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Adaptive biomarker-based design applied to an early phase trial in Oncology

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Disclaimer and acknowledgments

The views expressed here are solely mine and do not represent my employer, organization, or any affiliated entity.

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The results reported herein are part of a collaboration between Servier, Saryga, and the MRC Biostatistics Unit.

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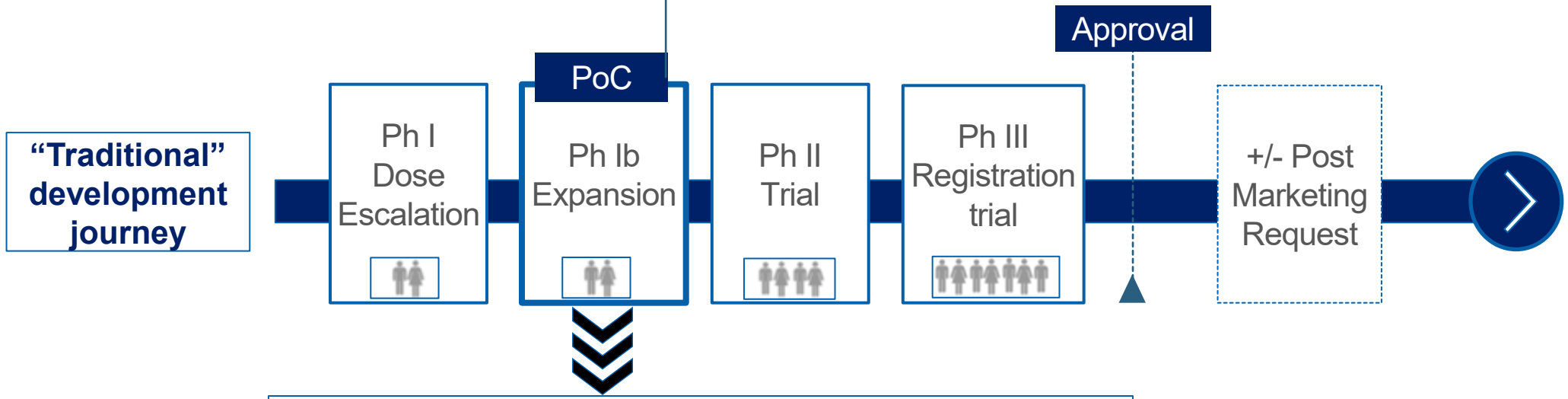
Motivation

Goal: Quickly establish that the drug is worth pursuing further, on the overall indication or in a biomarker subgroup



Putative biomarker (BMK) predictive of treatment responses
- Measured on a continuous scale
- No predefined cutoff for BMK+ patients

Enrich on BMK + or not ?

No, lack of evidence in patients to support BMK hypothesis

Yes, to avoid the risk of missing an efficacy signal

PoC = Proof of Concept

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Don’t Miss a Signal

Option 1

No Enrichment Fixed Design

BMK assessed at the end of the study

- Risk of **missing a signal** when treatment benefit is limited to a **small BMK+ subgroup**

Option 2

Enrichment Fixed Design

BMK Enrichment at the beginning of the study

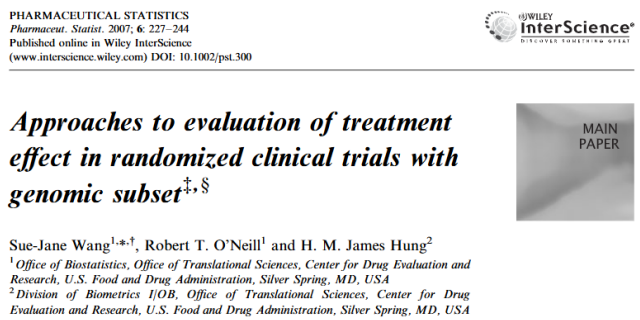
- Risk of **missing a signal** when the **cutoff** of the BMK is **not well established**
- Cannot establish that the **BMK-neg patients** do not respond
- **Longer recruitment** duration

Option 3

ADAPTIVE DESIGN (AD)

BMK Enrichment at the interim stage of the study

- AD offers **more power** than the non-AD for **detecting an effect** in a BMK+ subgroup



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WILEY InterScience

Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset ‡, §

MAIN PAPER

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Many uncertainties at this early stage

Uncertainties about :

- The predictive value of the BMK
- The cutoff value of the BMK used to identify patients in the BMK+ subgroup
- The proportion of patients who are in the BMK+ subgroup
- The magnitude of the treatment effect in patients BMK+ and BMK-

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Our design proposal

Interim Analysis

Ph Ib Expansion

Treatment
Single-arm study

→ **If no robust cutoff found**
i.e. 1st data not supportive of the BMK hypothesis
→ **No enrichment strategy**
i.e. continue as initially planned (classical design)

→ **If robust cutoff found**
i.e. 1st data supportive of the BMK hypothesis
→ **Enrichment strategy**
i.e. recruit patients likely to respond

Evaluation of the
- **Predictive value** of the biomarker of interest
- **Robust biomarker cutoff** that will guide the next recruitments

Assuming:
- **No prognostic value** of the BMK of interest (as cannot be verified in a single-arm study)
- **Intermediate clinical endpoint** with a reasonable correlation relationship with the clinical endpoint
- **Preliminary analytical validation of the bioassay** used to measure the BMK of interest

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Criterion to find a robust cut-off

Comparison of **3 approaches** to find a robust cut-off: ‘cut-off‘ or ‘no cut-off‘ based on the following rules:

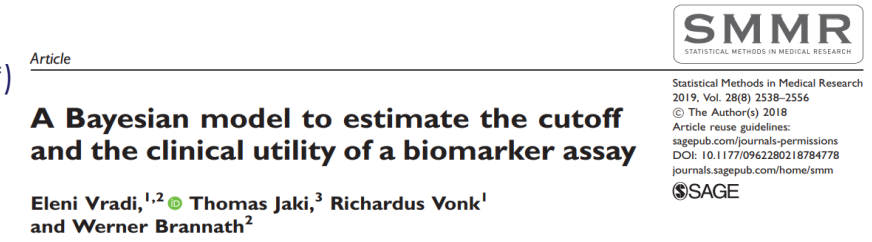
- **Naïve**: at least 15% of responses in at least pp% of the population;
- **Naïve with step function**: find cut-off by fitting a step function(*) and then see whether there are at least 15% of responses in at least pp% of the population with this cut-off value;
- **Probability based**: find cut-off by fitting a step function(*), check if there are at least pp% of the population above the cut-off value and declare to find cutoff if $P(p_1 - p_0 > diff_{thr}) > p_{thr,}$ where p_0 is the response rate in the BMK- subgroup and p_1 is the response rate in the BMK+ subgroup

(*) Same principle (fit a step function) of (**) but with Ordinary Least Squares instead of a Bayesian model (due to convergence issues with the Bayesian model with a small sample size).

Assuming to not have much prior information on the BMK-response shape of the curve and to avoid the issue of misspecified model.

No other method has been used to compare this approach. The aim was initially to assess the feasibility of an adaptive enrichment design at PhI stage.

(**)



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Criterion to find a robust cut-off

- Evaluation under two scenarios:
  - non-predictive with high response rate scenario (**NPHR)** where $p_1=p_0=0.15$
  - predictive with high response rate scenario (**PHR)** where $p_1=0.25$ and $p_0=0.05$

- **Gain:** the difference between the probability of declaring to find a cutoff under the alternative and the null scenarios

➢ **Chosen approach:**

If **80**% certain that there is **10**% of difference in response rate between the 2 groups in at least **10**% of the population.

Approach	pp%	$diff_{thr}$	p_{thr}	False positives under $NPHR_{q_1}$	True Positives under PHR_{q_1}	Gain: True - False Positives
'Naive'	10	-	-	0.74	0.83	0.10
	20	-	-	0.73	0.83	0.11
	30	-	-	0.74	0.82	0.09
'Naive with step function'	10	-	-	0.41	0.65	0.23
	20	-	-	0.35	0.56	0.20
	30	-	-	0.27	0.37	0.11
'Probability based'	10	0.1	0.7	0.29	0.55	0.26
			0.8	0.24	0.50	**0.26**
			0.9	0.14	0.37	0.23
		0.15	0.7	0.24	0.50	0.26
			0.8	0.16	0.40	0.24
			0.9	0.10	0.28	0.18
		0.2	0.7	0.19	0.42	0.22
			0.8	0.13	0.33	0.20
			0.9	0.07	0.21	0.14
	20	0.1	0.7	0.23	0.45	0.23
			0.8	0.19	0.41	0.22
			0.9	0.13	0.32	0.19
		0.15	0.7	0.19	0.42	0.24
			0.8	0.13	0.33	0.19
			0.9	0.08	0.25	0.18
		0.2	0.7	0.13	0.33	0.20
			0.8	0.10	0.27	0.17
			0.9	0.06	0.18	0.12
	30	0.1	0.7	0.14	0.31	0.17
			0.8	0.13	0.29	0.15
			0.9	0.09	0.23	0.14
		0.15	0.7	0.13	0.28	0.16
			0.8	0.10	0.24	0.14
			0.9	0.05	0.15	0.10
		0.2	0.7	0.10	0.23	0.13
			0.8	0.06	0.18	0.12
			0.9	0.04	0.12	0.08

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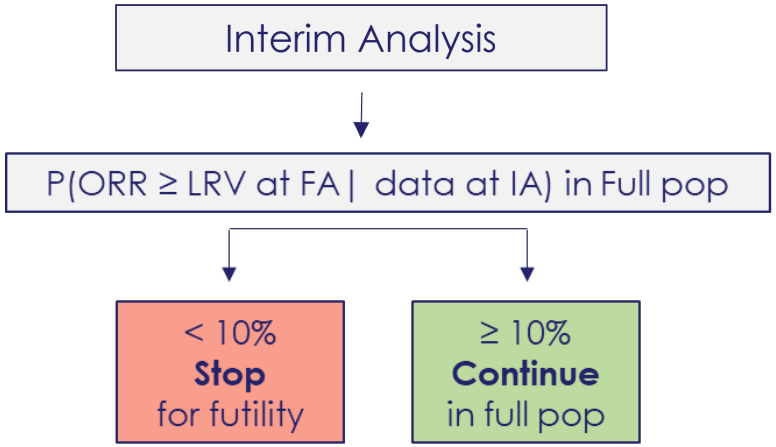
Original design

- The primary outcome of the trial is the overall response rate (ORR)

Decision rules at Interim analysis (IA)



Decision rules at final analysis (FA)

No Go: Pr(ORR ≥ Target Value (TV) | data at FA) ≤ 10%
Go: Pr(ORR ≥ Low Reference Value (LRV) | data at FA) ≥ 80%
Consider: Not a Go or a No Go

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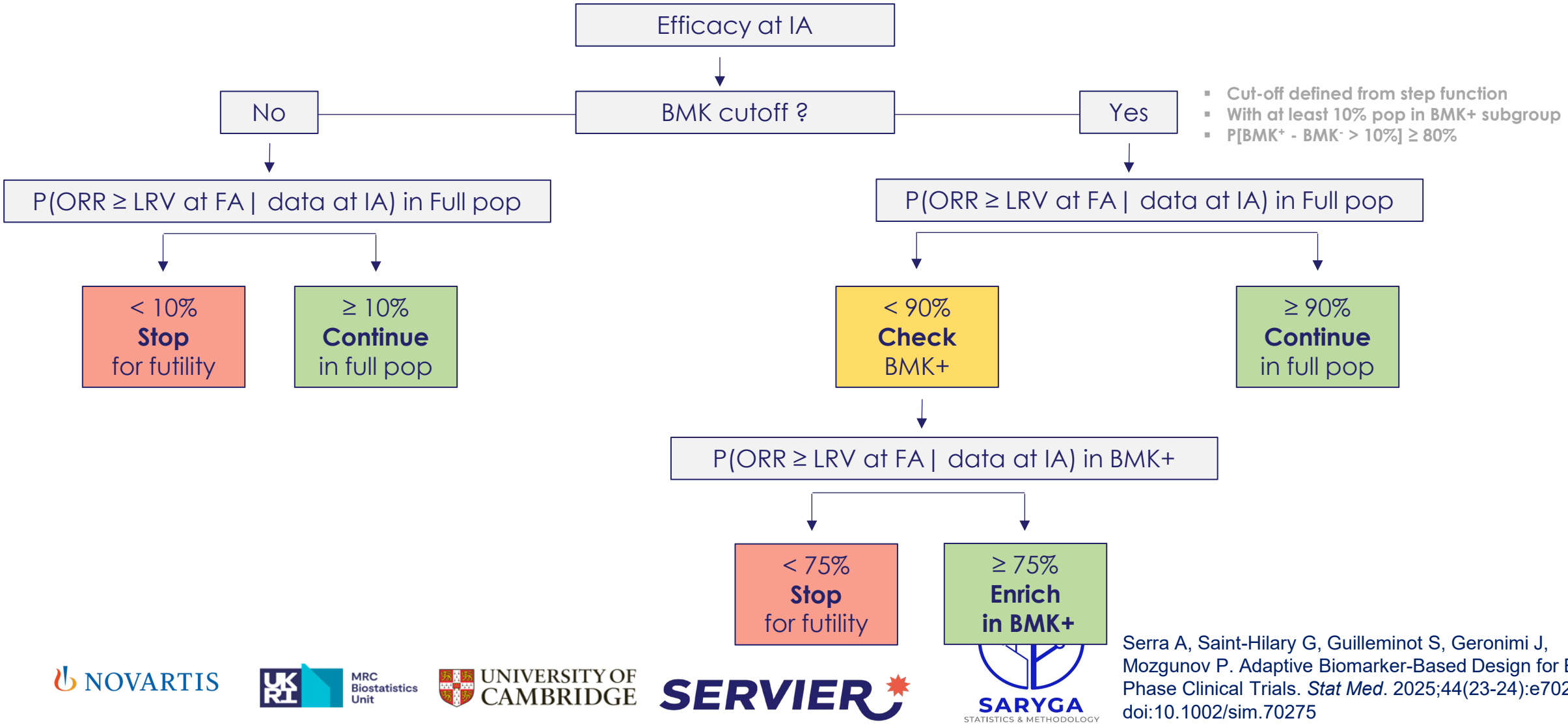
Proposed BMK-based design

Decision rules at final analysis (FA)

No Go: Pr(ORR ≥ Target Value (TV) | data at FA) ≤ 10%
Go: Pr(ORR ≥ Low Reference Value (LRV) | data at FA) ≥ 80%
Consider: Not a Go or a No Go

Decision rules at Interim analysis (IA)



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Simulation setting

- Number of patients: N= 14 at the interim analysis (IA) and 27 at the final analysis (FA)
- BMK Normally distributed ~ N(3.46 , σ = 1.3) - *based on a Ph Ib expansion on a Servier project*
- One single cutoff – On/Off relationship between the BMK and the treatment response
- Several scenarios with different response rates above (p_1) and below (p_0) the true cutoff, different prevalence of BMK+ patients (q_+), different values of TV and LRV

Scenario	p_0	p_1	q_+	Overall p	TV/LRV
Non-Predictive High Response (NPHR)	15%	15%	50%	15%	15%/5%
Non-Predictive Medium Response (NPMR)	5%	5%	50%	5%	15%/5%
Predictive High Response (PHR)	5%	25%	50%	15%	15%/5%
Predictive Medium Response (PMR)	5%	15%	50%	10%	15%/5%

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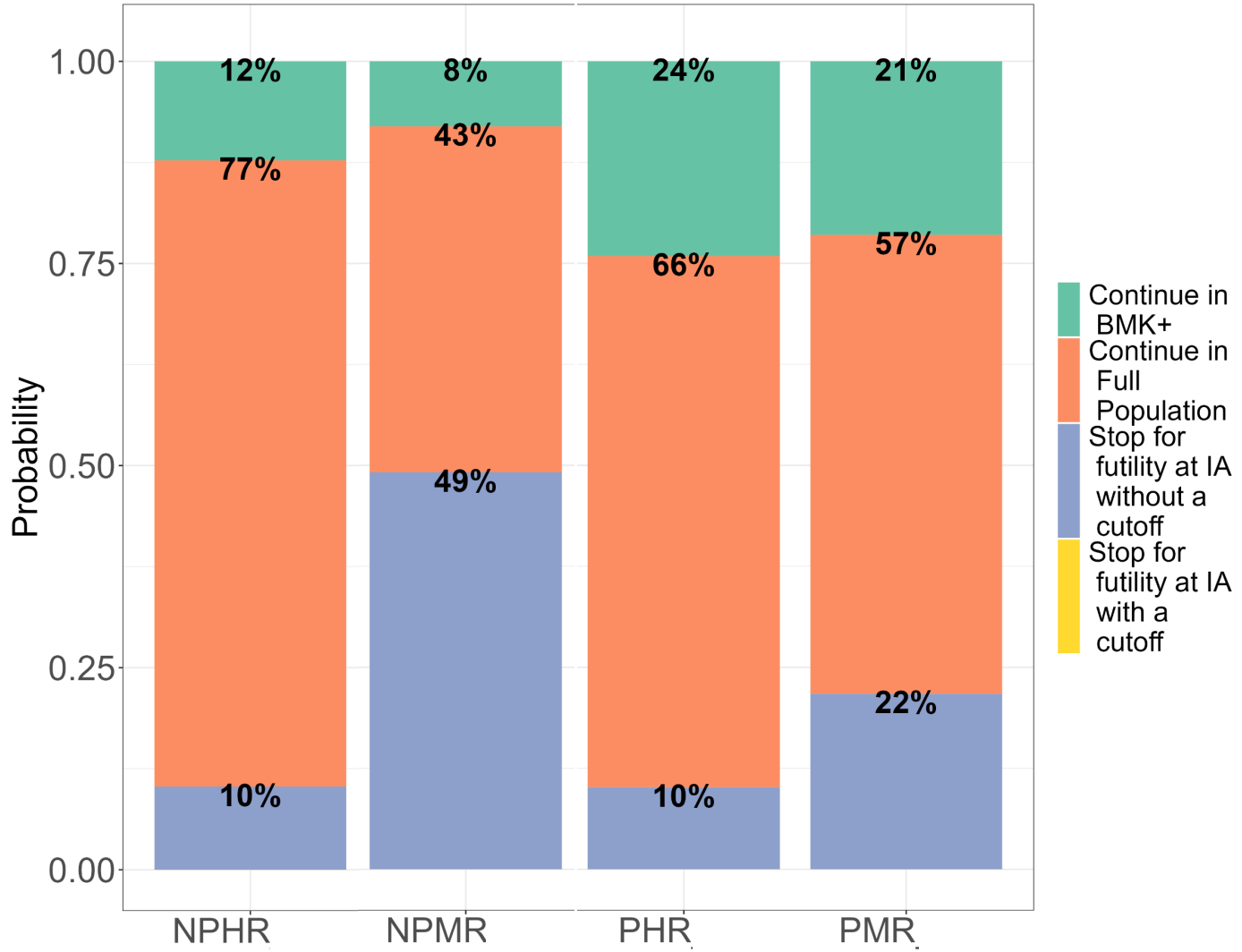
Numerical results – conditional decisions at IA



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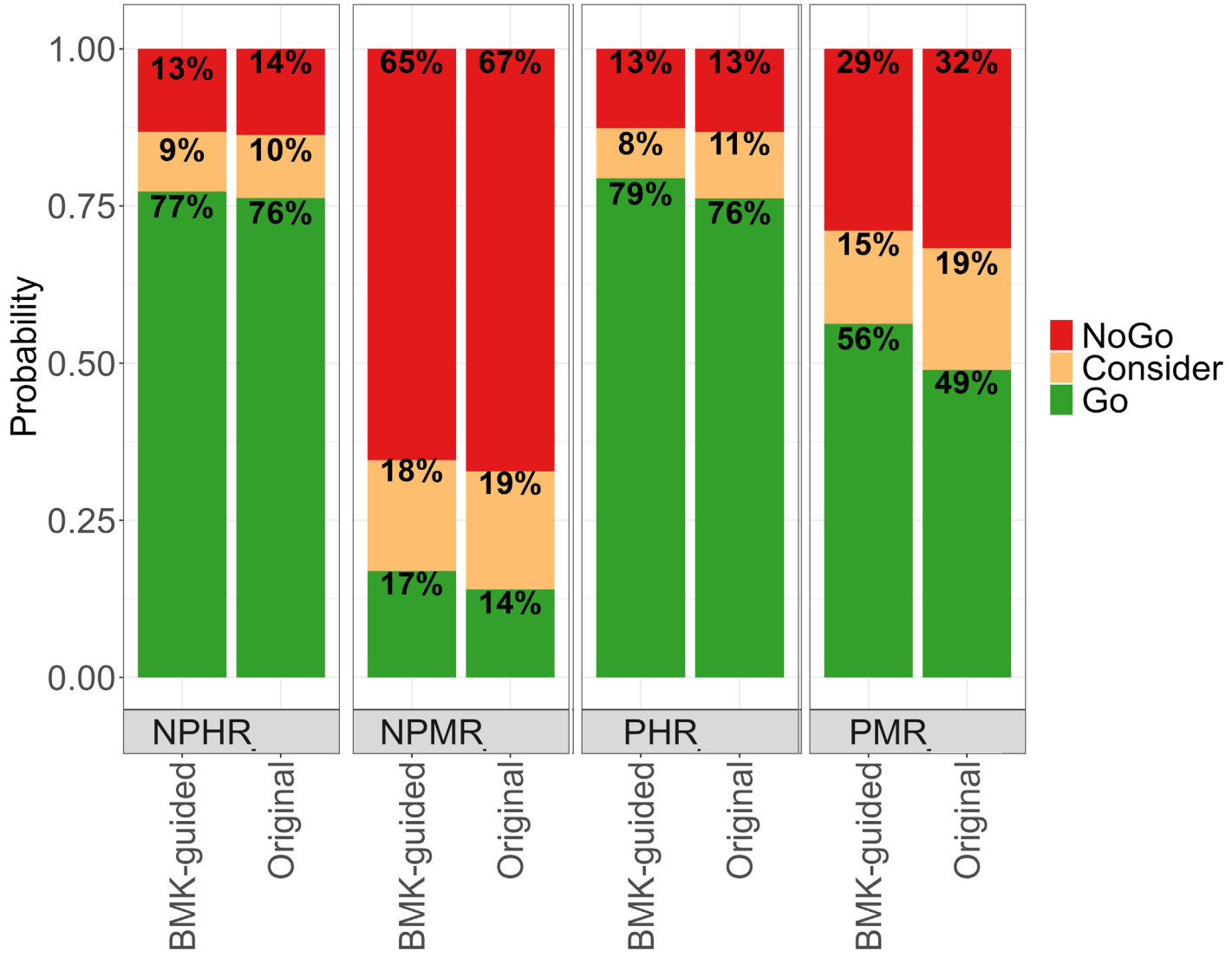
Numerical results – overall decisions at FA



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Discussion

- The **proposed adaptive design** has been shown to **outperform** the **non-adaptive approach** with a **gain up to 60%** in the overall **probability to Go** compared to the classical design when there is a true biomarker cutoff

- **Limited false enrichment** when there is no true biomarker cutoff, and overall, the probability to Go/No Go is almost the same as per the classical design

- **Sensitivity analyses** have been performed considering **different variations of the trial setting** and different distributions of the biomarker. The proposed design has shown to **provide consistent results** across the considered settings

- The proposed **method** to declare the presence or absence of a **biomarker cutoff** at the time of the interim analysis seemed to **perform quite well** under all analysed scenarios, considering such a small sample size. Further work is needed to compare this approach to other classical approaches (e.g. Youden index, SIDES approach).

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Thank you

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