Design of Randomized Phase II Clinical Trials with a Potential Predictive Biomarker

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Phase II trials are designed to decide whether to take an experimental therapy to a definitive phase III trial.

Possible phase III trial designs with the possibility of using a biomarker

(1) Enrichment design

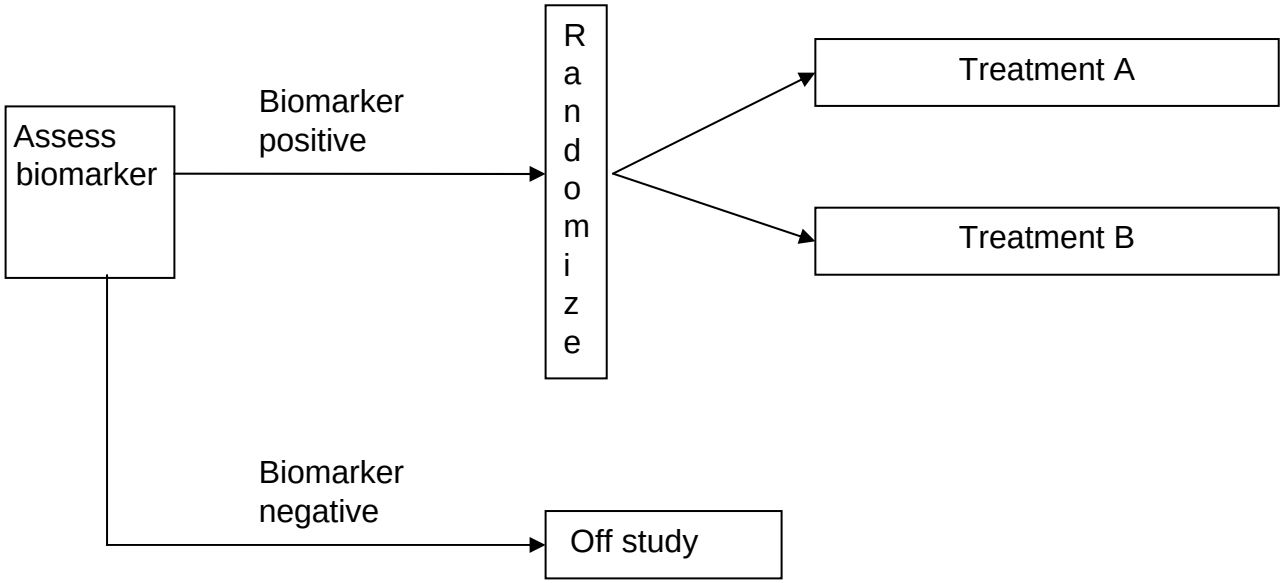
(2) Biomarker stratified design

(3) Standard phase III design ignoring the biomarker

(4) Biomarker strategy design

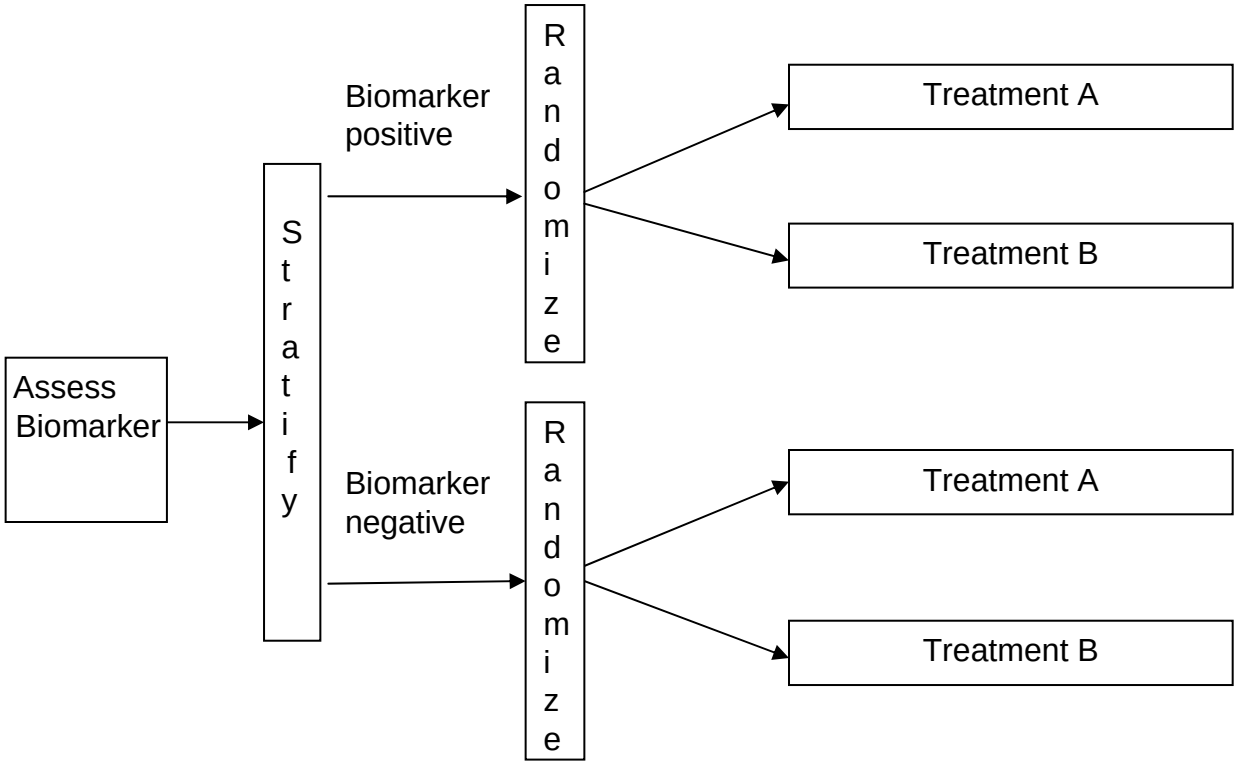
Possible phase III trial designs with a biomarker

(1) Enrichment design



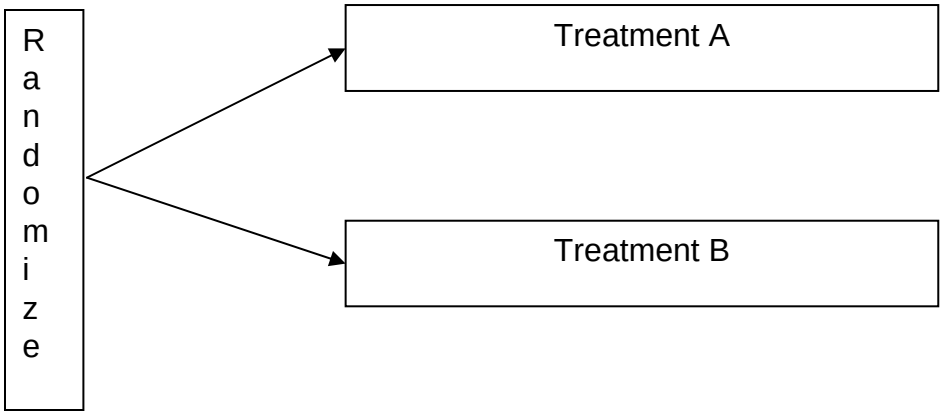
Possible phase III trial designs with a biomarker

(2) Biomarker stratified design



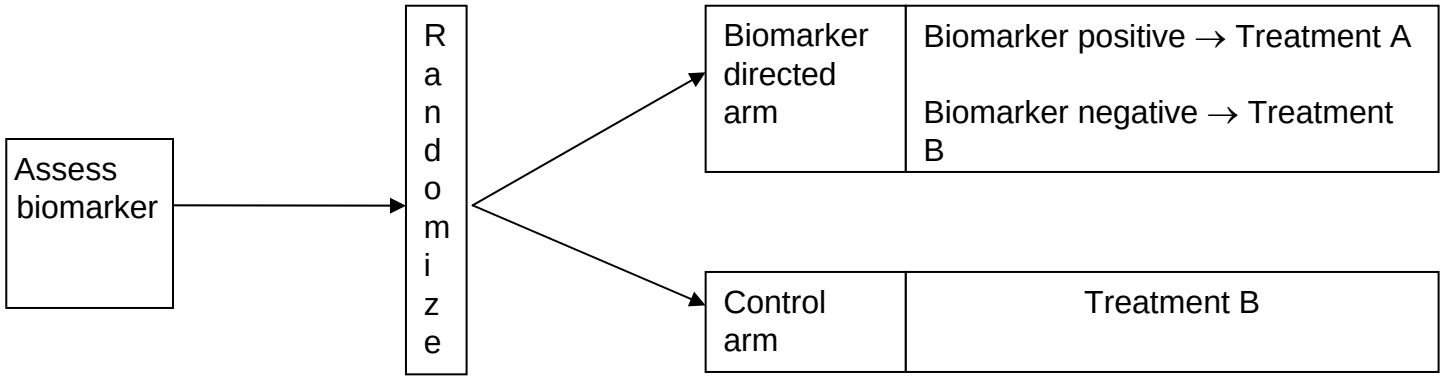
Possible phase III trial designs with a biomarker

(3) Standard phase III design ignoring the biomarker



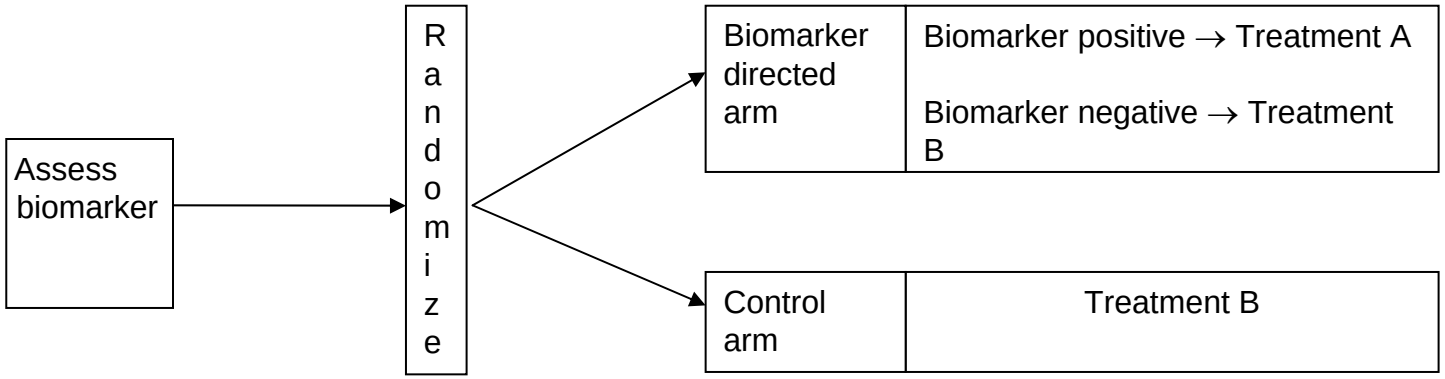
Possible phase III trial designs with a biomarker

(4) Biomarker-strategy design



Possible phase III trial designs with a biomarker

(4) Biomarker-strategy design –Not Generally Recommended



Proposed randomized phase II trial design with a biomarker:

Possible recommendations for the phase III trial after completing the phase II trial

(1) Enrichment design

(2) Biomarker stratified design

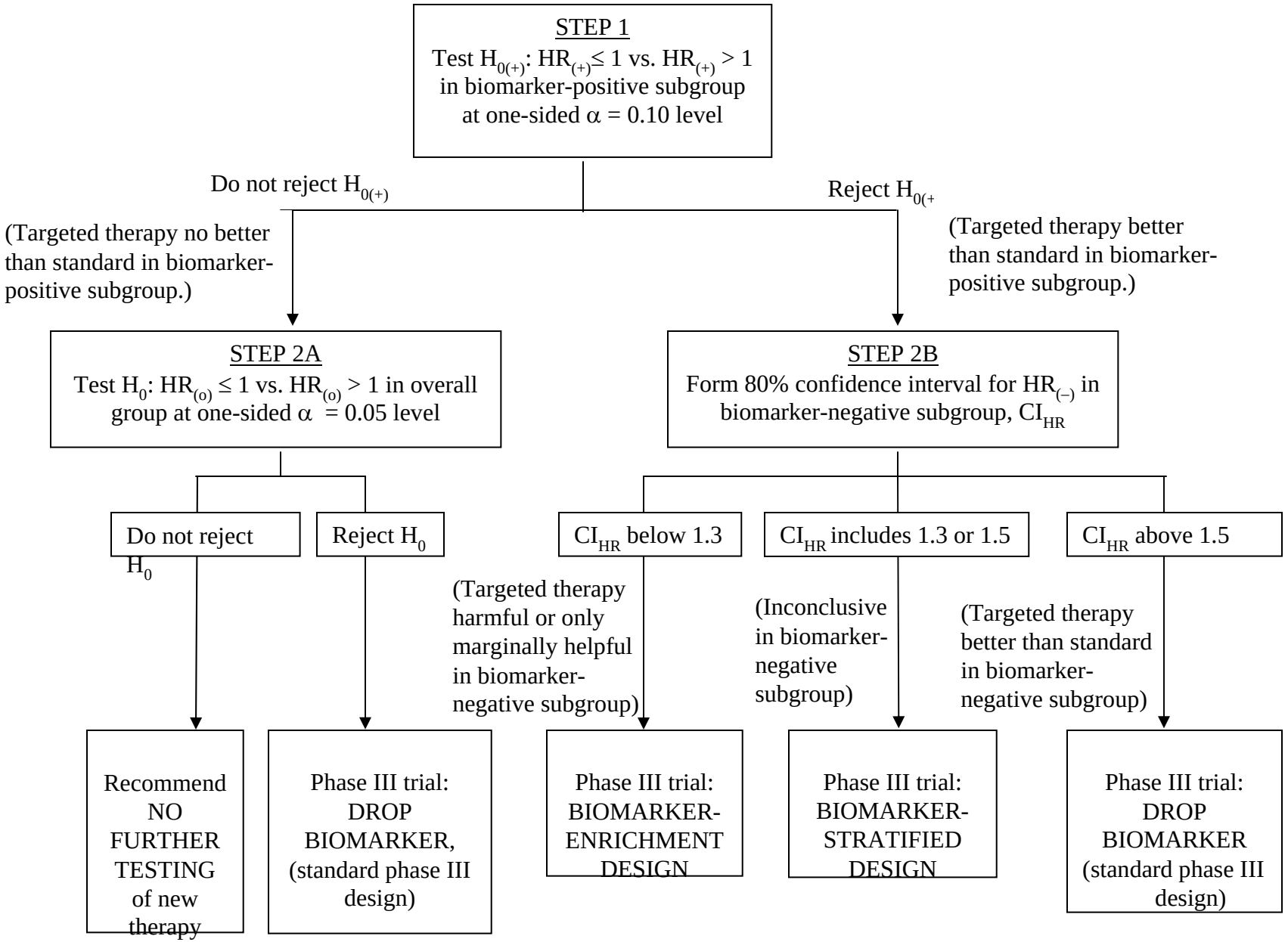
(3) Standard phase III design ignoring the biomarker

(4) No further testing of new therapy

When designing a phase II trial, one needs to have a target efficacy of the treatment in mind.

We will use a target of a hazard ratio of 2.0 in the biomarker-positive subgroup.

This approximately corresponds to a doubling of the median progression-free survivals.


STEP 1
Test $H_{0(+)}$: $HR_{(+)} \leq 1$ vs. $HR_{(+)} > 1$ in biomarker-positive subgroup at one-sided $\alpha = 0.10$ level
Do not reject $H_{0(+)}$
(Targeted therapy no better than standard in biomarker-positive subgroup.)
Reject $H_{0(+}$
(Targeted therapy better than standard in biomarker-positive subgroup.)
STEP 2A
Test H_0: $HR_{(o)} \leq 1$ vs. $HR_{(o)} > 1$ in overall group at one-sided $\alpha = 0.05$ level
STEP 2B
Form 80% confidence interval for $HR_{(-)}$ in biomarker-negative subgroup, CI_{HR}
Do not reject H_0
Reject H_0
CI_{HR} below 1.3
CI_{HR} includes 1.3 or 1.5
CI_{HR} above 1.5
(Targeted therapy harmful or only marginally helpful in biomarker-negative subgroup)
(Inconclusive in biomarker-negative subgroup)
(Targeted therapy better than standard in biomarker-negative subgroup)
Recommend NO FURTHER TESTING of new therapy
Phase III trial: DROP BIOMARKER, (standard phase III design)
Phase III trial: BIOMARKER-ENRICHMENT DESIGN
Phase III trial: BIOMARKER-STRATIFIED DESIGN
Phase III trial: DROP BIOMARKER (standard phase III design)

Simulations

Trial designed to detect a doubling of the median PFS in the biomarker subgroup (hazard ratio=2) with 90% power at the one-sided 10% significance level

Trial requires 56 PFS events in the biomarker-positive subgroup.

Approximate sample sizes=70 biomarker-positive patients
140 biomarker-negative patients

Simulated 50,000 trials.

Biomarker Subgroup

Positive			Negative		
Expt Tx. Median	Control Median	HR	Expt Tx. Median	Control Median	HR
4	4	1.0	4	4	1.0

Probability of recommendations for phase III trial design

Enrichment Design	6%
Biomarker-stratified design	4%
No biomarker (standard phase III)	3%
No further testing	87%

Biomarker Subgroup

Positive			Negative		
Expt Tx. Median	Control Median	HR	Expt Tx. Median	Control Median	HR
8	4	2.0	4	4	1.0

Probability of recommendations for phase III trial design

Enrichment Design	53%
Biomarker-stratified design	36%
No biomarker (standard phase III)	1%
No further testing	10%

Biomarker Subgroup

Positive			Negative		
Expt Tx. Median	Control Median	HR	Expt Tx. Median	Control Median	HR
6	4	1.5	6	4	1.5

Probability of recommendations for phase III trial design

Enrichment Design	1%
Biomarker-stratified design	52%
No biomarker (standard phase III)	38%
No further testing	10%

Biomarker Subgroup

Positive			Negative		
Expt Tx. Median	Control Median	HR	Expt Tx. Median	Control Median	HR
7	4	1.75	7	4	1.75

Probability of recommendations for phase III trial design

Enrichment Design	<1%
Biomarker-stratified design	51%
No biomarker (standard phase III)	48%
No further testing	1%

Biomarker Subgroup

Positive			Negative		
Expt Tx. Median	Control Median	HR	Expt Tx. Median	Control Median	HR
8	4	2	6	4	1.5

Probability of recommendations for phase III trial design

Enrichment Design	2%
Biomarker-stratified design	79%
No biomarker (standard phase III)	18%
No further testing	2%

Biomarker Subgroup

Positive			Negative		
Expt Tx. Median	Control Median	HR	Expt Tx. Median	Control Median	HR
7	4	1.75	3	4	0.75

Probability of recommendations for phase III trial design

Enrichment Design	76%
Biomarker-stratified design	2%
No biomarker (standard phase III)	<1%
No further testing	22%

Biomarker Subgroup

Positive			Negative		
Expt Tx. Median	Control Median	HR	Expt Tx. Median	Control Median	HR
6	6	1.0	4	4	1.0

Probability of recommendations for phase III trial design

Enrichment Design	6%
Biomarker-stratified design	4%
No biomarker (standard phase III)	2%
No further testing	87%

Summary

It is possible to design a randomized phase II trial with a biomarker and a *reasonable sample size*, to help determine what type of biomarker phase III trial design to use.

References and collaborators

Freidlin, McShane, Polley, and Korn (2012), Randomized phase II trial designs with biomarkers. Journal of Clinical Oncology 30:3304-3309

Freidlin, McShane and Korn (2010), Randomized clinical trials with biomarkers: design issues. Journal of the National Cancer Institute 102:152-160