Design Elements of Clinical Trials Involving Biomarkers

Canadian Cancer Trials Group
New Investigator Clinical Trials Course

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Learning Objectives

At the end of the lecture the participants will be able to:

1. Distinguish the difference between prognostic and predictive biomarker
2. Understand three types of biomarker related clinical trial designs: biomarker enrichment design, biomarker stratify design, biomarker adaptive design.
3. Get basic idea on how to identify cut-point for a continuous biomarker.
Outline

• Prognostic and predictive biomarkers

• Design of Clinical Trials that involves biomarker
  - Biomarker enriched designs
  - Biomarker stratified designs
  - Biomarker adaptive designs

• Cut point issues for continuous biomarkers
Prognostic and predictive biomarker

• Classification of Biomarkers in Clinical Trials

- **Prognostic biomarker**: A measurement that is associated with clinical outcome in the absence of therapy or with standard therapy.

- **Predictive biomarker**: Biological characteristics of patients measured at baseline, that helps identify patients who are likely or not likely to benefit from a therapy.
## Prognostic and predictive biomarker

<table>
<thead>
<tr>
<th>Is the biomarker prophostic</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Neither prognostic nor predictive</td>
<td>Predictive but not prognostic</td>
</tr>
<tr>
<td>Yes</td>
<td>Prognostic but not predictive</td>
<td>Both prognostic and predictive</td>
</tr>
</tbody>
</table>
Prognostic and predictive biomarker

• In statistical term: **Interaction** effect between treatment Z and a biomarker W for response variable Y

\[(Y|Z, W) \sim \beta_0 + \beta_1 Z + \beta_2 W + \beta_3 ZW\]

- Neither prognostic nor predictive: \(\beta_2 = 0, \beta_3 = 0\)
- Prognostic but not predictive: \(\beta_2 \neq 0, \beta_3 = 0\)
- Predictive but not prognostic: \(\beta_2 = 0, \beta_3 \neq 0\)
- Both predictive and prognostic: \(\beta_2 \neq 0, \beta_3 \neq 0\)
Prognostic and predictive biomarker

• Examples of biomarker
  ➢ Prognostic
  ➢ But no predictive
  ➢ No treatment effect
    ➢ T: Treatment arm
    ➢ C: Control arm

![Graph showing the difference between biomarker positive and negative outcomes in treatment and control arms.](image)
Prognostic and predictive biomarker

- Examples of biomarker
  - **Prognostic**
  - **But no predictive**
  - Treatment benefit equally
    - T: Treatment arm
    - C: Control arm
Prognostic and predictive biomarker

**BR.21: Histology is Prognostic but not Predictive**

HR (adenocarcinoma) = 0.71 (95% CI, 0.56 – 0.92)
HR (squamous cell) = 0.67 (95% CI, 0.50 – 0.90)

Interaction p-value = 0.97

*Clark GM. Mol Oncol 2008; 1:406-12*
Prognostic and predictive biomarker

• Examples of biomarker

  ➢ Predictive
  ➢ But no prognostic
  ➢ Treatment benefit only the biomarker positive group but not the biomarker negative group
Prognostic and predictive biomarker

Biomarker Positive, T
Biomarker Positive, C
Biomarker Negative, T
Biomarker Negative, C
Prognostic and predictive biomarker

BR.21: Smoking is Predictive but not Prognostic

HR (never smokers) = 0.42 (95% CI, 0.28 – 0.64)
HR (ever smokers) = 0.87 (95% CI, 0.71 – 1.05)

Interaction p-value = 0.006

Clark GM. Mol Oncol 2008; 1:406-12
Design biomarker clinical trials

• Different type of design with biomarkers

   ➢ Biomarker enriched designs

   ➢ Biomarker stratified designs

   ➢ Biomarker adaptive design
Design biomarker clinical trials

• Biomarker enriched designs (Targeted designs)
Design biomarker clinical trials

• To use biomarker enrichment designs, we need

  ➢ Validated diagnostic test to identify Marker positive and Marker negative patients

  ➢ Strong biological evidence that Marker negative patients will not benefit from the Target Therapy

  ➢ Only Marker positive patients will be randomized to Target Therapy and Standard Therapy groups
Design biomarker clinical trials

• Examples of biomarker enriched designs

➢ Trastuzumab (Herceptin) for HER2 positive breast cancer patients (Shak S. Overview of the trastuzumab (Herceptin) anti-HER2 monoclonal antibody clinical program in HER2-overexpressing metastatic breast cancer. Herceptin Multinational Investigator Study Group. Semin Oncol 1999;26:71-7.)

• Overall survival from Vemurafenib trial for melanoma patients with BRAF mutation

Design biomarker clinical trials

• Biomarker stratified designs

Marker+

Randomization

Targeted Therapy

Standard Therapy

Marker−

Randomization

Targeted Therapy

Standard Therapy
Design biomarker clinical trials

• To use biomarker *stratified* designs, we need
  
  ➢ Validated diagnostic test to identify Marker positive and Marker negative patients

  ➢ Marker negative patients may have benefit from the Target Therapy

  ➢ Both Marker positive and negative patients will be randomized to Target Therapy and Standard Therapy groups
Design biomarker clinical trials

• Challenges for analyzing data from biomarker stratified designs
  - The statistical analysis plan have to be pre-specified
  - Multiple study populations could inflate type I error rates (have to control overall alpha < 0.05)
  - Scenario A: If treatment is more like to be effective in biomarker positive group
  - Scenario B: If there is limited confident in the predictive biomarker
Design biomarker clinical trials

• Test I: Sequential approach
  ➢ Step 1: Test treatment effect in the biomarker positive group with alpha = 0.05
    ➢ If significant, then stop!
    ➢ If negative, go to step 2
  ➢ Step 2: Test treatment effect in the biomarker negative group with alpha = 0.05

• Test II: Fall-back approach
  ➢ Step 1: Test treatment effect in the overall population with alpha = 0.03 (a reduced significant level)
    ➢ If significant, then stop!
    ➢ If negative, go to step 2
  ➢ Step 2: Test treatment effect in the biomarker positive population with the remaining (unused) significant level alpha = 0.02

Design biomarker clinical trials

• Example of biomarker stratified design

Marker Validation for Erlotinib in Lung Cancer
Design biomarker clinical trials

• Using archived tumour specimens to conduct prospective-retrospective analysis of a randomized phase III trial to identify predictive biomarker
  
  ➢ This requires archived specimens be available on most patients
  
  ➢ The Statistical analysis plan have to be developed beforehand
  
  ➢ Example:

  ➢ CO.17 with K-RAS mutation
Design biomarker clinical trials

• Biomarker adaptive design

Unselected patients

Randomization

Target Therapy

Standard Therapy

Design biomarker clinical trials

• To use biomarker adaptive designs, we need

  ➢ Tumour specimen to be collected from all patients at study entry
  ➢ Value of the biomarker is NOT used as an eligibility criteria
  ➢ Allow phase III trial without pre-specify the cut-point for biomarker
  ➢ Statistical inferences for treatment effects:

Design biomarker clinical trials

• Example of biomarker adaptive design for prostate cancer with serum prostatic acid phosphatase (AP) biomarker.
Design biomarker clinical trials

- An example of ki67 biomarker for breast cancer patients (Demo data)

Interaction p-value: 0.03

http://statapps.tk/biomarker_interaction/
Many biomarkers are continuous variables.

It is critical to establish a validate cut-point for biomarker

Example of using median Ki-67 as cut-point gives total different results

http://statapps.tk/biomarker_interaction/
Continuous biomarker

- Treat biomarker as a continuous variables

Liu, Jiang and Chen (2015): *Statistics in Medicine*
Continuous biomarker

• Actionable predictive biomarker? Clinically useful vs Statistically significance
  ➢ Idea situation: exists an obvious threshold (or a cut point)
  ➢ Clinically useful situation: exists a potential threshold
  ➢ Clinically not useful situation: a moderate but statistically significant linear relationship
Idea

$$\beta_0 + \{\beta_1 + \beta_3 I(W \geq c)\}Z$$

Treatment effect

Biomarker score

$\beta_1$ + $\beta_3$
Clinically useful

\[ \beta_0 + \beta(W) Z \]
Clinically not useful

$$\beta_0 + (\beta_1 + \beta_3 W)Z$$
General: multiple cut points

$$\beta_0 + \{\beta_1 + \beta_3 I(c_1 \leq W \leq c_2)\}Z$$
➢ Statistical methods to estimate optimal cut-points

➢ R package is now available for biomarker threshold models (the bhm package).

➢ Source code from the Comprehensive R Archive Network (https://CRAN.Rproject.org/package=bhm). To install the package:

```r
> install.packages("bhm")
```

Fitting Biomarker Threshold Models

Description

{bhm} is an R package for Biomarker Threshold Models. It uses either Hierarchical Bayes method or profile likelihood method (Chen, et al, 2014 and Tian, et al, 2016) to identify a cut-point (threshold parameter) for the biomarker in either generalized linear models or Cox proportional hazards model. The model is specified by giving a symbolic description of the linear predictor and a description of the distribution family.

Usage

bhm(x, ...)

## S3 method for class 'formula'
bhm(formula, family, data, control = list(...), ...)

# use
# bhm(y ~ biomarker)
#
# to fit a prognostic model with biomarker term only
# use
#
# bhm(y ~ biomarker+treatment)
Summary

• Predictive and prognostic biomarkers

• Clinical trials design account for biomarkers

• How to deal with continuous biomarkers