Phase III Design Considerations for Molecularly Targeted Agents

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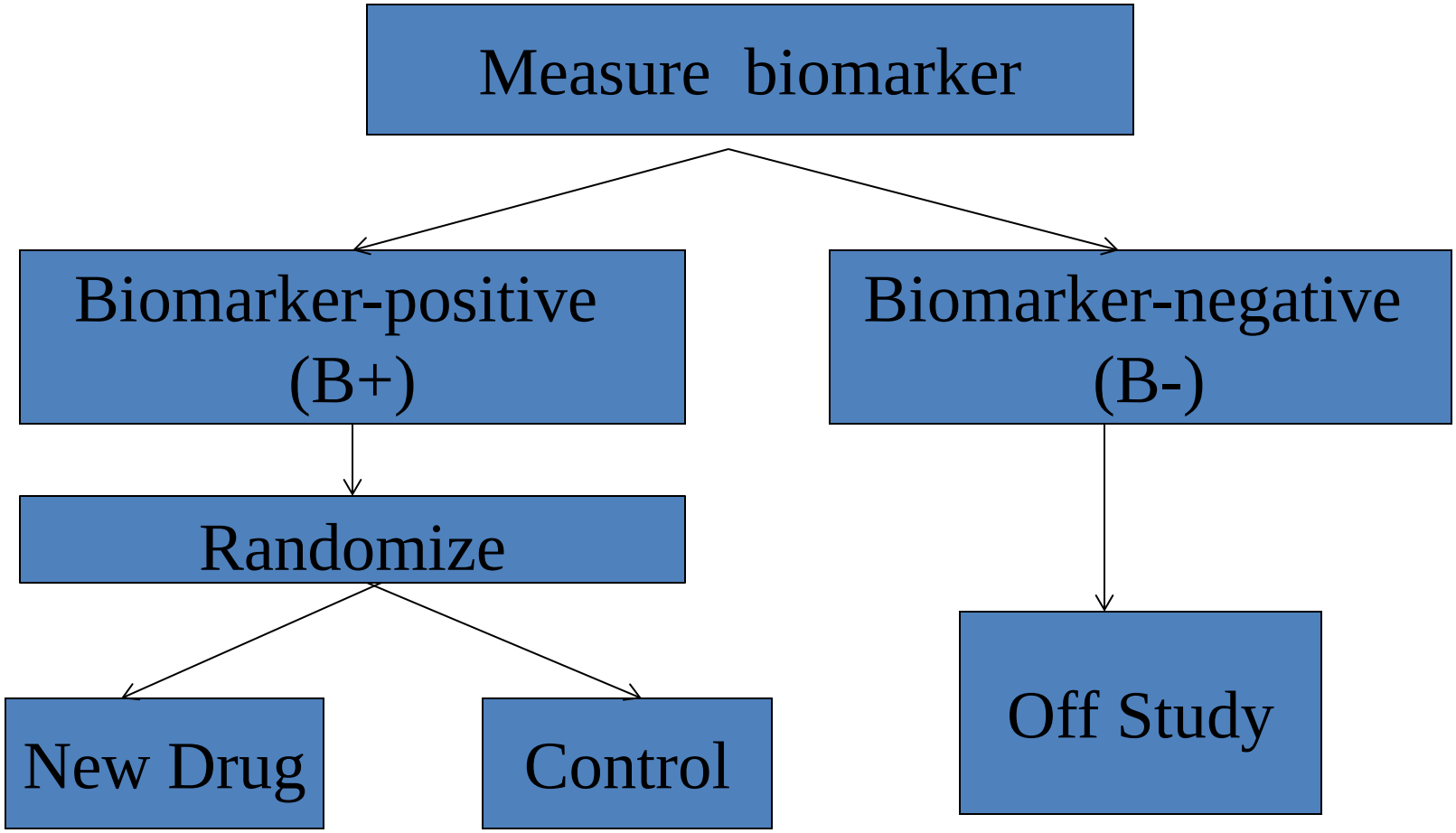
- Molecularly targeted agents may only benefit a subgroup of a histologically defined population
- Successful evaluation requires co-development of biomarkers to identify sensitive subpopulations
- Various design strategies to integrate treatment and biomarker evaluation are available
- Choice of Phase III design depends on the biomarker’s credentials

Focus of this talk

- Binary biomarker separates the population of interest into biomarker-positive (B+) and biomarker-negative (B-) subgroups
- Analytical validity of the biomarker assay has been established
- Biomarker credentials are sufficient to assume that B- patients benefit only if B+ patients benefit

Biomarker with strong credentials: use Enrichment design



Example: BRIM3 study

Vemurafenib in metastatic melanoma

- 2107 patients screened to identify 675 patients with BRAF mutation

- BRAF mutated patients randomized to vemurafenib vs. standard chemotherapy

- Overall survival HR 0.37, 95% CI 0.26–0.55

Reference: Chapman et al NEJM 2011

Limitations of Enrichment design:

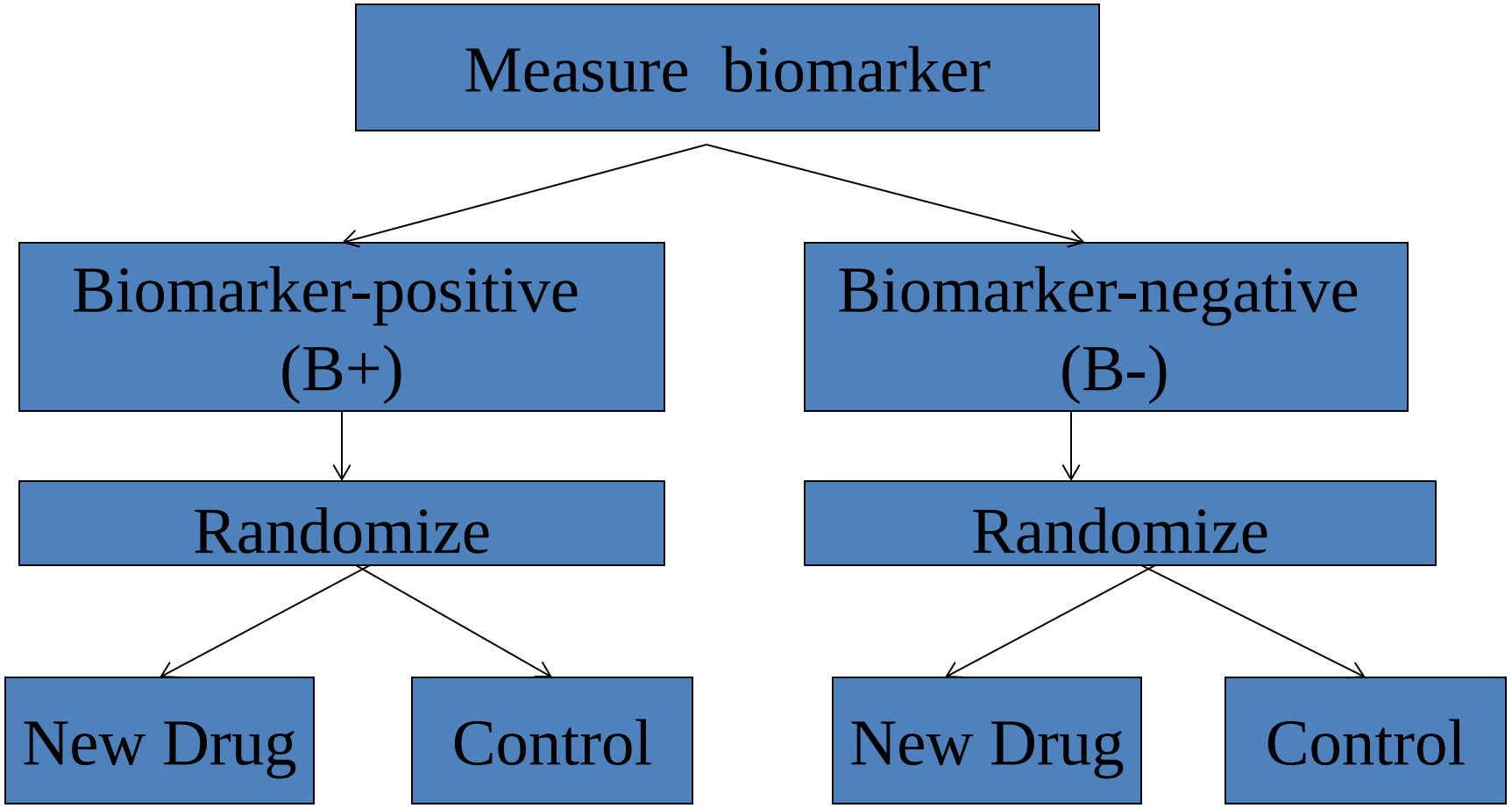
Unless external evidence clearly limits benefit to

B+ patients, a positive enrichment study leaves open:

- Whether the treatment benefit extends to biomarker-negative patients

- Whether the costs and inconvenience of routine use of the biomarker to select patients for treatment are justified

Biomarker credentials are not compelling: use Biomarker-stratified (randomize-all) designs



Goals of biomarker-stratified Phase III:

- Asses benefit in each biomarker subgroup
- Recommend drug to patients who benefit
- Do not recommend drug to patients who do not benefit

Assess benefit in each biomarker subgroup

For biomarker positive subgroup (B+)

$$H_{0+}: \delta_+ = 0 \qquad vs. \qquad H_{A+}: \delta_+ > 0$$

For biomarker negative subgroup (B-)

$$H_{0-}: \delta_- = 0 \qquad vs. \qquad H_{A-}: \delta_- > 0$$

Where δ_+ and δ_- are treatment effects in B+ and B-, respectively.

Three possible Null hypotheses

1) Global Null $H_0 = H_{0+} \bigcap H_{0-}$

2) No benefit in B- $H_{A+} \bigcap H_{0-}$

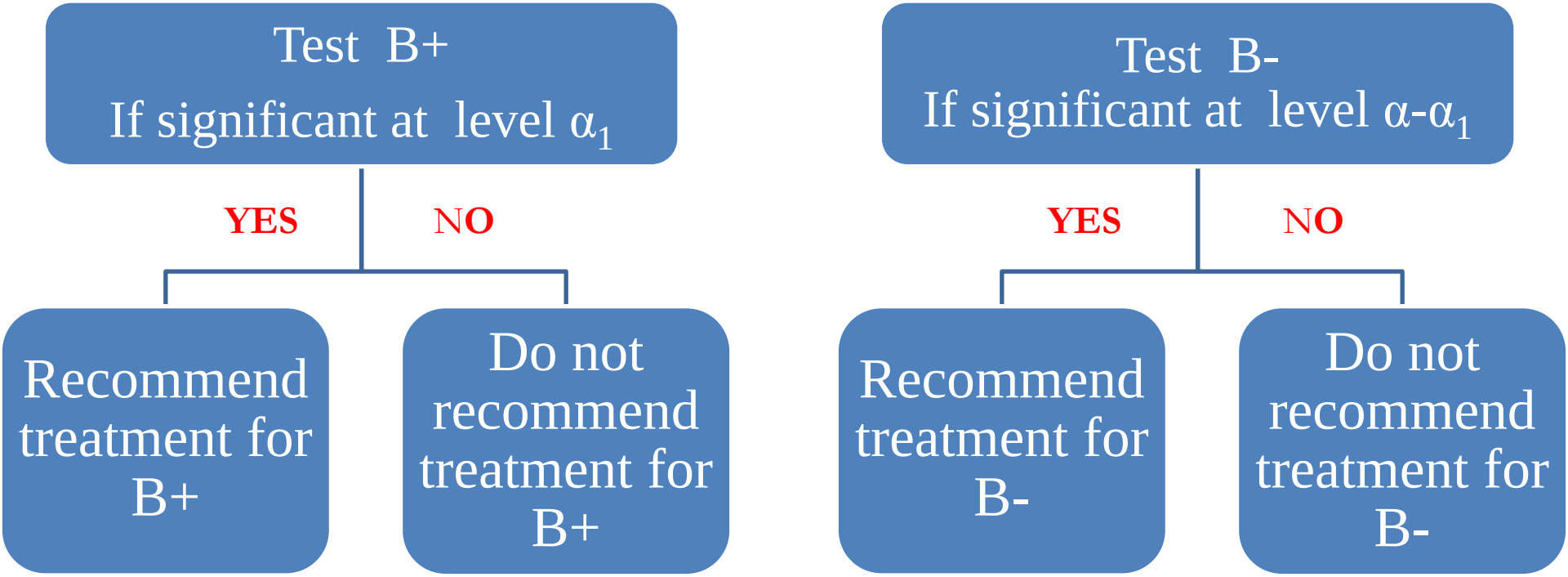
3) No benefit in B+ $H_{0+} \bigcap H_{A-}$

Type I errors to control

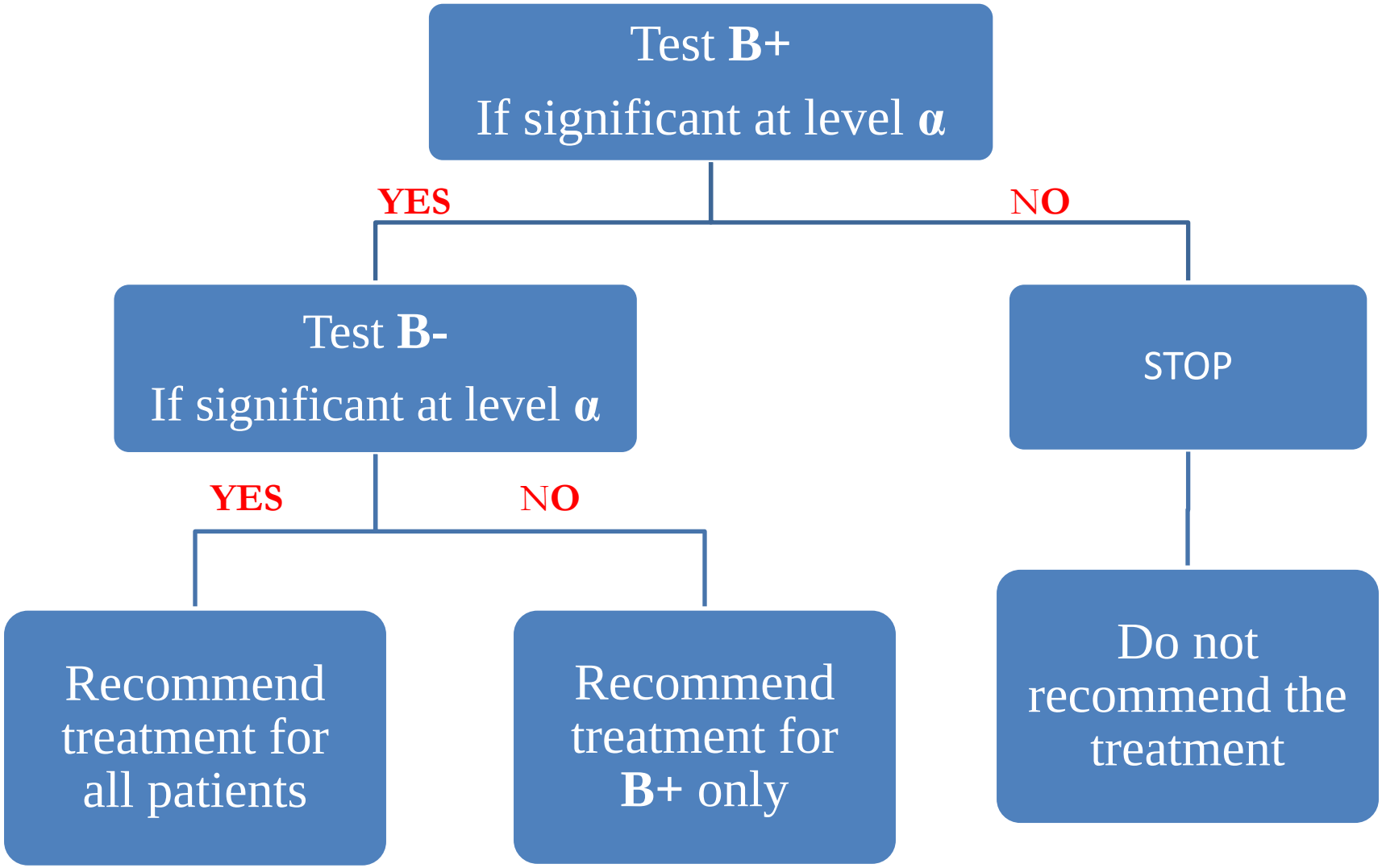
1) $\Pr[\text{Reject } H_{0+} \text{ or } H_{0-} \mid H_0] < \alpha$

2) $\Pr[\text{Reject } H_{0-} \mid H_{A+} \cap H_{0-}] < \alpha^*$

Subgroup-specific parallel strategy



Subgroup-specific sequential strategy



For subgroup-specific designs

$$\Pr[\text{Reject } H_{0+} \text{ or } H_{0-} \mid H_0] < \alpha$$

$$\Pr[\text{Reject } H_{0-} \mid H_{A+} \cap H_{0-}] < \alpha$$

Example: PRIME study

Panitumumab in metastatic colorectal cancer

- Biomarker: KRAS status

- KRAS WT 656 patients,

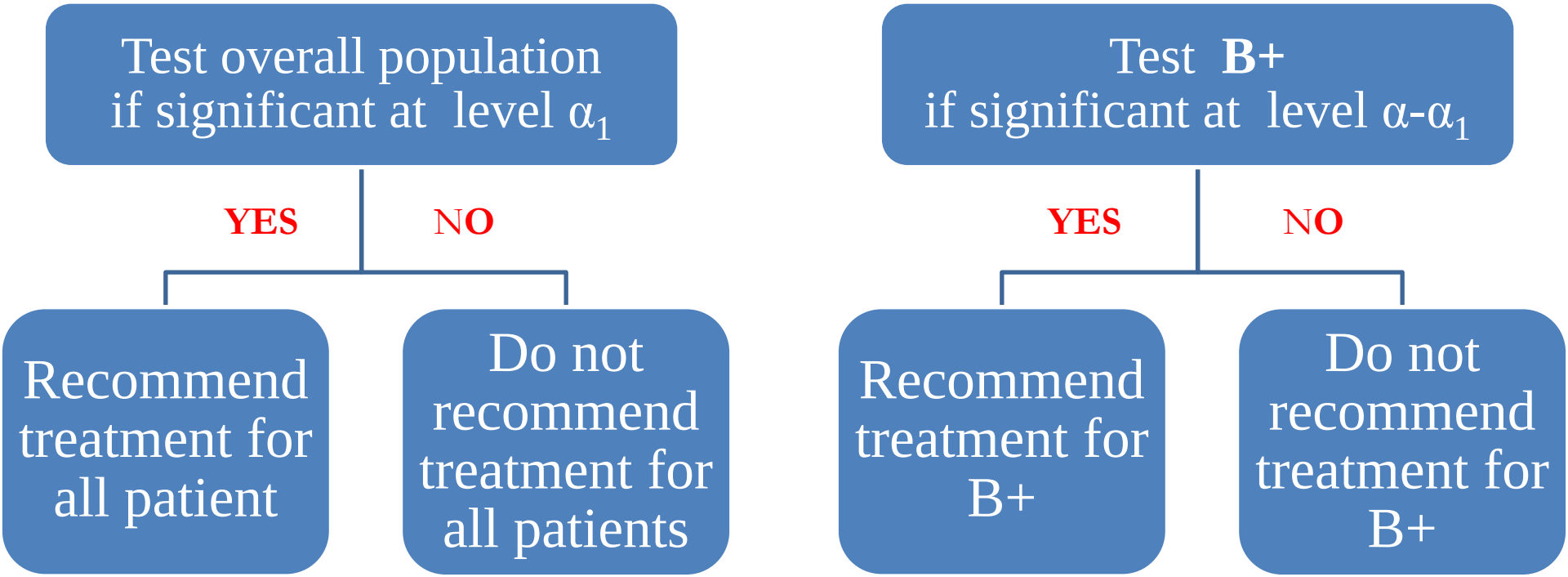
Hazard Ratio 0.80 95%CI (0.66, 0.97)

- KRAS MT 440 patients

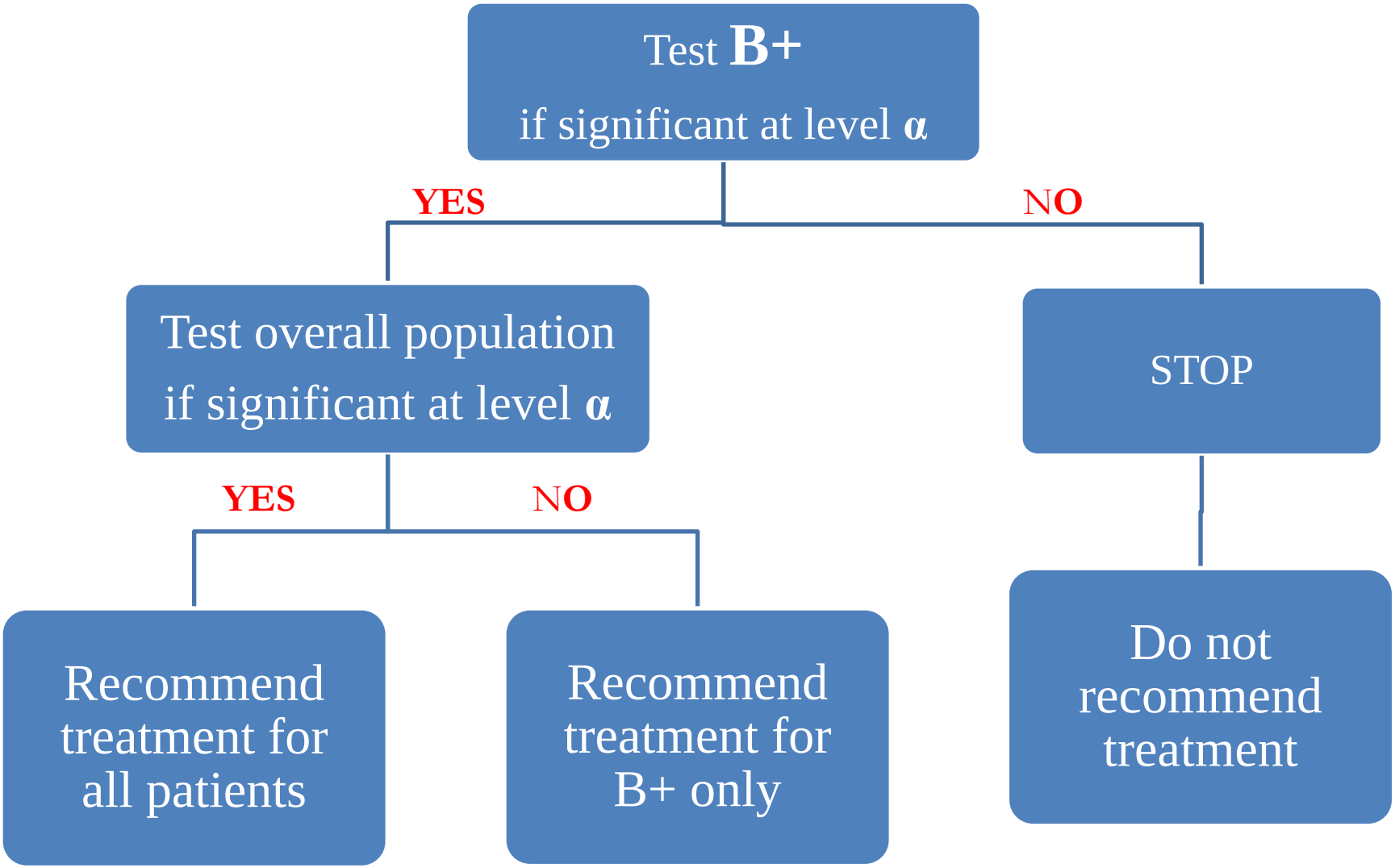
Hazard Ratio 1.29 95%CI (1.04, 1.62)

Reference: Douillard et al JCO 2010

Biomarker-positive/overall parallel strategy



Biomarker-positive/overall sequential strategy



For biomarker-positive/overall designs

$\Pr[\text{Reject } H_{0+} \text{ or } H_{0-} \mid H_0] < \alpha$

$\Pr[\text{Reject } H_{0-} \mid H_{A+} \cap H_{0-}]$ is not controlled (could be as high as 100%)

Biomarker-positive/overall strategy may formally recommend treatment for biomarker-negative patients even though the treatment is ineffective in these patients

Reason: even with no benefit in B- patients a statistically significant effect can be still observed in the overall population if the effect in B+ patients is large

Example: Lapatinib+letrozole vs.

Placebo +letrozole in metastatic breast cancer

Biomarker: HER2 status

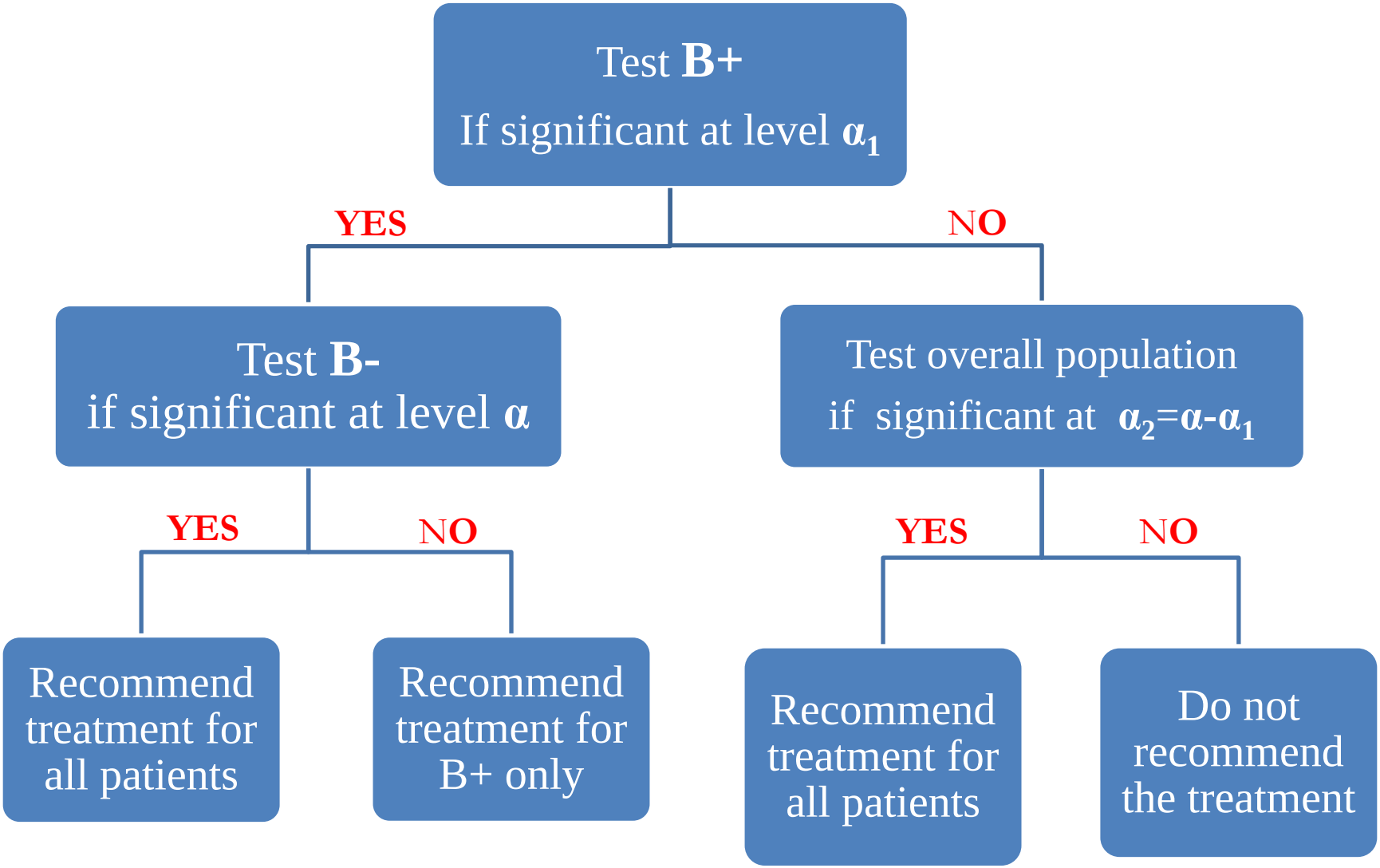
- HER2-positive (n=219)
  HR=.71 p-value=.019

- Overall population (n=1286)
  HR=0.86 p-value=.026

- HER2-negative (n=952)
  HR=0.9 p-value=.188

Reference: Johnston et al JCO 2009

Marker Sequential Test
MaST(α, α_1)



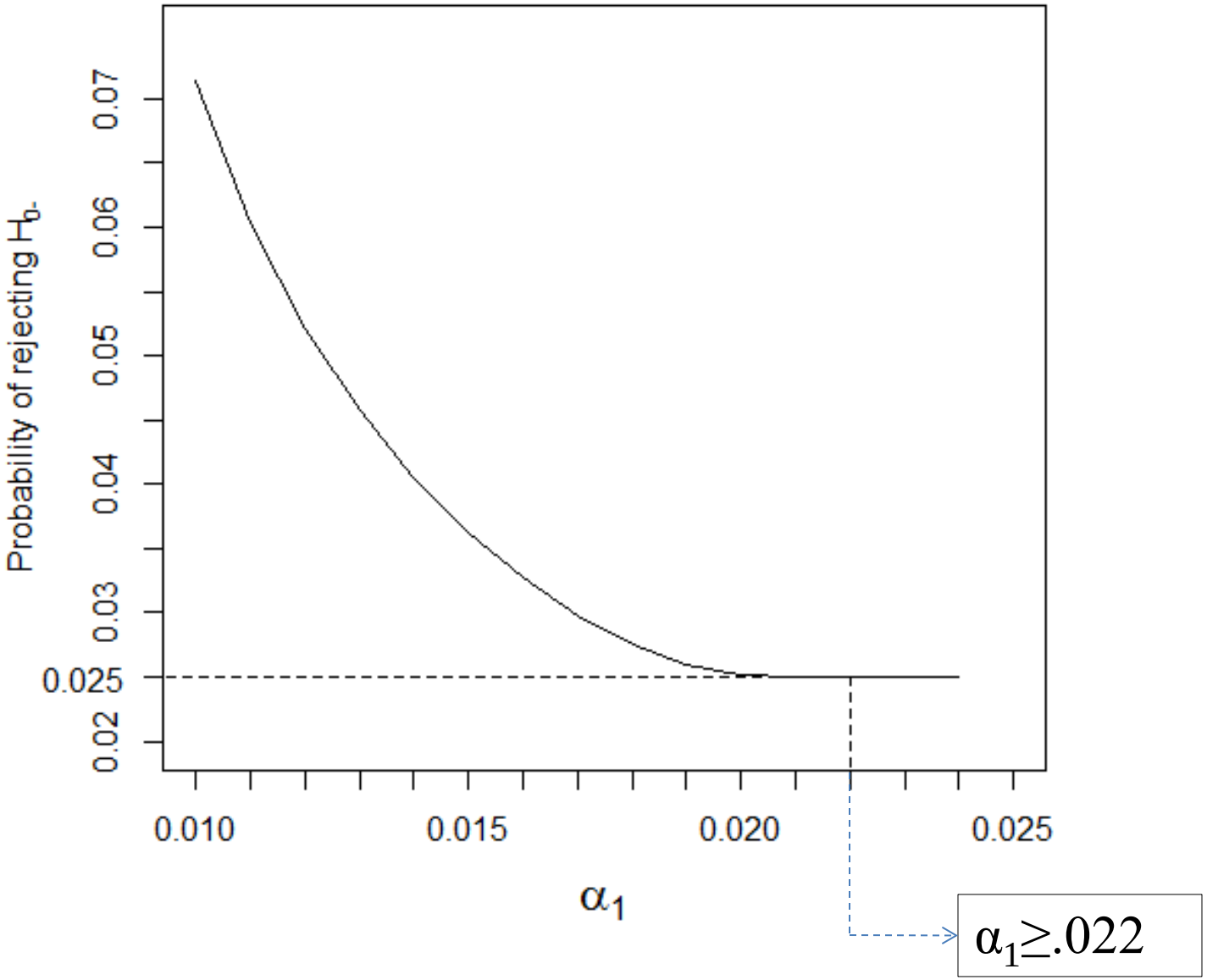
Reference: Freidlin et al Clinical Trials 2013

For MaST(α, α_1) procedure

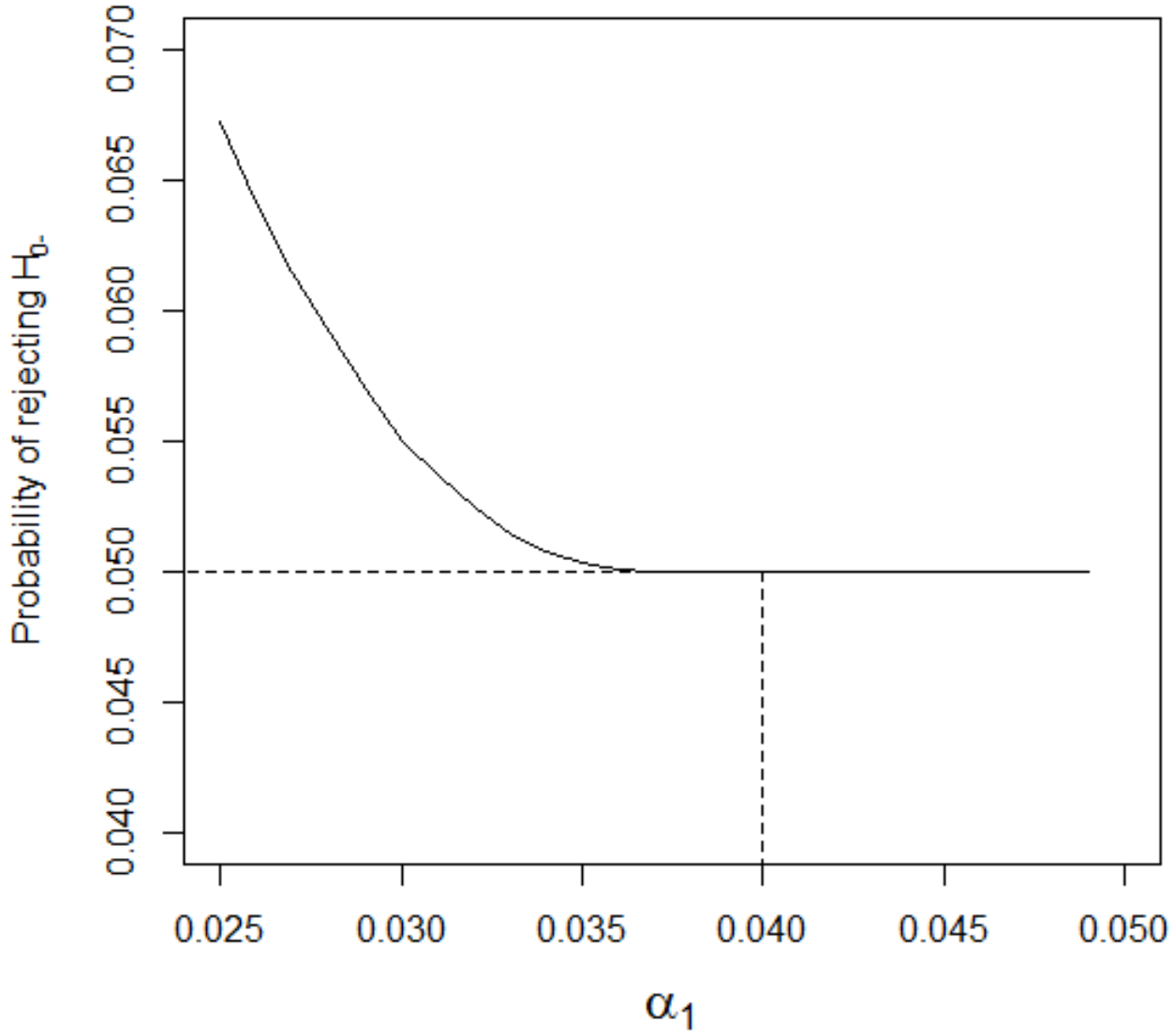
$\Pr[\text{Reject } H_{0+} \text{ or } H_{0-} \mid H_0] < \alpha$

$\Pr[\text{Reject } H_{0-} \mid H_{A+} \cap H_{0-}]$ depends on α_1

Probability of rejecting H_{0-} as a function of α_1 (for α=0.025)

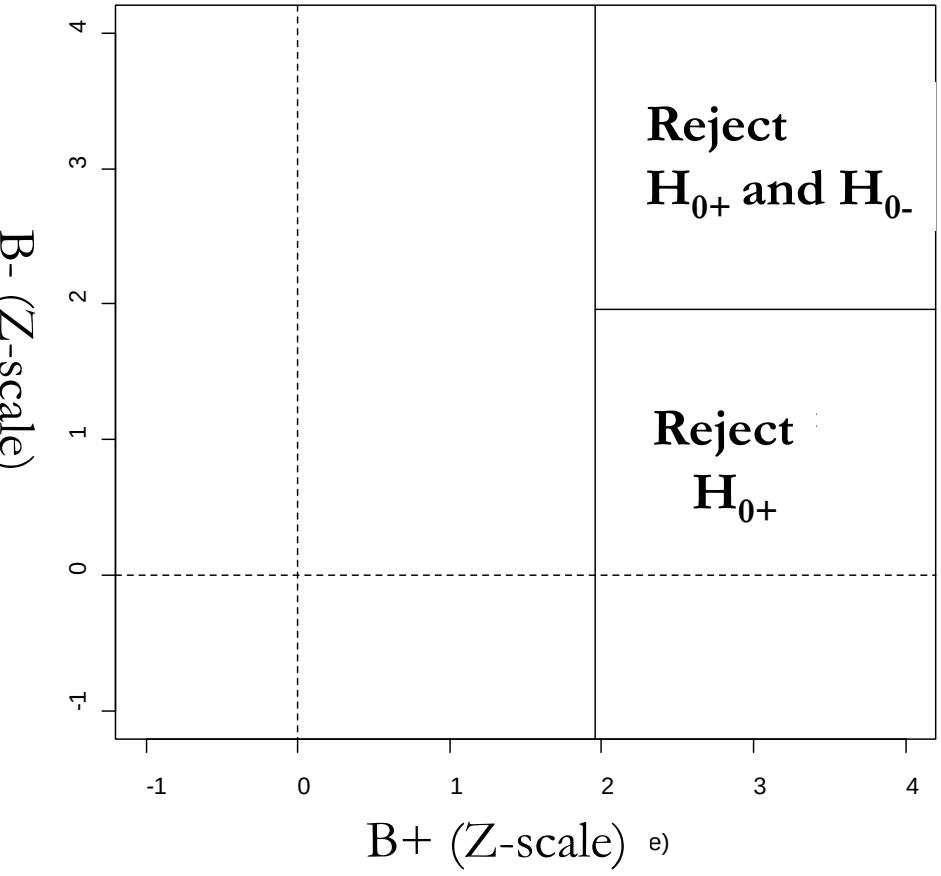


Probability of rejecting H_{0-} as a function of α_1 (for α=0.05)

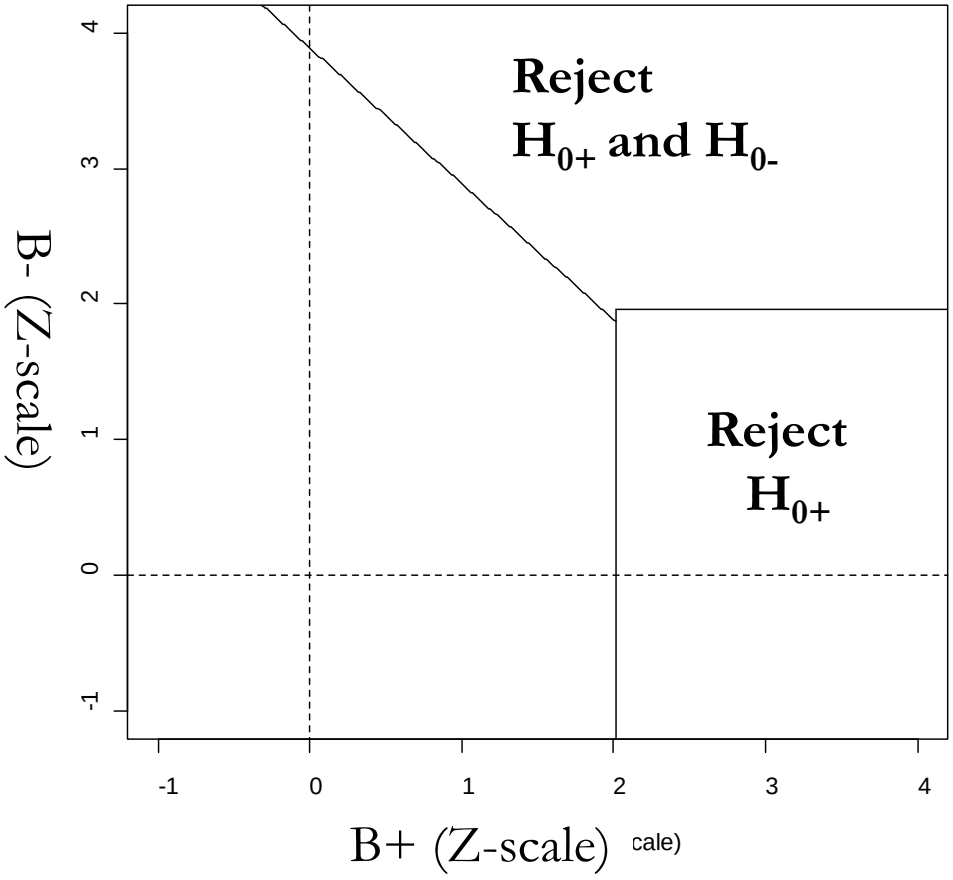


Rejection regions

Sequential subgroup-specific test



MaST(.025, .022)



Power comparison (B+ prevalence 30%)

True hazard ratio		Power				
		Overall test	Sequential subgroup-specific test		MaST(.025,.022)	
BM+	BM-		BM+	BM-	BM+	BM-
1	1	.0249	.0256	.0007	.0241	.0025
.60	1	.469	.902	.023	.894	.024
.71	1	.243	.600	.015	.584	.019
.60	.60	1	.902	.901	.999	.998
.60	.71	.997	.902	.839	.985	.923
.71	.71	.981	.600	.552	.921	.874

MaST design allows one to

- minimize the probability of recommending ineffective treatment for B- patients
- maximize power for treatments with homogeneous treatment effect

Example: E1910 Blinatumomab in ALL

n=285, MAST(α=.025 α_1=.02)

Biomarker: MRD

Interim monitoring
(Group-specific and MaST designs)

Efficacy

First B+ subgroup, if positive then B- subgroup

(no overall population testing)

Futility

B+ subgroup: if negative the entire study stops

B - subgroup: if negative B- accrual is stopped

Interim monitoring (efficacy and futility)

- Start with B+ patients (enrichment design) → if early signal in B+ expand enrollment to B- (Liu et al, Clin Trials 2010)
- Can use an early endpoint similar to Phase II/III
- Analyze using sequential subgroup-specific strategy

Sample size consideration (MaST)

Biomarker with relatively strong credentials - need enough B+ patients to detect a meaningful benefit in B+ subgroup:

- Subgroup-specific calculation using α to size B+ (minor loss of power)

- Use α_1 to size B+ subgroup (minor increase in sample size, e.g., $\leq$4% for a design with overall α=.025)

Design considerations: prevalence of B+

- MaST is recommended when B+ prevalence is <70%
- If B+ prevalence is low limit size of B- cohort
- If B+ prevalence is >80% use sequential subgroup-specific strategy (possibly with relaxed α for B- subgroup)

Unavailable biomarker subgroup

- Biomarker status may be unavailable in a fraction study patients

- Subgroup-specific analysis does not include unavailable status patients

- MaST: two options for these patients
  1) do not include
  2) include in the overall analysis

MaST: unavailable status pts in overall test

(proportion unavailable – ρ_{ub})

- False-positive for H_{A+} is controlled at .025

- $\Pr[\text{Reject } H_{0-} \mid H_{A+} \cap H_{0-}]$ could exceed .025, e.g., for ρ_{ub}=20% it could be as high as .03

- Adjustment to α_2 (assuming MCAR)

$$\alpha_2^* = 1 - \Phi\left(\frac{1}{\sqrt{1-\rho_{UB}}} \left(Z_{\alpha_2} - Z_{\beta^*} \right) - Z_{\beta^*} \right)$$

Recommendations

- Optimize predictive value of biomarker before designing phase III
- Select phase III design based on biomarker credentials
- Ensure adequate control of relevant false-positive error rates

References

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