Canadian Cancer Trials Group

Design Elements of Clinical Trials Involving Biomarkers

Canadian Cancer Trials Group

New Investigator Clinical Trials Course

Bingshu E. Chen, Ph.D.

Queen's University

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

	Is the biomarker predictive?	
Is the biomarker prognostic	No	Yes
No	Neither prognostic nor predictive	Predictive but not prognostic
Yes	Prognostic but not predictive	Both prognostic and predictive

Prognostic and predictive biomarker

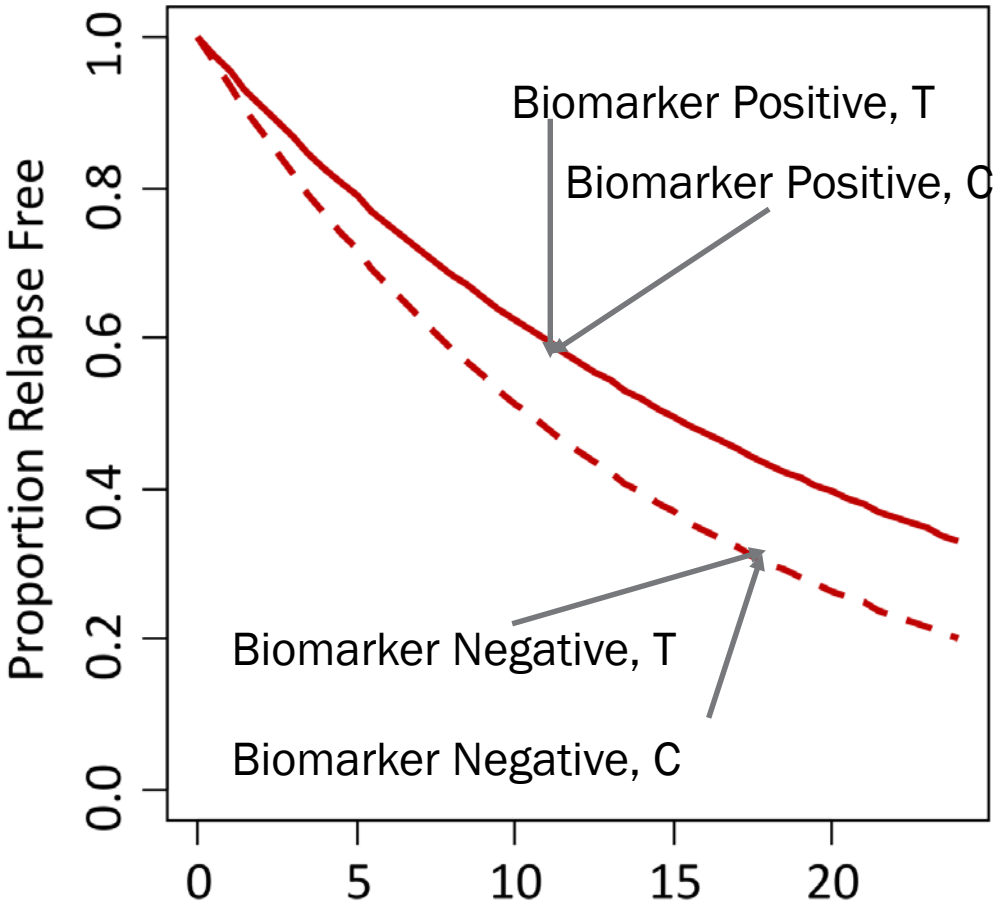
- In statistical term: Interaction effect between treatment Z and a biomarker W for response variable Y

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

- 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

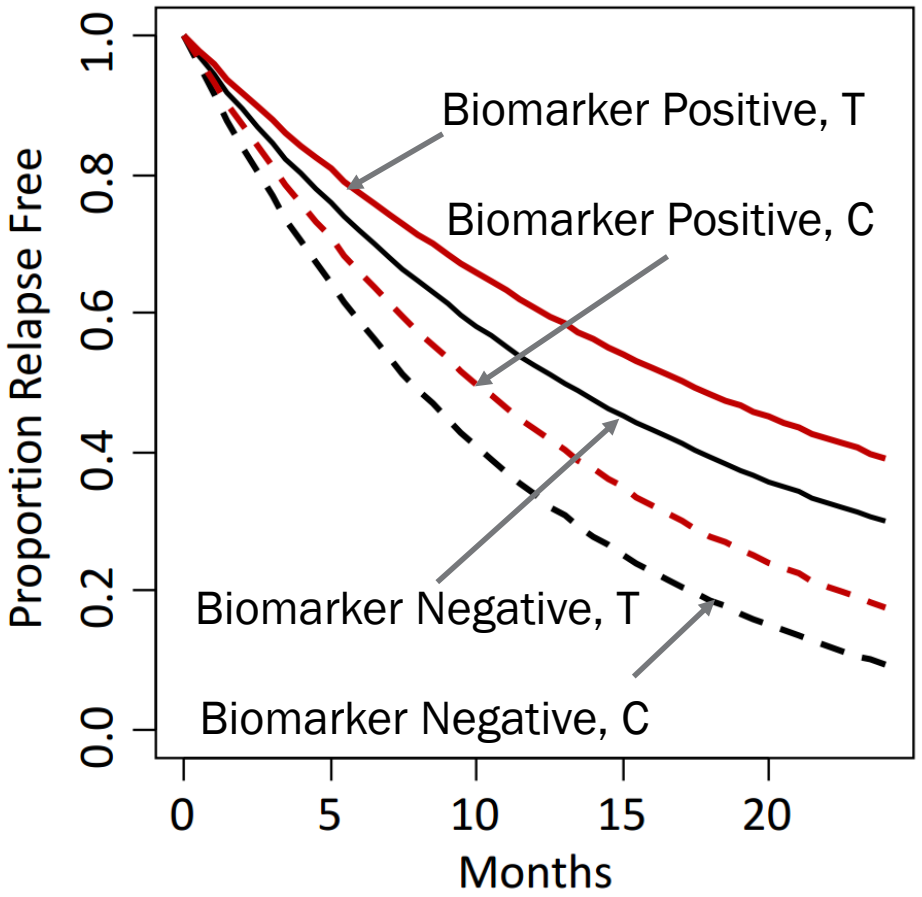
- Examples of biomarker
  - Prognostic
  - But no predictive
  - No treatment effect
    - T: Treatment arm
    - C: Control arm



Canadian Cancer Trials Group

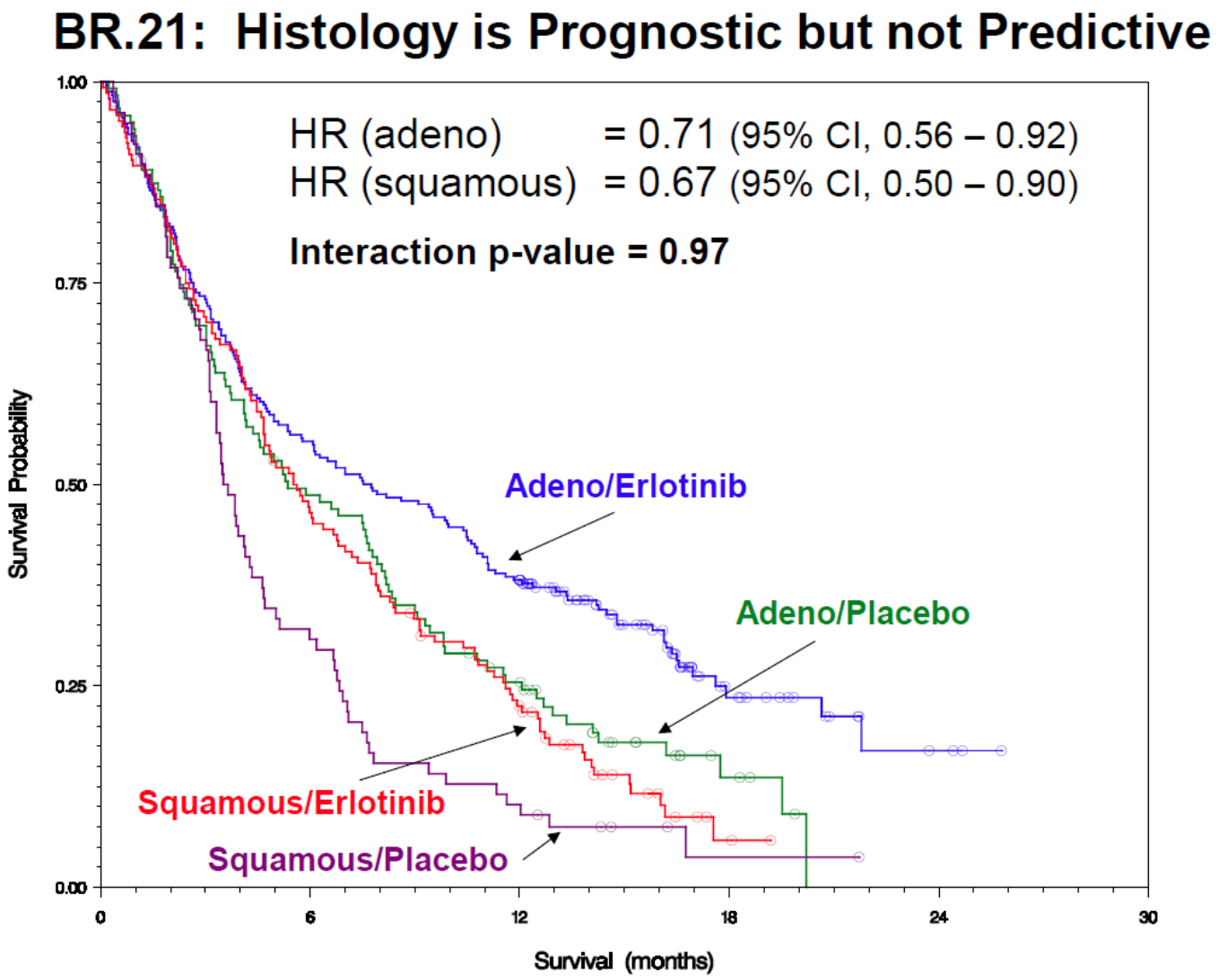
Prognostic and predictive biomarker

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



Canadian Cancer Trials Group

Prognostic and predictive biomarker



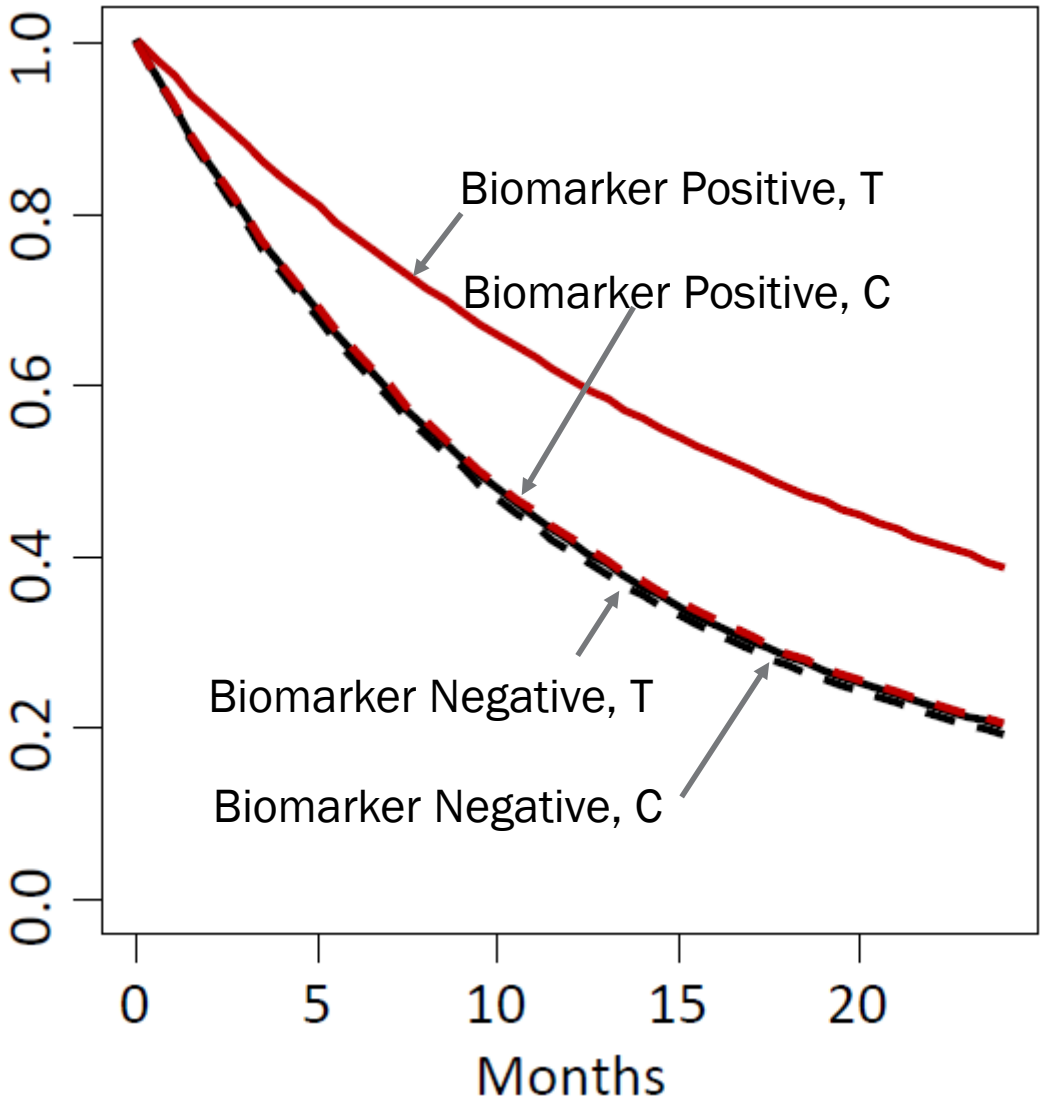
Clark GM. Mol Oncol 2008; 1:406-12

Canadian Cancer Trials Group

Prognostic and predictive biomarker

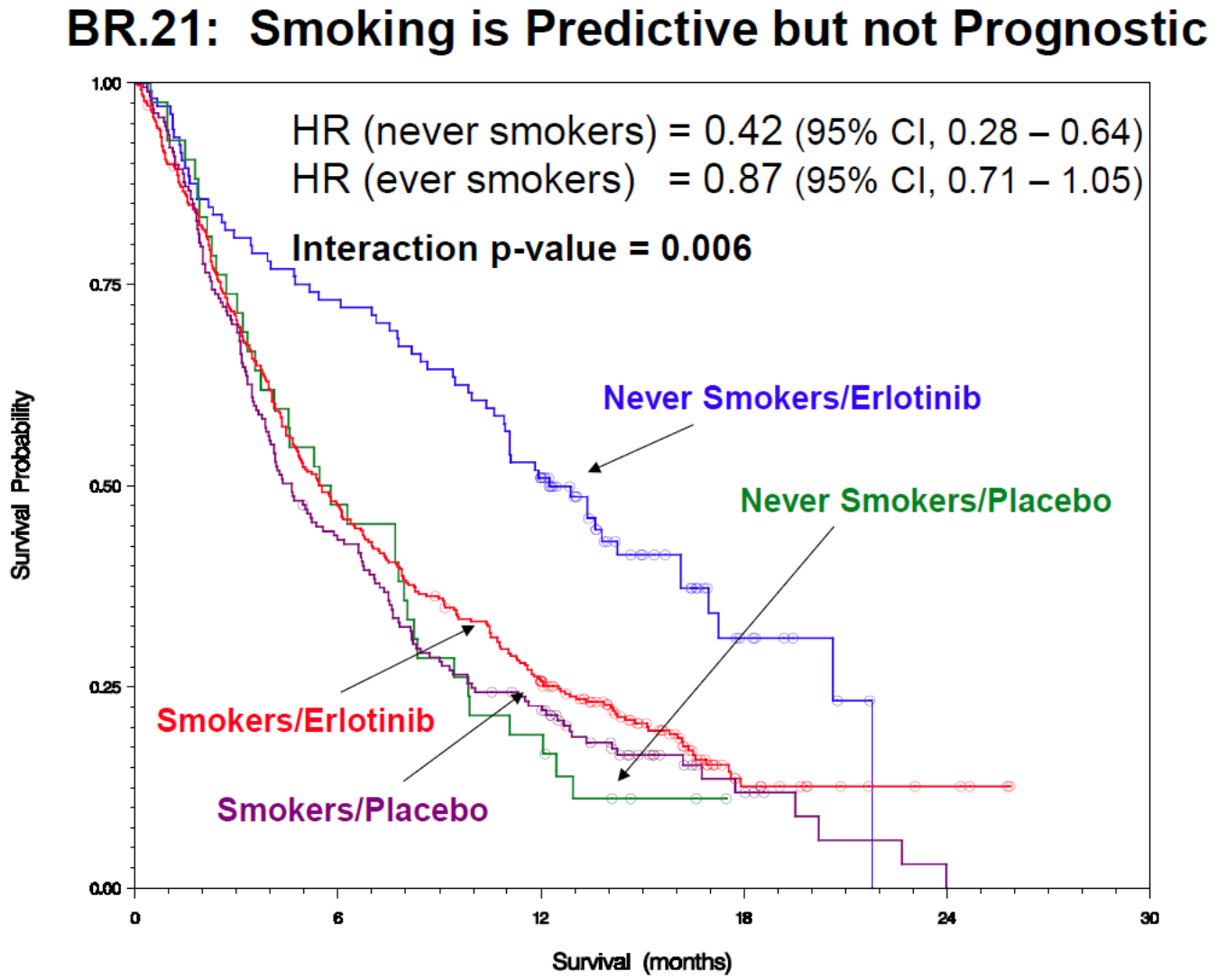
- Examples of biomarker
  - Predictive
  - But no prognostic
  - Treatment benefit only the biomarker positive group but not the biomarker negative group

Prognostic and predictive biomarker



Canadian Cancer Trials Group

Prognostic and predictive biomarker



Clark GM. Mol Oncol 2008; 1:406-12

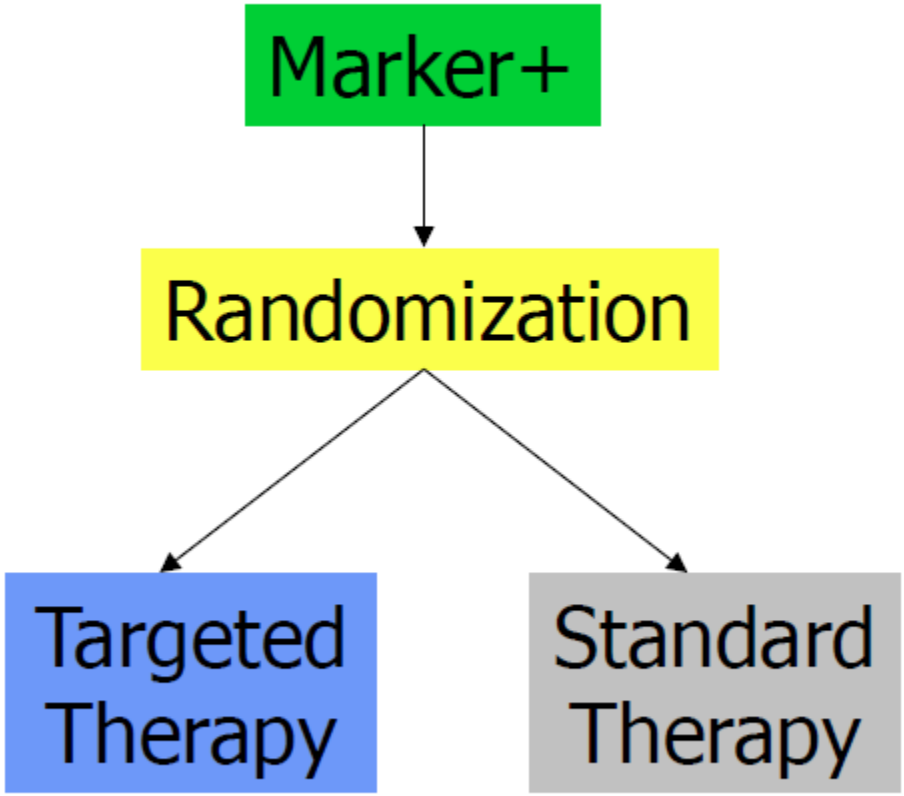
Canadian Cancer Trials Group

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

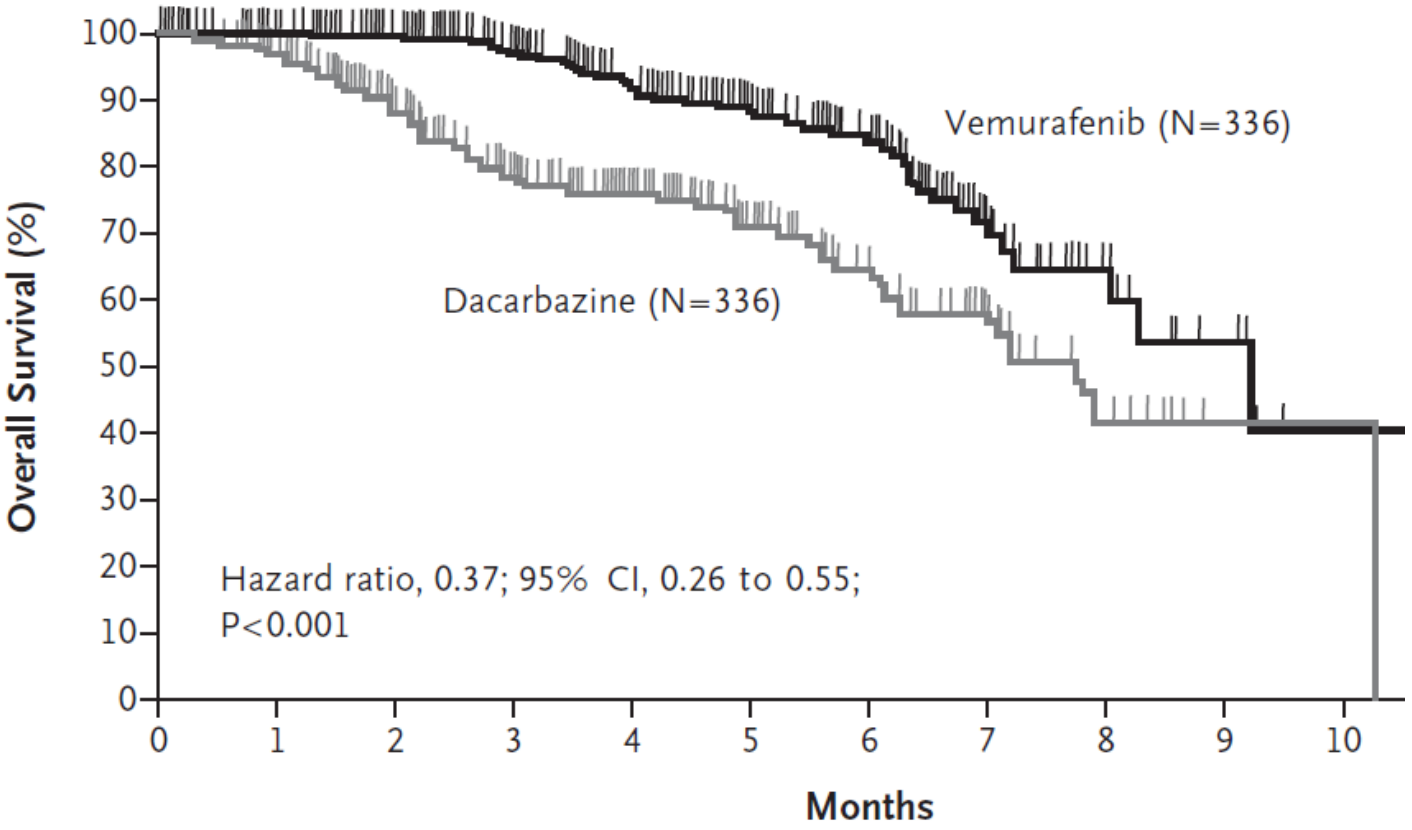
Design biomarker clinical trials

- 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.)

  - Vemurafenib for BRAF V600E mutation melanoma patients (Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.)

- Overall survival from Vemurafenib trail for melanoma patients with BRAF mutation

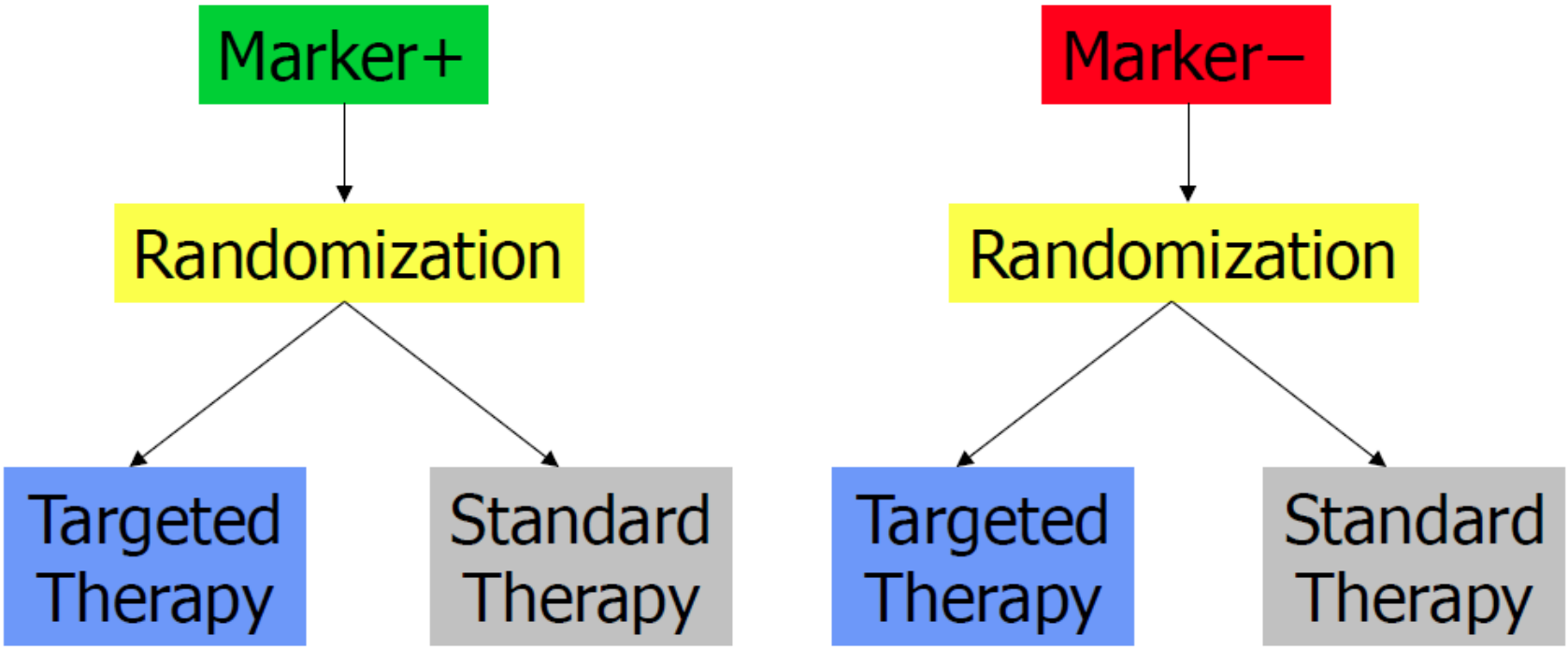


Chapman PB, et al (2011) NEJM page 2511

Canadian Cancer Trials Group

Design biomarker clinical trials

- Biomarker stratified designs



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

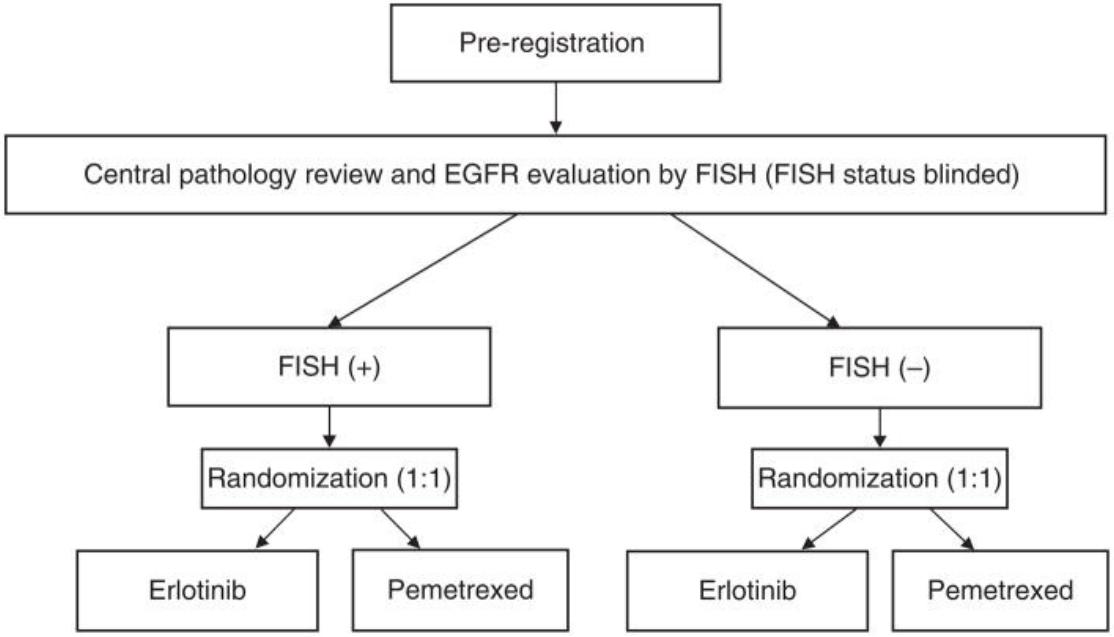
Design biomarker clinical trials

- 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

Simon R, Wang SJ. Pharmacogenomics J 2006;6:166-73.

Design biomarker clinical trials

- Example of biomarker stratified design



Mandrekar SJ, Sargent DJ. Clinical Trials 2010;7:567-73.
Marker Validation for Erlotinib in Lung Cancer

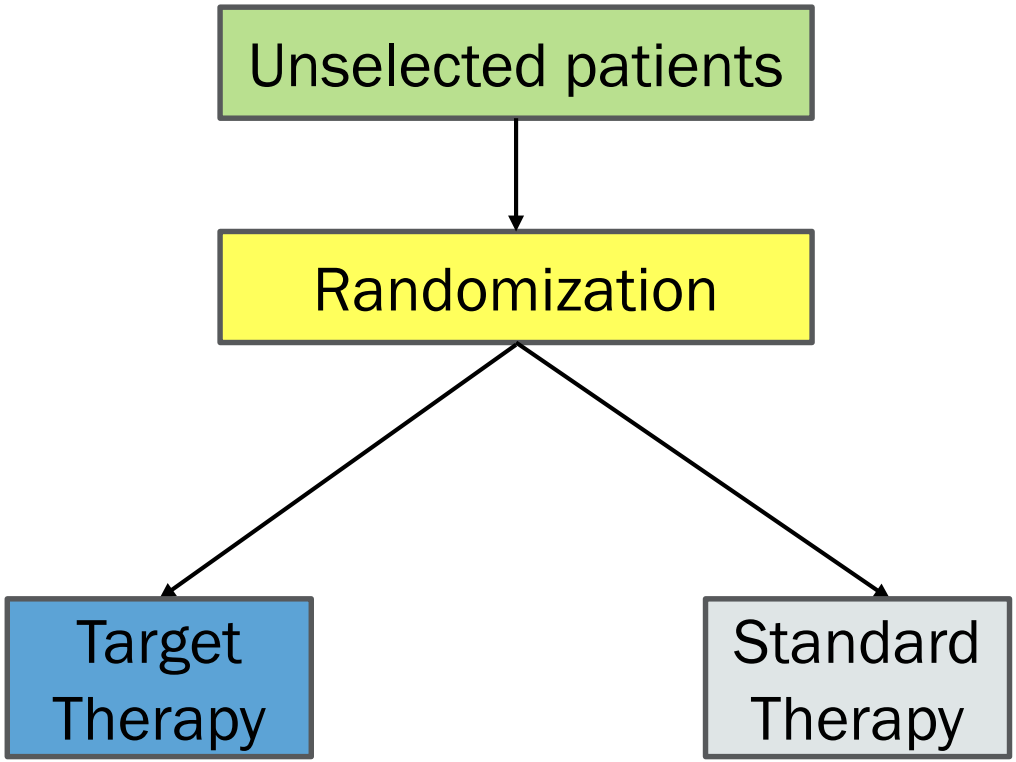
Design biomarker clinical trials

- 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



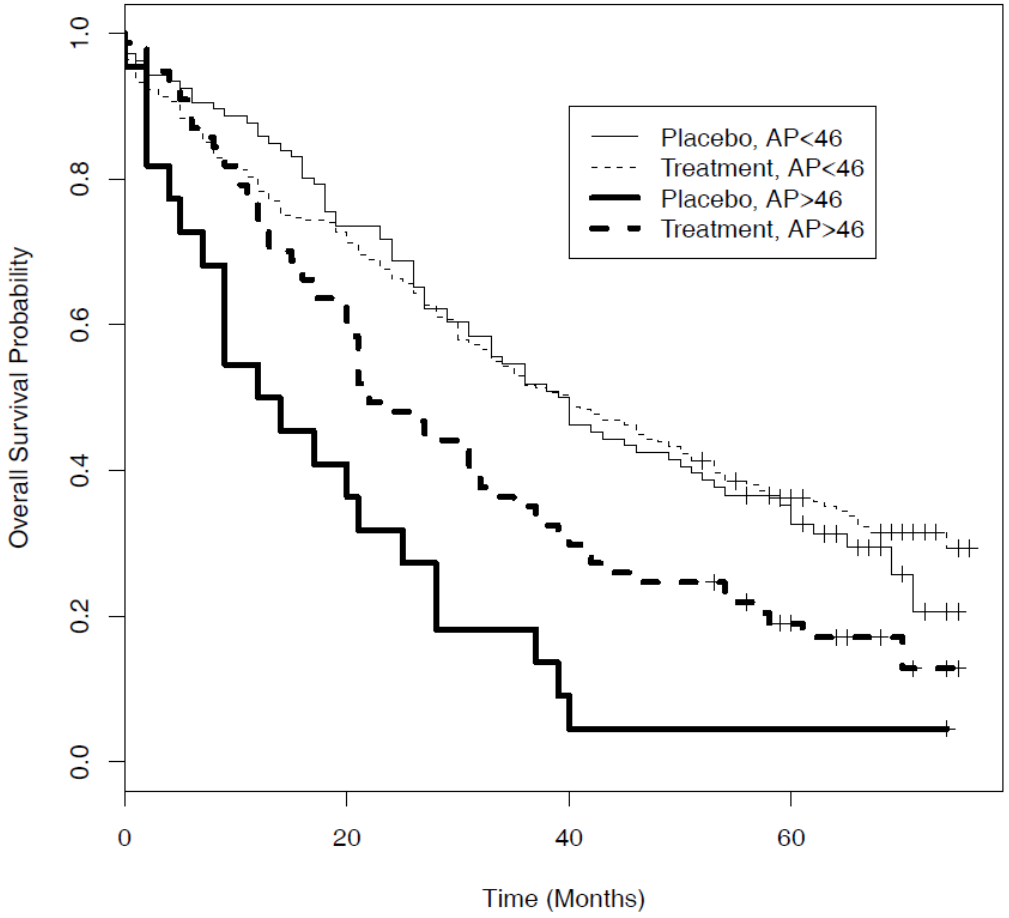
Jiang, W. and Simon, R. (2007) JNCI 1036-1043

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:
    - Jiang, W. and Simon, R. (2007). JNCI 1036-1043
    - Chen, B. E., Jiang, W. and Tu, D. (2014). Computational Statistics and Data Analysis. 324-334.

Design biomarker clinical trials

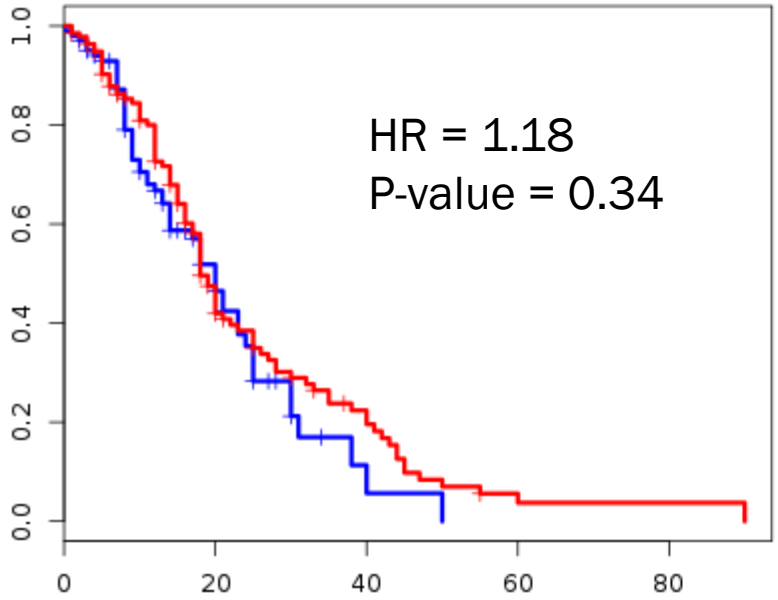
- Example of biomarker adaptive design for prostate cancer with serum prostatic acid phosphatase (AP) biomarker.

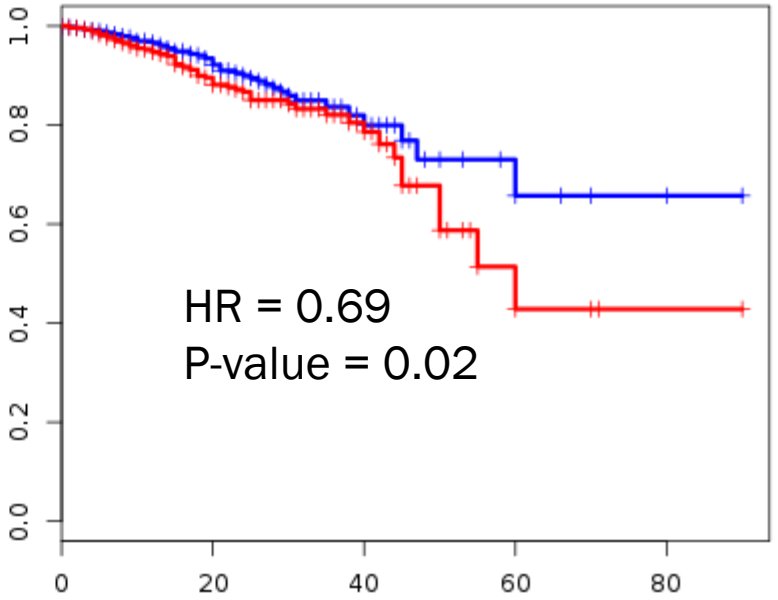


Canadian Cancer Trials Group

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/

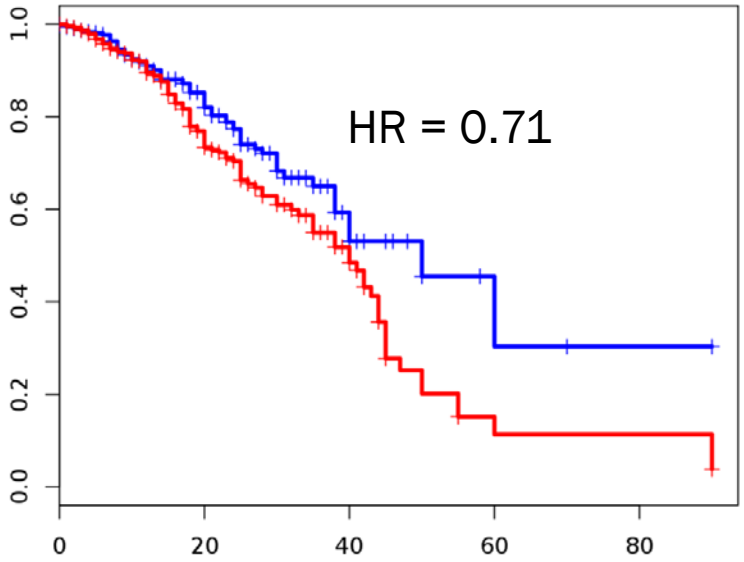
Canadian Cancer Trials Group

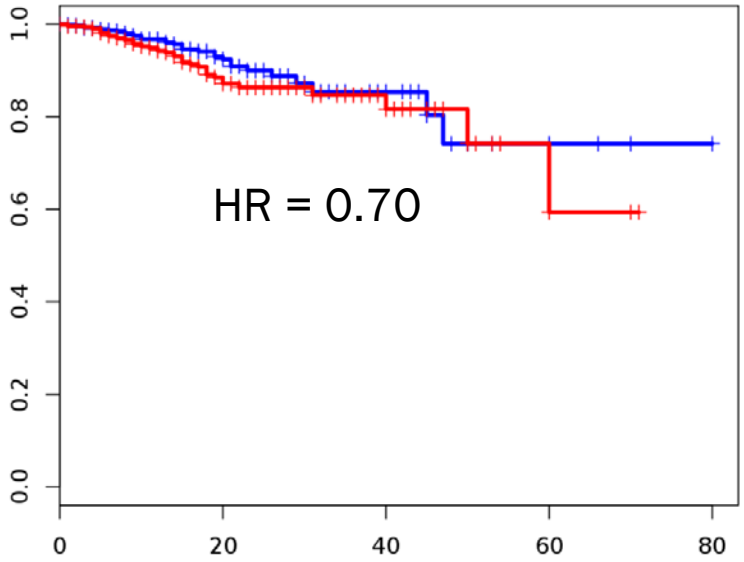
Continuous biomarker

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

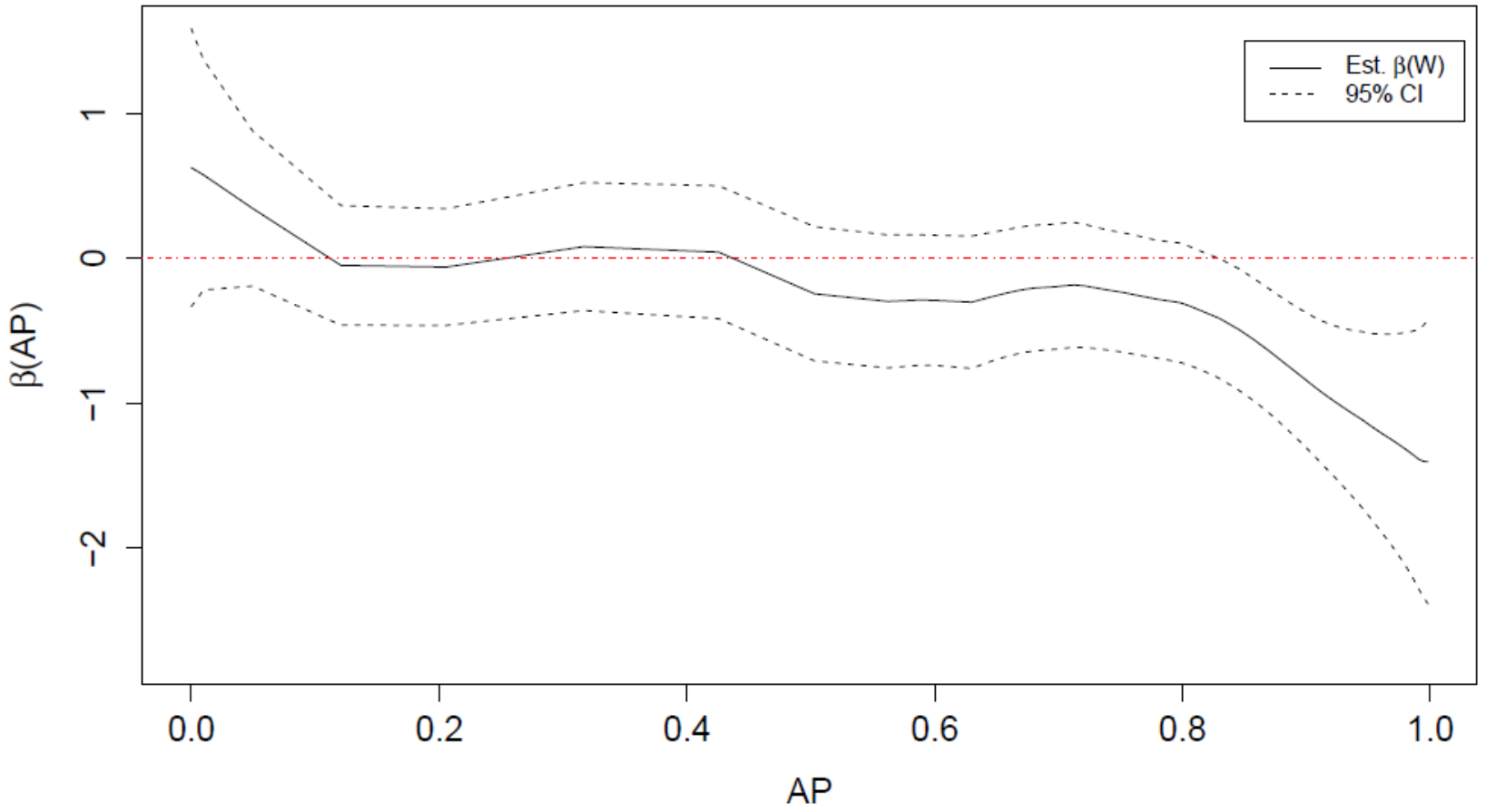




http://statapps.tk/biomarker_interaction/

Continuous biomarker

- Treat biomarker as a continuous variables



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

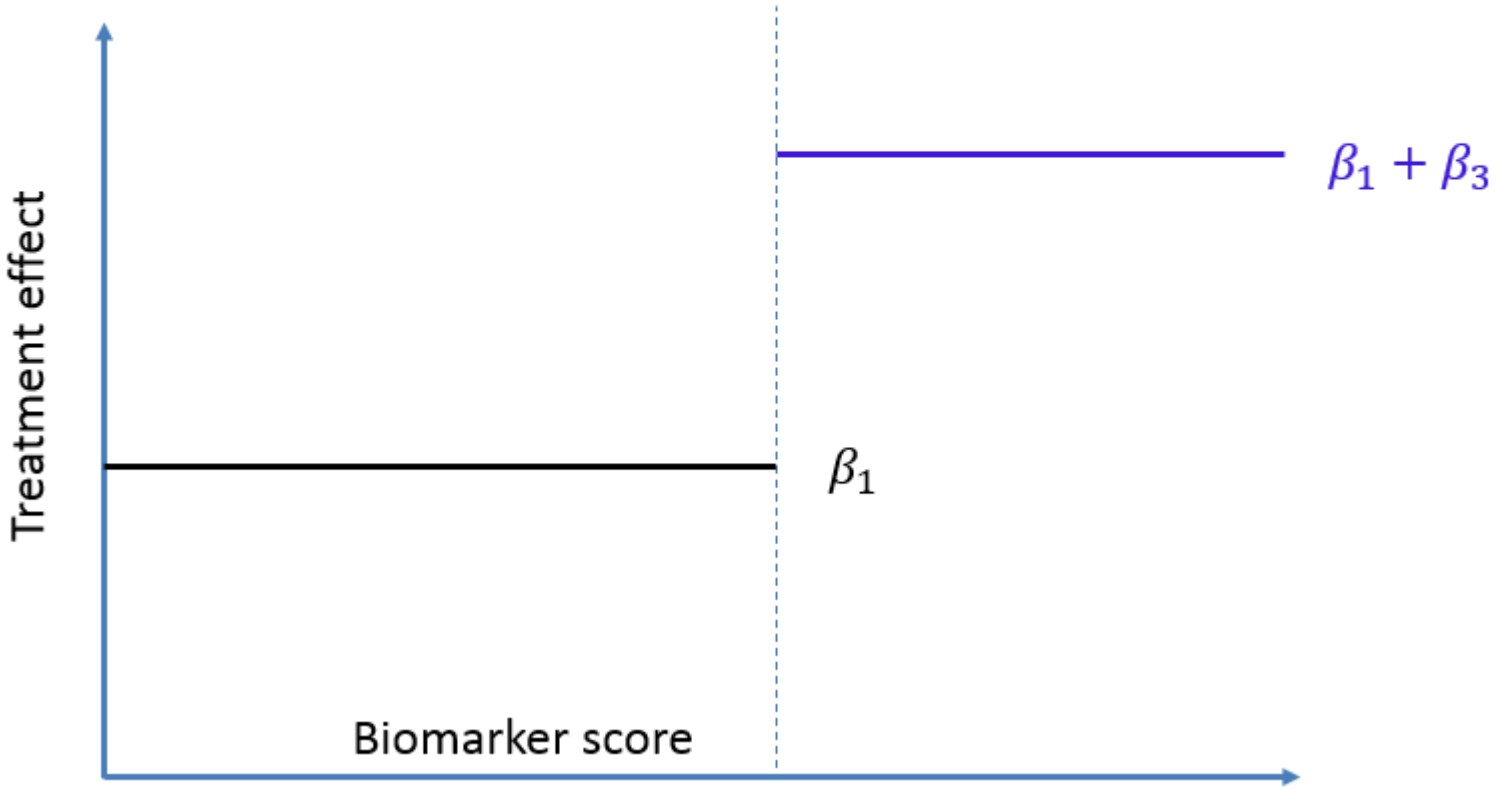
Canadian Cancer Trials Group

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

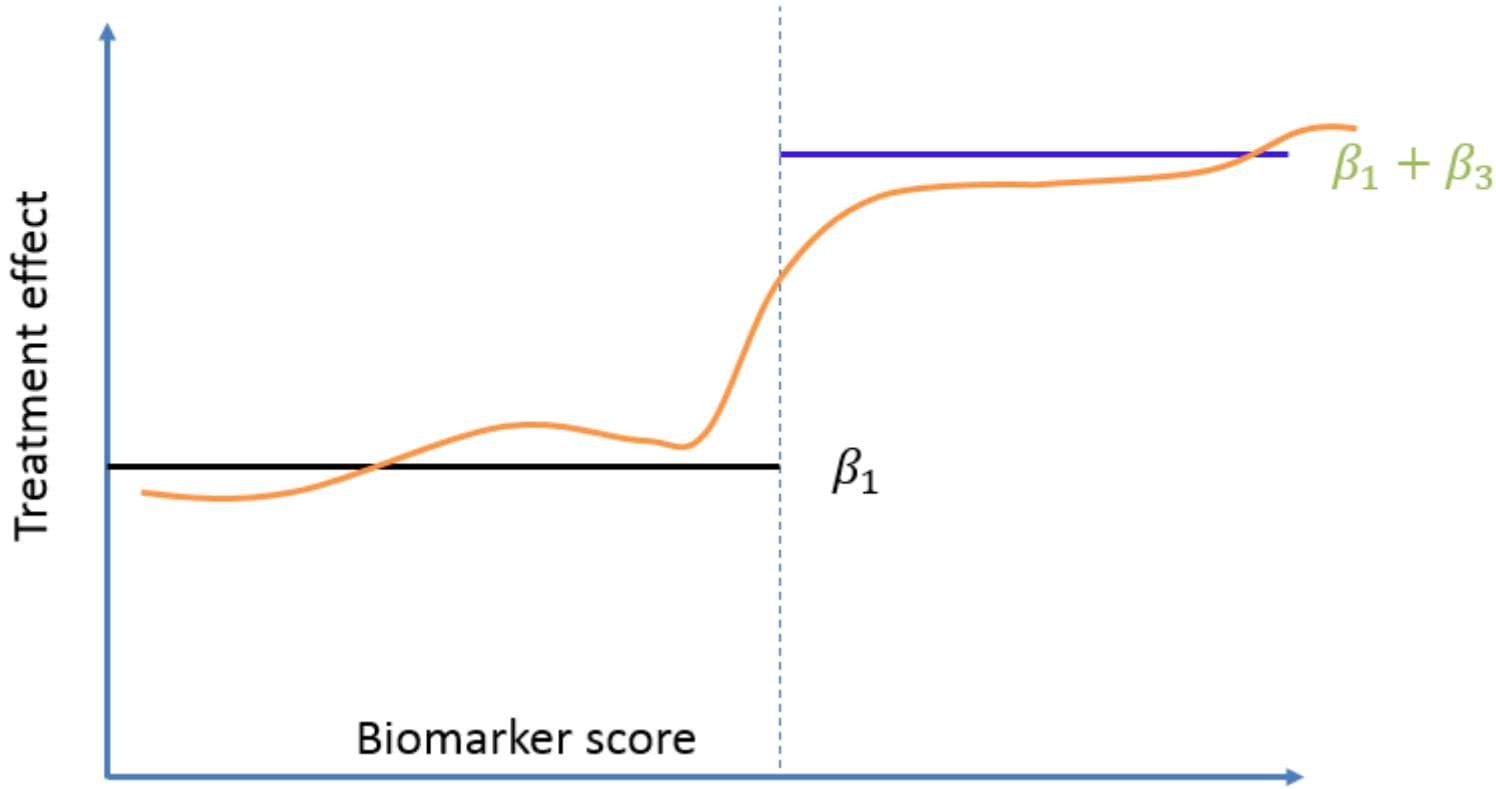
$$\beta_0 + \{\beta_1 + \beta_3 I(W \geq c)\}Z$$



Canadian Cancer Trials Group

➢ Clinically useful

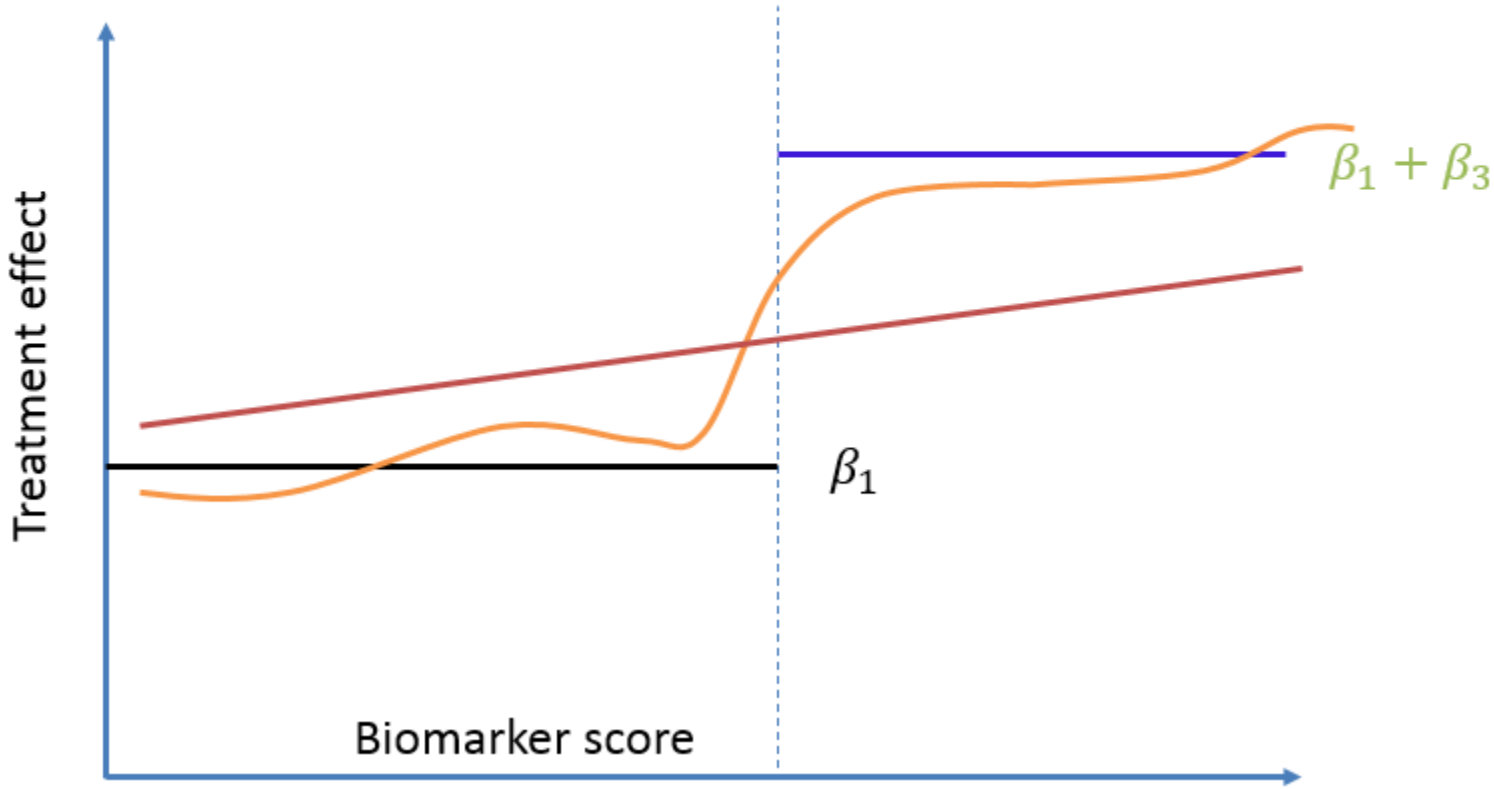
$$\beta_0 + \beta(W)\, Z$$



Canadian Cancer Trials Group

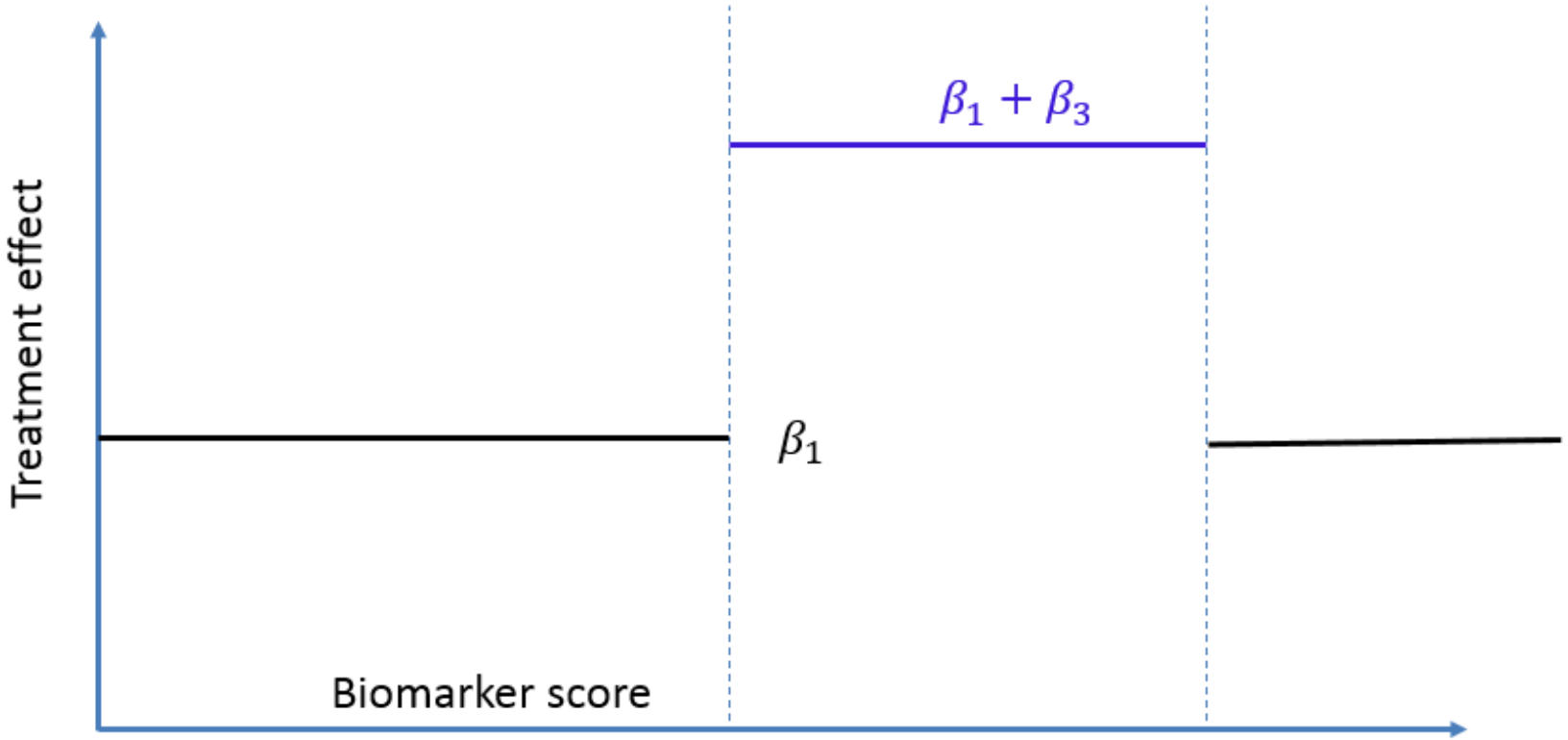
- Clinically not useful

$$\beta_0 + (\beta_1 + \beta_3 W)\, Z$$



- 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:

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

Fang, T., Mackillop, W., Jiang, W., Hildesheim, A., Wacholder, S. and Chen, B. E. (2017). Computational Statistics and Data Analysis. 53-62.

Fitting Biomarker Threshold Models

Description

{bhm} is a R package for Biomarker Threshold Models. It uses either Hierarchical Bayes method or proflie likehood method (Chen, et al, 2014 and Tian, et al, 2016) to identify a cut-point (thershold 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