Inventory Guide of Biomarker based Clinical Study Design

- PHuse Japan 3rd. SDE -

(Dec. 3rd/2015)

Yasuhiko Imai, CP&P supervisor
Translational Research, BMS Japan
Agenda

1. Introduction

2. Inventory for Biomarker based Clinical Study Design

3. Pharmacometriicians’ Perspective
Definition for BMs

‘A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’

# Classification for BMs (1/2)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamic Biomarker</td>
<td>CRP, IL-6, TNF-α, FDG-PET,</td>
</tr>
<tr>
<td>Prognostic Biomarker</td>
<td>Amyloid β peptide (AB) 1-42 , Mamma Print, BNP,</td>
</tr>
<tr>
<td>Predictive Biomarker</td>
<td>HER2, EGFR, KRAS mutation, BCR-ABL, CYP2D6, CYP2C9, CYP2C19, ER and PR,</td>
</tr>
<tr>
<td></td>
<td>PML/RARα, UGT1A1, TMPT, HLA-B*5701, DPYD, Oncotype, MammaPrint,</td>
</tr>
<tr>
<td>Surrogate Biomarker</td>
<td>LDL cholesterol, HbA1c, PSA, Carcinoembryonic antigen (CEA)</td>
</tr>
</tbody>
</table>
## Classification for BMs (2/2)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamic Biomarker</td>
<td>CRP, IL-6, TNF-α, FDG-PET,</td>
</tr>
<tr>
<td>Prognostic Biomarker</td>
<td>Amyloid β peptide (AB) 1-42 , Mamma Print, BNP,</td>
</tr>
<tr>
<td>Predictive Biomarker</td>
<td>HER2, EGFR, KRAS mutation, BCR-ABL, CYP2D6, CYP2C9, CYP2C19, ER and PR, PML/RARα, UGT1A1, TMPT, HLA-B*5701, DPYD, Oncotype, Mamma Print,</td>
</tr>
<tr>
<td>Surrogate Biomarker</td>
<td>LDL cholesterol, HbA1c, PSA, Carcinoembryonic antigen (CEA)</td>
</tr>
</tbody>
</table>
Prognostic/Predictive BMs

- **Prognostic**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Test</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

- **Predictive**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Test</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

- **Predictive & Prognostic**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Test</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>
Clinical qualification

- Co-development ~ Companion Biomarkers
  - What is objective to qualify Clinical Biomarkers?

- Clinical validity
  - Intended to use for Clinical Study

- Clinical utility
  - Intended to use for actual patient-treatment

- Retrospective ~ Prospective ~ Retrospective ~ Prospective analysis
Agenda

1. Introduction

2. Inventory for Biomarker based Clinical Study Design

3. Pharmacometricians’ Perspective
Randomized Clinical Trial (RCT) design

No objective for Clinical qualification of biomarkers

May be used to Initially identify candidate biomarkers by Retrospective analysis for RCTs (ex. KRAS and Cetzuximab).

- For a prognostic biomarker
  The clinical utility or validity of the biomarkers may need to be confirmed in prospective studies.

- For a predictive biomarker
  The clinical utility or validity of the biomarkers may be lack thereof and the clinical utility or validity of the biomarkers may be required to validate in prospective studies.
Biomarker by Treatment Interaction Design

All subjects

Diagnosis of Biomarker

Biomarker positive

Randomization

Standard treatment

Test treatment

Biomarker negative

Randomization

Standard treatment

Test treatment

Biomarker by Treatment Interaction Design

Could be used to confirm the Clinical validity of the biomarker previously qualified

- Biomarker positive
  - Randomization
    - Standard treatment
    - Test treatment

- Biomarker negative
  - Randomization
    - Standard treatment
    - Test treatment

A Cancer and Leukemia Group B trial to investigate benefit of adjuvant chemotherapy in stage NSCLC patients http://www.cancer.gov/clinical trials/CALGB-30506 (accessed on 31 May 2012)
Biomarker-Strategy Design

Biomarker-Strategy Design

(a) Generally less efficient than the traditional randomized design.

Enrichment Design and Hybrid Design

(a) All subjects

- Diagnosis of Biomarker
  - Biomarker +
    - Randomization
      - Standard treatment
      - Test treatment
  - Biomarker –
    - Off study

(b) All subjects

- Diagnosis of Biomarker
  - Biomarker +
    - Randomization
      - Standard treatment
      - Test treatment
  - Biomarker –
    - Standard treatment


(a) Possible to test the prospective validation of a prognostic biomarker in a clinical application.


Adaptive Signature Design

Adaptive Signature Design

The BMs-identification should be pre-specified. This design would be a practical approach when evidence about the predictive biomarker is insufficient before conducting the clinical study.

Biomarker-Adaptive Threshold Design

Basic RCT (S vs T)

Comparison between T and S using statistical test at $\alpha_1$ for all patients

Significant

- Succeeded in showing the efficacy of T for all patients

Not significant

- Comparison between T and S using statistical test at $\alpha_2$ for biomarker-positive subgroup

Significant

- Succeeded in showing the efficacy of T for the subgroup

Not significant

- Fail to show efficacy of T

**Biomarker-Adaptive Threshold Design**

Basic RCT (S vs T) → +Adjusting optimal cut-off point of the biomarker

Under pre-setting for TYPE I errors, estimating of the cut-off points would be "inexplicable".

Succeeded in showing the efficacy of T for all patients

Comparison between T and S using statistical test at $\alpha_2$ for biomarker-positive subgroup

Significant → Succeeded in showing the efficacy of T for the subgroup

Not significant → Fail to show efficacy of T

Adaptive Accrual Design

Basic RCT (S vs T)

Interim analysis of comparison between T and S for biomarker-negative patients

Futility
- End of accrual of biomarker-negative patients
- Comparison between T and S for biomarker-positive patients

Unclarity
- Continuance of accrual of biomarker-positive/negative patients
- Comparison between T and S for all patients and for biomarker-positive patients

Adaptive Accrual Design

A greater power than a standard RCT design (non-adaptive trial); however, the design accrues many more biomarker-positive patients and may require a much longer trial duration depending on the prevalence of the biomarker. In addition, the futility boundary is somewhat conservative and less than optimal as it is set to be in the region where the observed efficacy for the standard treatment is greater than that for the test treatment.

Bayesian Adaptive Design

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Biomarker 1</td>
<td>+</td>
</tr>
<tr>
<td>Biomarker 2</td>
<td>+</td>
</tr>
<tr>
<td>Biomarker 3</td>
<td>+</td>
</tr>
</tbody>
</table>

Statistical Issues

• Confounding and Interaction
  – Not only enrollment bias, also in association between BMs and Clinical Outcomes
  – Subgroup analysis and Model-based analysis

• Multiplicity
  – Futility, Enrichment, Adaptive, Biomarker classification

• Statistical Significance vs. Clinical significance

• Bayes vs. Non-Bayes
Agenda

1. Introduction

2. Inventory for Biomarker based Clinical Study Design

3. Pharmacometricians’ Perspective
Directed Acyclic Graph for Causal-Effect relationships between Dose/Exposure/Response
Directed Acyclic Graph for Causal-Effect relationships between Treatment/Exposure/BM/Response
Today’s conclusion

• We need ..... 
  – Prospective discussion among all stakeholders
    as like NCI Biomarker study registry
    (http://win.biomarkerregistry.org)

  – Intensive Collaboration among all stakeholders