Design of Phase II Clinical Trials with a Potential Predictive Biomarker

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Ed Korn
Biometric Research Branch
National Cancer Institute

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 a biomarker

(1) Enrichment design

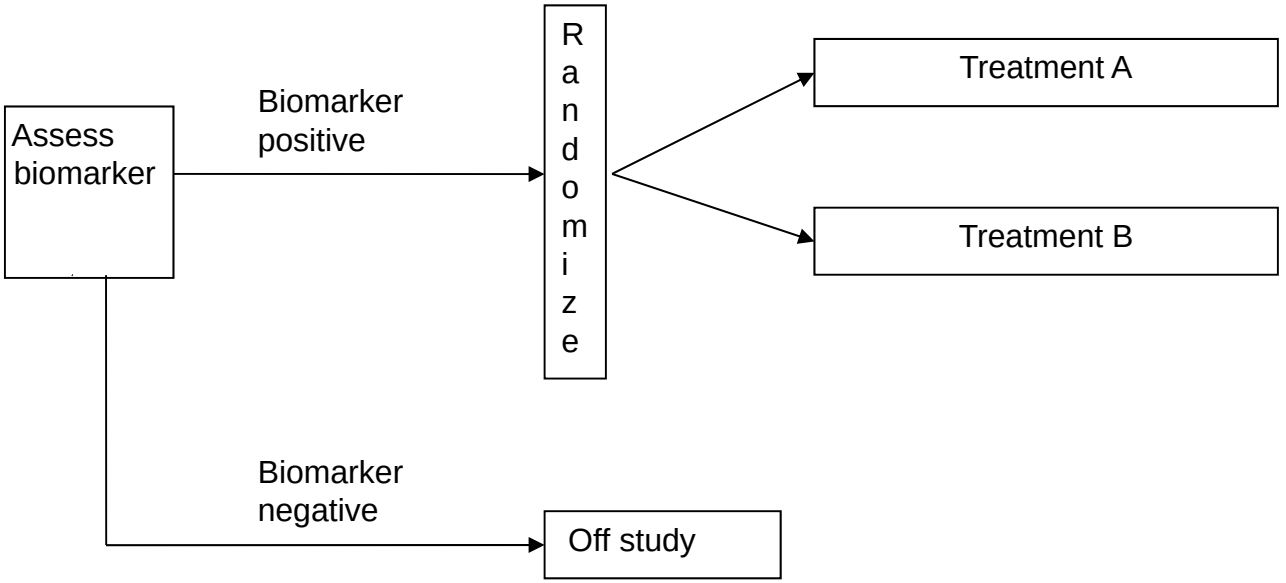
(2) Biomarker stratified design

(3) Standard phase III design ignoring the biomarker

[(4) Biomarker strategy design]

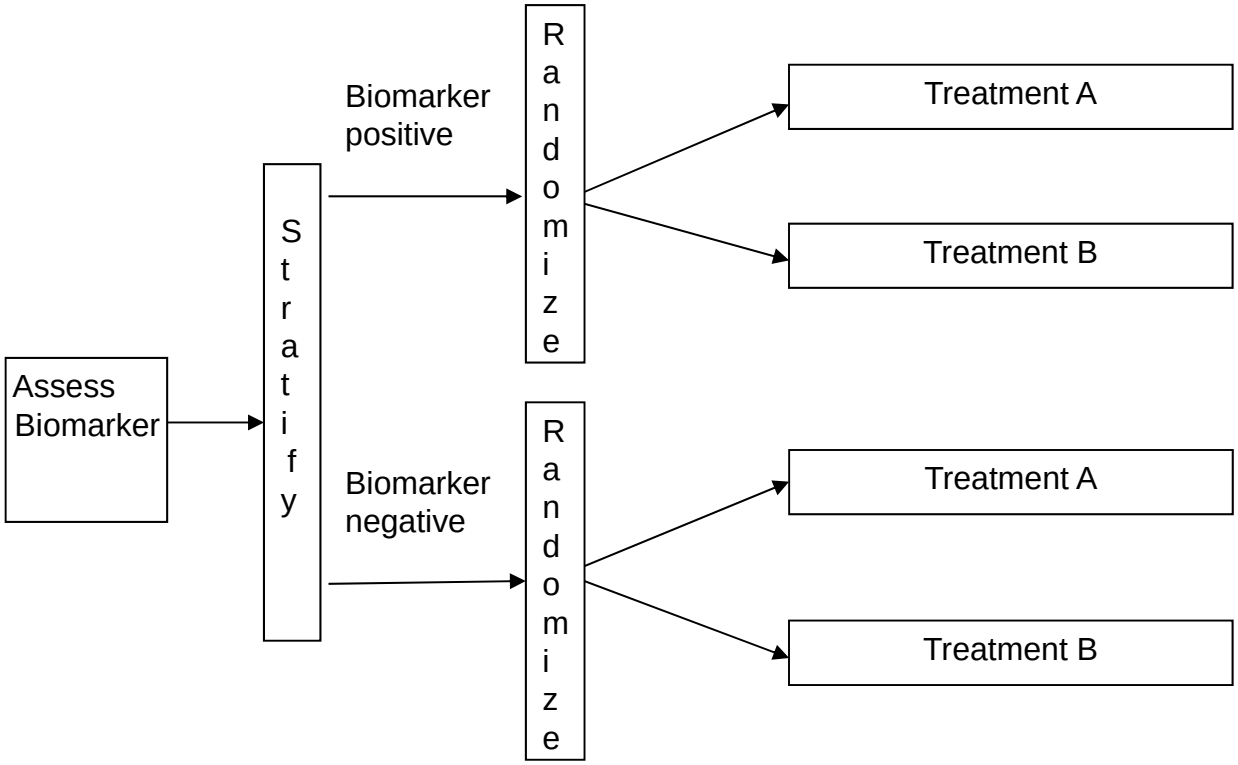
Possible phase III trial designs with a biomarker

(1) Enrichment design



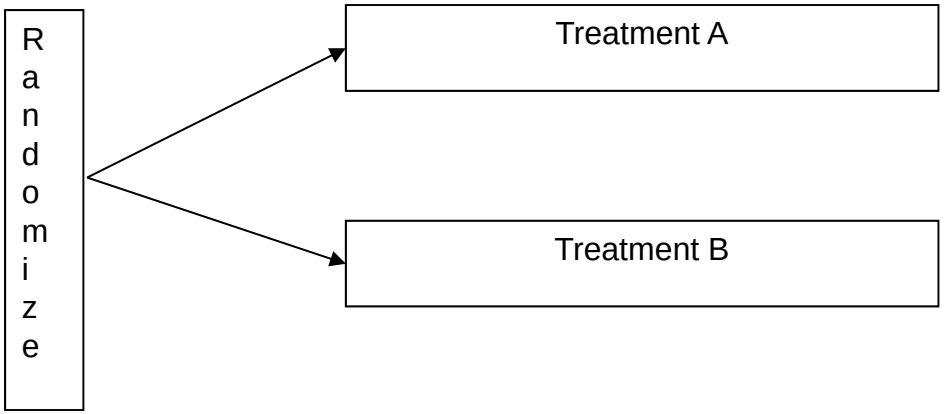
Possible phase III trial designs with a biomarker

(2) Biomarker stratified design



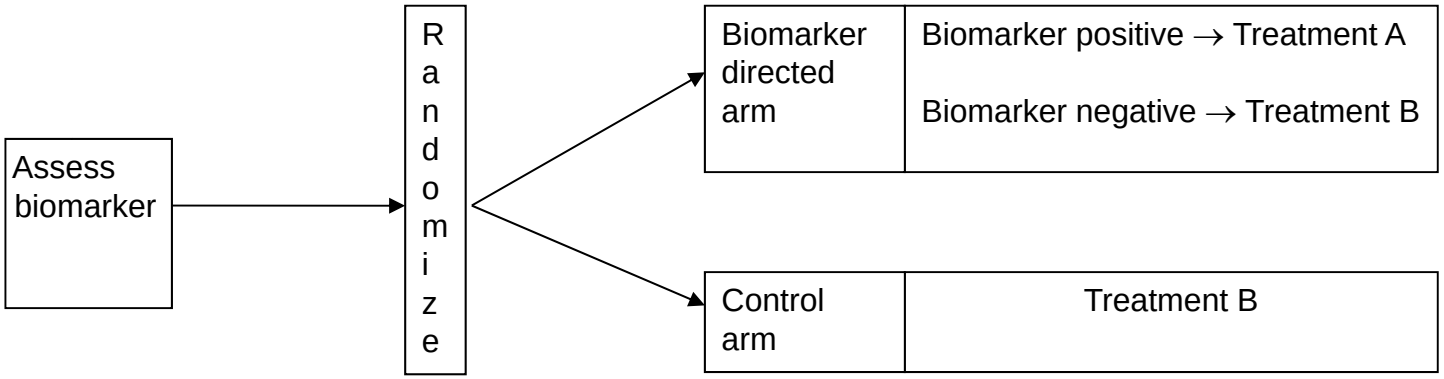
Possible phase III trial designs with a biomarker

(3) Standard phase III design ignoring the biomarker



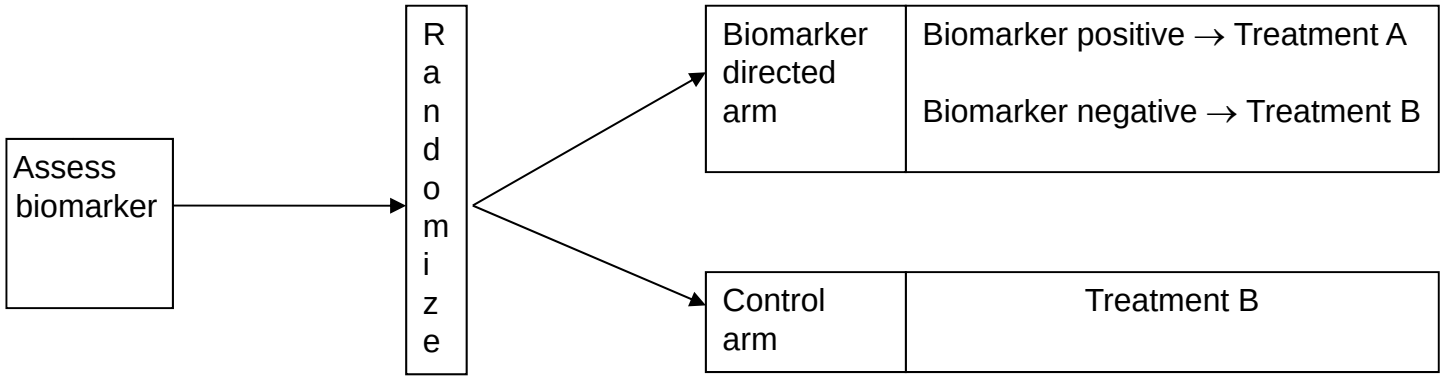
Possible phase III trial designs with a biomarker

(4) Biomarker-strategy design



Possible phase III trial designs with a biomarker

(4) Biomarker-strategy design –Not Generally Recommended



Single-Arm Phase II versus Randomized Screening Phase II Design

When can a single-arm design be used instead of a randomized screening design?

When can a single-arm design be used?

(1) Single agent (or experimental agent combined with inactive agents) and responses expected if agent is active

[(2) New treatment is expected to be much more effective than historical treatments with response rate or time-to-event endpoint]

[(3) New treatment with time-to-event endpoint and data from a large collection of historical trials are available]

When can a single-arm design *with a biomarker* be used?

Unless one knows that the biomarker is not prognostic, restricted to:

(1) Single agent (or experimental agent combined with inactive agents) and responses expected if agent is active

Single-arm designs with a biomarker -- Options

(a) Only perform a phase II trial in the B+ group.

(b) Perform two phase II trials concurrently – one in the B+ group and one in the B- group

c) Perform phase II trial in the B+ group. If the trial is positive, then perform a phase II trial in the B- group.

(d) Perform two-stage trial in the B+ group. If the trial passes its first stage, continue the B+ trial and also begin a trial in the B- group.

Single-arm designs with a biomarker -- Options

(e) Perform an unrestricted phase II trial. Examine the biomarker status of the patients after the trial.

(f) Perform an unrestricted phase II trial. But, if the trial is negative, continue enrollment of only the B+ patients to obtain a B+ phase II trial.

(g) Perform an unrestricted two-stage phase II trial. But, if the trial is negative at either stage, continue enrollment of only the B+ patients to obtain a B+ phase II trial.

Single-arm designs with a biomarker --
Recommendation?

(g) Perform an unrestricted two-stage phase II trial.
But, if the trial is negative at either stage, continue enrollment of only the B+ patients to obtain a B+ phase II trial.

Simon two-stage phase II design:

12 at the first stage, with $\geq$1 response, continue
25 more at second stage.
With $\geq$4 responses out of 37, trial is positive.

Randomized phase II (screening designs) with a biomarker

--Experimental arm and control arm.

--All comers are randomized at first, but with biomarker status determined for analysis

--Design to be discussed uses a progression-free survival (PFS) endpoint

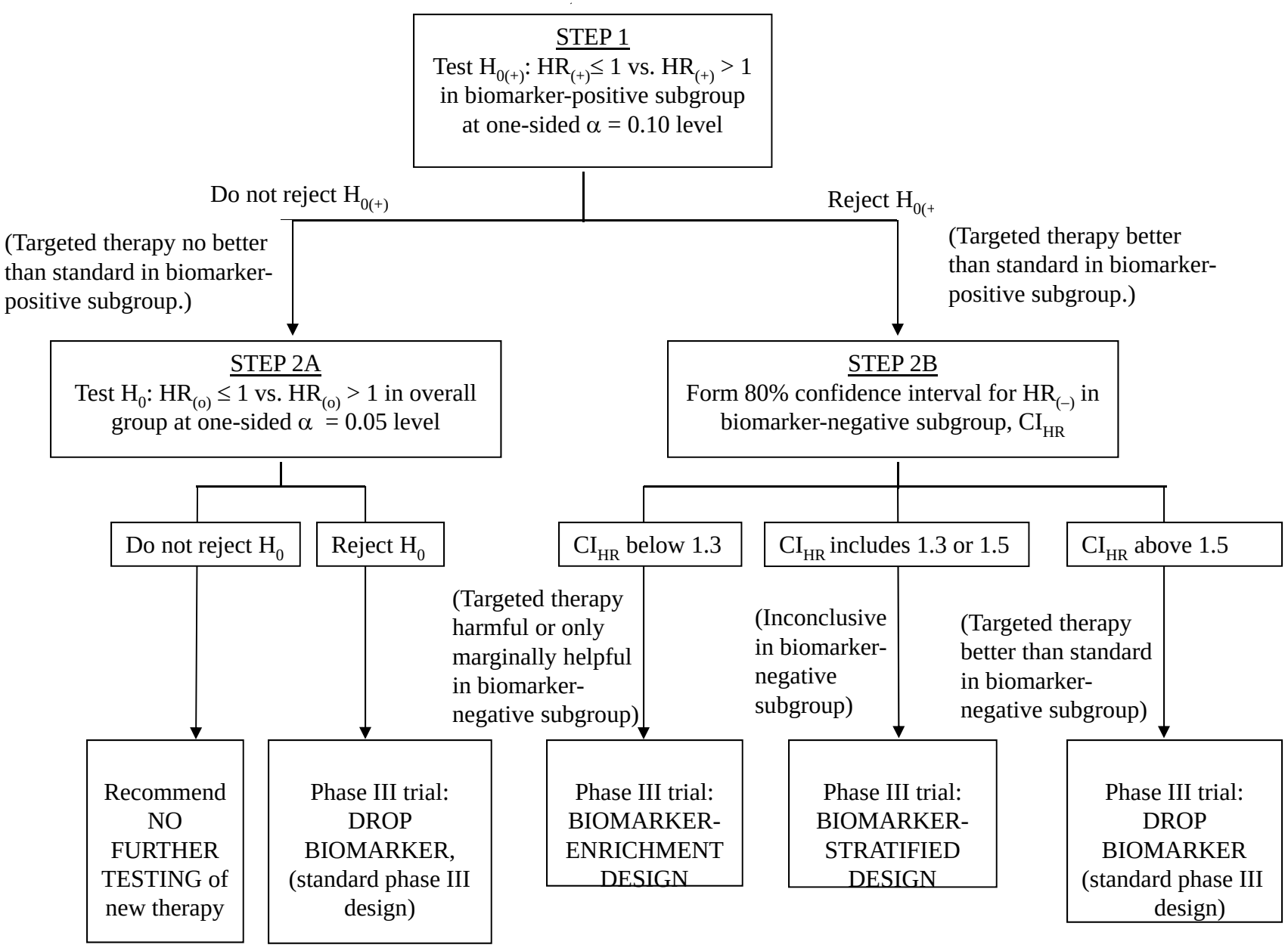
Possible recommendations for the phase III trial after completing the phase II trial

(1) Enrichment design

(2) Biomarker stratified design

(3) Standard phase III design ignoring the biomarker

(4) No further testing of new therapy


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, corresponding to 70 biomarker-positive patients.

Cut-off accrual to any biomarker subgroup at 140.

Results presented for 20% prevalence of biomarker-positive patents

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

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%

How would the proposed design work in the real world?

We take some real randomized phase III data, treat the observed hazard ratios for the Biomarker positive and negative groups as if they were truth, and see what our phase II design would have recommended.

Example 1: Phase III trial of gefitinib versus carboplatin-paclitaxel in NSCLC

Biomarker: EGFR mutation

Ref: Mok et al. 2009 (IPASS)

EGFR mutation subgroup

.	Positive (60%, n=261)		Negative (40%, n=176)	
	Control Median	HR	Control Median	HR
	6.0 mo	2.08	2.0 mo	0.35

Probability of recommendations for phase III trial design

Enrichment Design	98%
Biomarker-stratified design	0%
No biomarker (standard phase III)	0%
No further testing	2%

Average size of phase II trial = 175

Example 2: Phase III trial of radiotherapy with or without temozolomide for glioblastoma

Biomarker: methylation of MGMT promoter

Ref: Hegi et al. 2005

MGMT Subgroup

. Positive (45%,n=92)		. Negative (54%, n=114)	
Control Median	HR	Control Median	HR
5.9 mo	2.08	4.4 mo	1.61

Probability of recommendations for phase III trial design

Enrichment Design	1%
Biomarker-stratified design	75%
No biomarker (standard phase III)	21%
No further testing	2%

Average size of phase II trial = 157

Example 3: Phase III trial of cetuximab versus best supportive care for advanced colorectal cancer

Biomarker: K-ras mutation (positive marker=wild type)

Ref: Karapetis et al. 2008 (reanalysis of CO.17)

K-ras Subgroup

	Positive (58%,n=215)		Negative (42%, n=151)	
	Control Median	HR	Control Median	HR
	1.9 mo	2.50	1.8 mo	1.01

Probability of recommendations for phase III trial design

Enrichment Design	38%
Biomarker-stratified design	61%
No biomarker (standard phase III)	0%
No further testing	1%

Average size of phase II trial = 167

Example 4: Phase III trial of FOLIFIRI with or without cetuximab for metastatic EGFR-positive colorectal cancer

Biomarker: K-ras mutation (positive marker=wild type)

Ref: Van Cutsem et al. 2009

K-ras Subgroup

	Positive (64%,n=348)		Negative (36%, n=192)	
	Control Median	HR	Control Median	HR
	8.7 mo	1.47	8.1 mo	0.93

Probability of recommendations for phase III trial design

Enrichment Design	36%
Biomarker-stratified design	37%
No biomarker (standard phase III)	0%
No further testing	26%

Average size of phase II trial = 191

Summary

When a single-arm response rate trial is appropriate, it is straightforward to include a biomarker.

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

Some Additional References

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