incorporation of biomarker hypotheses into clinical plans
- Key features:
  - Prioritization of clinical benefit id biomarker hypotheses
  - Validation of primary biomarker hypothesis against qualified clinical benefit endpoints
  - Adaptive decision-making within programs to progress to decision of whole population or biomarker selected subset
  - Use of IVD candidate in late phase studies → available for simultaneous registration with product
  - Health authority buy-in

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Next Generation Personalized Medicine*

*Beckman RA, Schemmann GS, and Yeang CH. Impact of genetic dynamics and single-cell heterogeneity on development of nonstandard personalized medicine strategies for cancer. Proceedings of the National Academy of Sciences USA. Published online before print August 13, 2012, doi: 10.1073/pnas.1203559109
Heterogeneity Within Tumors

• Tumors are genetically unstable; this is the most efficient way for cancer to evolve*
• Genetic instability leads to multiple sub-populations of tumor cells
• Resistant sub-populations are selected in response to therapy
• This is likely the reason why targeted therapies generally work best as a complement to non-specific therapies like chemotherapy

Clinical Significance of the Mutator Hypothesis

- Heterogeneity
- Moving Target
A Simple Model

- Two drugs: Drug-1 and Drug-2
- Four cell types:
  - Sensitive cell S, killed by both Drug-1 and Drug-2
  - Resistant cell R1, killed only by Drug-2
  - Resistant cell R2, killed only by Drug-1
  - Incurable doubly resistant cell R1-2
- Genetic and epigenetic transitions between cell types
- Cell growth and death affected by drugs in dose dependent manner
- Partial resistance
- Patient can have a *mixture* of cells, which *evolves* over time

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Current Personalized Medicine: 28 months to incurable relapse
Next Generation Personalized Medicine: Cure
Key questions

- How general are the benefits of this illustrative example?
- How great are the potential benefits of next generation personalized medicine?
- When is it important to focus on prevention of resistance as an even higher priority than treatment of the current tumor?
In Silico “Clinical Trial”: 3 million “patients”
A **strategy** is a data-driven method for planning a sequence of therapies
- When to treat with a combination and when to treat with sequential monotherapy
- When to change therapies

Like therapies, **strategies** may be individualized

The simulation compared 6 strategies
- Strategy 0 is the personalized medicine strategy: the patient is treated with the best drug for the observed predominant cell type and switched to the alternative drug upon tumor progression or relapse.
- Strategies 1, 2.1, 2.2, 3, and 4 (see backup for detail):
  - Used the evolutionary model to predict the total cell number and the likelihood of forming an incurable cell at the next 45 day timepoint
  - Gave therapy that minimized either total cell number or incurable cell likelihood
  - Differed in method of prioritizing total cell number vs incurable cells
Benefit of next generation personalized medicine is very general
## Differences between Current Personalized Medicine and Next-Generation Personalized Medicine

<table>
<thead>
<tr>
<th><strong>Current Personalized Medicine:</strong></th>
<th><strong>Next Generation Personalized Medicine:</strong></th>
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<tbody>
<tr>
<td>Focus on average molecular characteristics</td>
<td>Minority subpopulations may be important</td>
</tr>
<tr>
<td>Focuses on current molecular characteristics and/or those at dx</td>
<td>Considers endgame, especially “penultimate states”</td>
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<td>Thinks primarily of current step</td>
<td>Attempts to think several steps ahead</td>
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<td>Mathematical optimization to inform current step (signatures)</td>
<td>Piecewise, or even global, optimization of entire treatment course</td>
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Next Generation Personalized Medicine: High Level Conclusions

- The current strategy used for personalized therapy of cancer is not the only possible one.
- Genetic heterogeneity and evolutionary dynamics can greatly influence the optimal strategy for personalized medicine.
- The systematic study of non-standard personalized medicine strategies as a function of population substructure and evolutionary dynamics is an important area for investigation.
  - It’s not just about these particular models or strategies.
- Benefits are potentially highly significant and very general across a large variety of tumor and therapy characteristics.
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