An Enrichment Basket Trial Design for Efficacy

Luke Ouma[1], Xinling Xu[1], Yeonhee Park[2], Kentaro Takeda[1]

[1]Astellas Pharma Europe

[2]Sungkyunkwan University, South Korea

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Disclosures

The views expressed and conclusions drawn are my own, and the content herein does not reflect or imply endorsement with my current employer.

Outline

1. Motivation & Aim
2. Proposal: An enrichment basket trial design
3. Simulation study
4. Results & Discussion

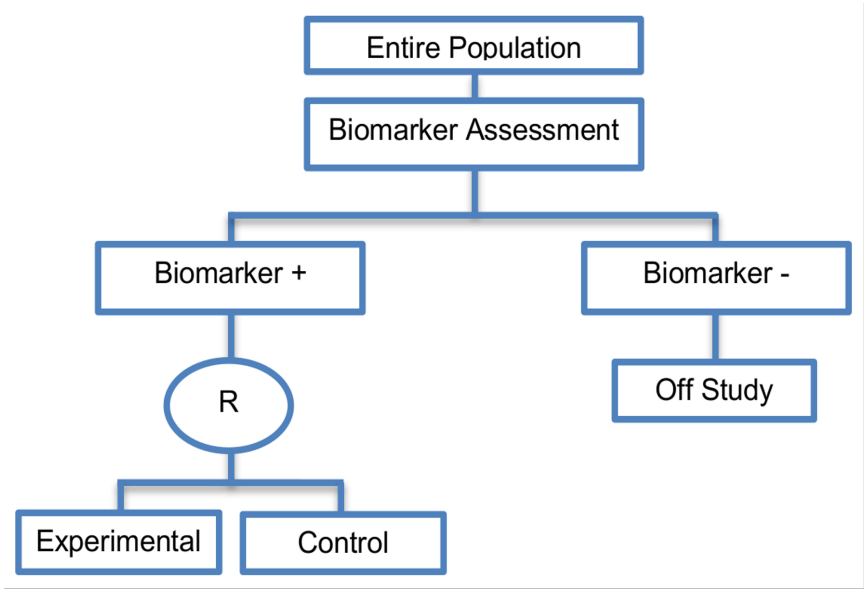
Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

Table 2. Preliminary Best Response According to Cohort.*

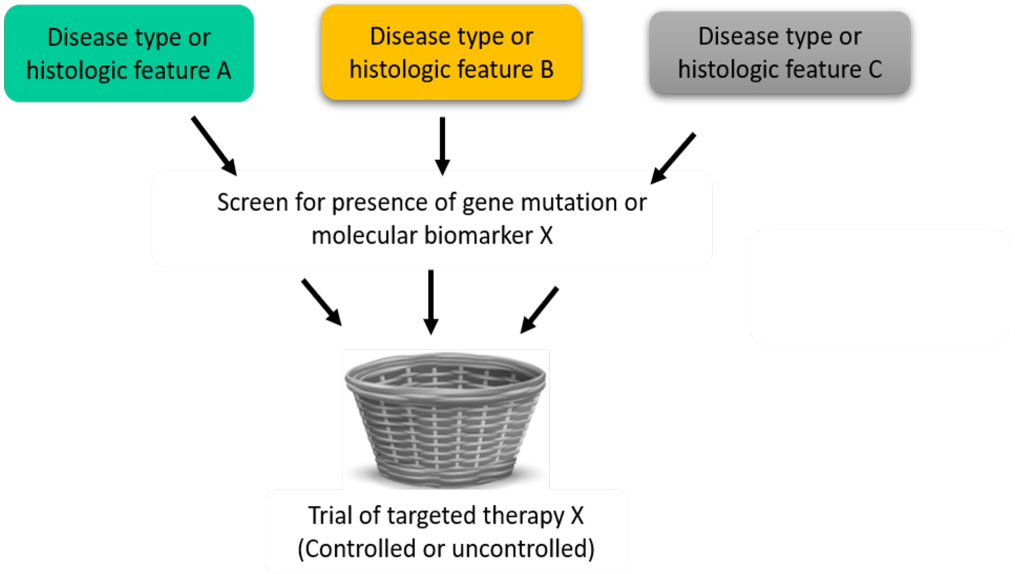
Variable	NSCLC (N=20)	Colorectal Cancer		Cholangio-carcinoma (N=8)	ECD or LCH (N=18)	Anaplastic Thyroid Cancer (N=7)
		Vemurafenib (N=10)	Vemurafenib + Cetuximab (N= 27)			
Patients with ≥1 postbaseline assessment — no.	19	10	26	8	14	7
Complete response — no. (%)	0	0	0	0	1 (7)	1 (14)
Partial response — no. (%)	8 (42)	0	1 (4)	1 (12)	5 (36)	1 (14)
Stable disease — no. (%)	8 (42)	5 (50)	18 (69)	4 (50)	8 (57)	0
Progressive disease — no. (%)	2 (11)	5 (50)	7 (27)	3 (38)	0	4 (57)
Missing data — no. (%)†	1 (5)	0	0	0	0	1 (14)
Overall response — no. (%) [95% CI]	8 (42) [20–67]	0	1 (4) [<1–20]	1 (12) [<1–53]	6 (43) [18–71]	2 (29) [4–71]

- Basekt trial - evaluates a targeted therapy across multiple diseases that share a common characteristic.
- Single arm designs, homegeneity assumptions are common, but less of adapting treatment assignment based on individual patient characteristics.

Motivation & Aim



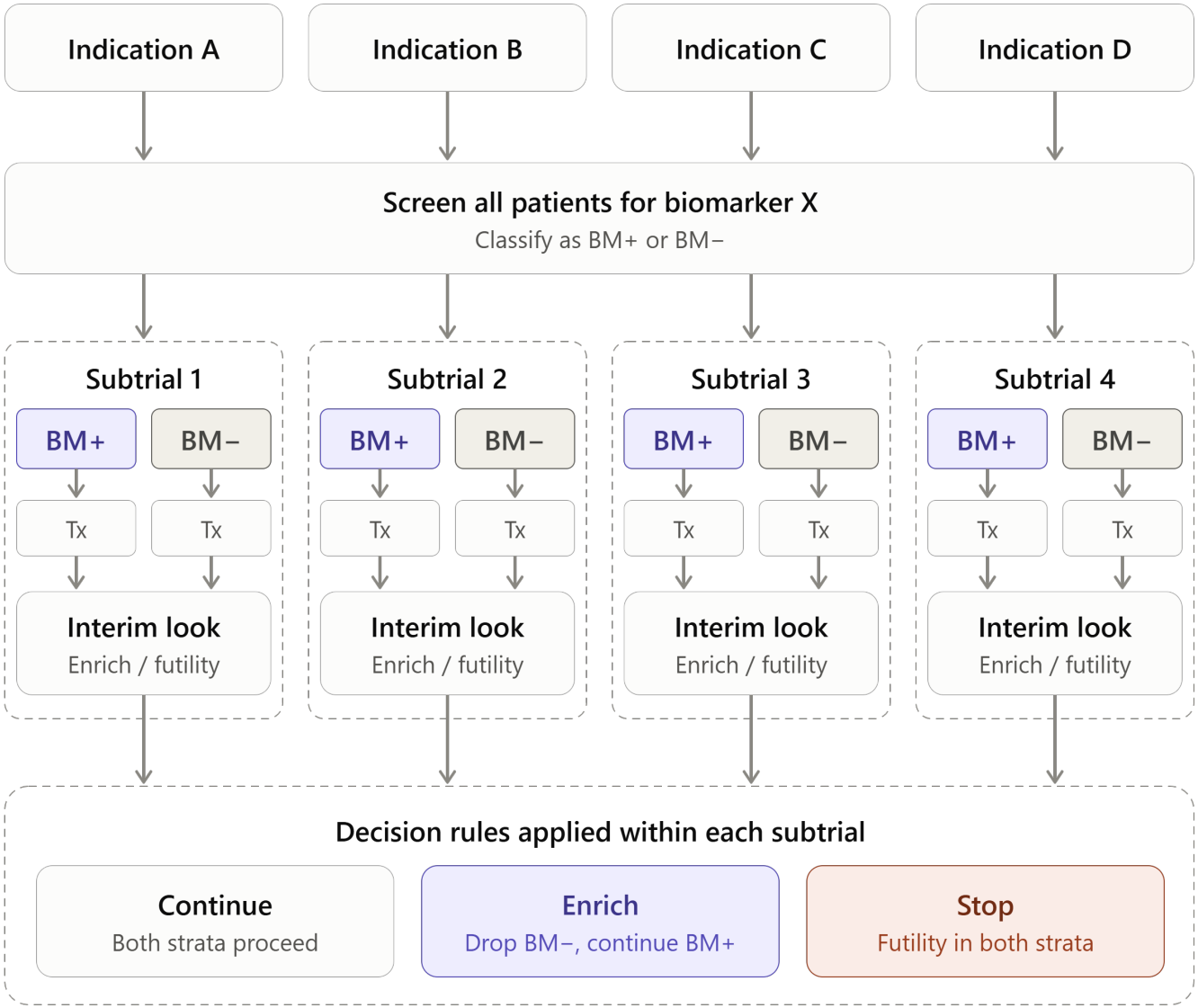
Traditional enrichment design



Basket trial

- There may be a rationale to include all-comer population.
- **Q:** Can we extend the basket design to incorporate adaptive enrichment, potentially introducing some efficiencies.

Proposal - Design



Proposal - Notation

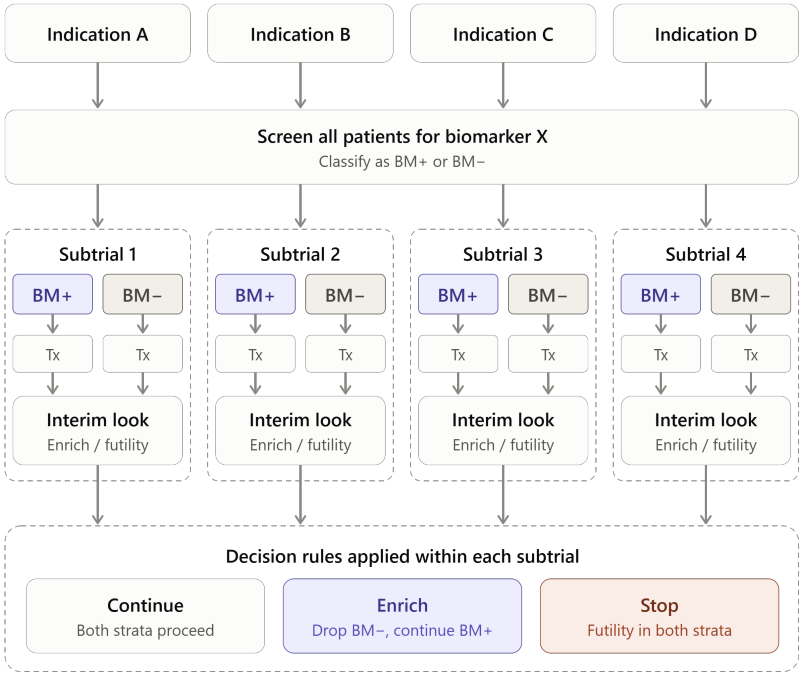
- Consider a basket trial investigating k unique disease types, (i.e., K subtrials), each enrolling upto n_k patients in that indication.
- Y_{ki} - binary outcome for the i^{th} individual; $\boldsymbol{X}_{ki}$ - biomarker profile.
- $p_k(x) = \Pr(Y_{ki} = 1 \mid X_{ki} = x)$ - true response probability for biomarker stratum $x \in \{0, 1\}$ in indication k.
- $\mathcal{D}_t = \{(X_{ki}, Y_{ki}),\ i = 1, \ldots, n_{kt},\ k = 1, \ldots, K\}$ denote accrued data by the t-th look, and n_{kt} is the number of patients enrolled upto that timepoint t
- T - pre-specified analyses.
- $\mathcal{D}_t = \{(X_{ki}, Y_{ki}),\ i = 1, \ldots, n_{kt},\ k = 1, \ldots, K\}$ - accrued data by the t-th look

Proposal

- Consider a basket trial investigating k unique disease types, (i.e., K subtrials).
- We propose a 2-stage adaptive design where:
  - In stage I, biomarker +ve and -ve patients receive the targeted treatment;
  - In stage II [subsequent stages], restrict patient enrollment to treatment-sensitive individuals and enrich the trial population.
- At interim analysis, estimate the probability of efficacy using the given the accrued data. Consider both Enrichment and Futility stopping rules.

  Otherwise, continue enrollment until the next interim look.
- Undertake final analysis ie., evaluate the treatment efficacy - once the maximum sample size has been reached or the accrual has been stopped for all indications due to futility.

Proposal



Enrichment: if $\Pr(Y_{ki} = 1|\boldsymbol{X}_{ki}, \mathcal{D}_t) < \eta_k$, terminate the accrual for the kth indication with biomarker profile $\boldsymbol{X}_{ki}$, where η_k is a pre-specified threshold.
Futility: a basket is admissible if $\Pr(p_k(\boldsymbol{X}_{ki}) > \phi_k|\mathcal{D}_t) \geq Q_f$. ϕ_k = lowest acceptable efficacy response rate.

- Final analysis: If $\Pr(p_k(\boldsymbol{X}_{ki}) > \phi_k|\mathcal{D}_t) \geq Q$, declare treatment efficacious for the kth indication with biomarker profile $\boldsymbol{X}_i$, $Q = 0.90$.

Proposal - Methodology

- We model the probability of response for the i^{th} patient as,

$$\text{logit}\{\Pr(Y_{ki} = 1 \mid X_{ki})\} = \alpha_k + \beta_k X_{ki}, \tag{1}$$

- The model eq (1) can also be re-paratemerised as,

$$\text{logit}\{\Pr(Y_{ki} = 1|\boldsymbol{X}_{ki})\} = \alpha_k + \boldsymbol{\beta}^T \boldsymbol{X}_{ki} + \boldsymbol{\gamma}_k(I_k \boldsymbol{X}_{ki}), \tag{2}$$

  where $\boldsymbol{\beta}_k \equiv \boldsymbol{\beta} + \boldsymbol{\gamma_k} \geq \mathbf{0}$

- We impose a multi-level monotonicity constraint, $\boldsymbol{\beta}_k \geq \mathbf{0}$ for each k: higher biomarker level $\sim$ higher or equal log-odds of response across indications.

Biomarker effect constraints

The constraint $\beta_k \geq 0$ for all k ensures monotonicity: increasing the biomarker level cannot decrease the log-odds of response in any indication:

1. Unconstrained A direct normal prior is placed on β_k without any positivity restriction:

$$\beta_k \sim \mathcal{N}(\cdot, \cdot), \tag{3}$$

   where the location and scale parameters are specified by the borrowing structure.

2. Log transform: Monotonicity is enforced via a deterministic exponential transformation of an unconstrained latent parameter η_k:

$$\beta_k = \exp(\eta_k), \qquad \eta_k \sim \mathcal{N}(\cdot, \cdot). \tag{4}$$

   Since $\exp(\eta_k) > 0$ for any $\eta_k \in \mathbb{R}$, the constraint $\beta_k > 0$ is satisfied by construction for every posterior draw. The implied prior on β_k is log-normal.

3. Truncated normal: A normal prior on β_k truncated to the positive real line:

$$\beta_k \sim \mathcal{N}(\cdot, \cdot)\,\mathcal{I}(\beta_k > 0), \tag{5}$$

   where $\mathcal{I}(\cdot)$ is the indicator function imposing the truncation.

4. Gamma: The biomarker effect is given a Gamma prior with shape a and rate b:

$$\beta_k \sim \text{Gamma}(a, b). \tag{6}$$

   where $a > 1$ produces a smooth unimodal density peaked away from zero, while $a \leq 1$ places more mass near zero.

Proposal - Methodology

- Information borrowing proposal 1: Full hierachical model

$$\alpha_k \sim N(\mu_\alpha, \sigma_\alpha^2), \quad k = 1, \ldots, K.$$
$$\beta_k \sim \mathcal{N}(\mu_\beta, \sigma_\beta^2)$$

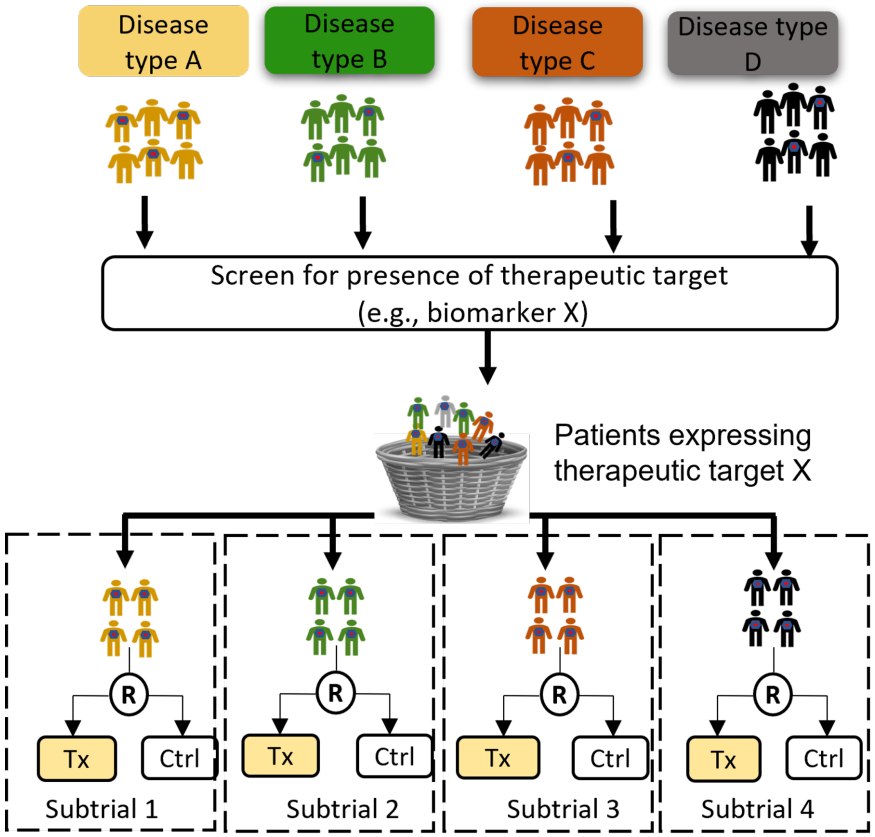
with weakly informative priors $\mu_\alpha \sim \mathcal{N}(0, 10^3)$, $\sigma_\alpha \sim$ Half-Cauchy$(0, 1)$.
$\mu_\beta \sim \mathcal{N}(0, 10^3)$ and $\sigma_\beta \sim$ Half-Cauchy$(0, 1)$

- Information borrowing proposal 2: partial hierachical model.

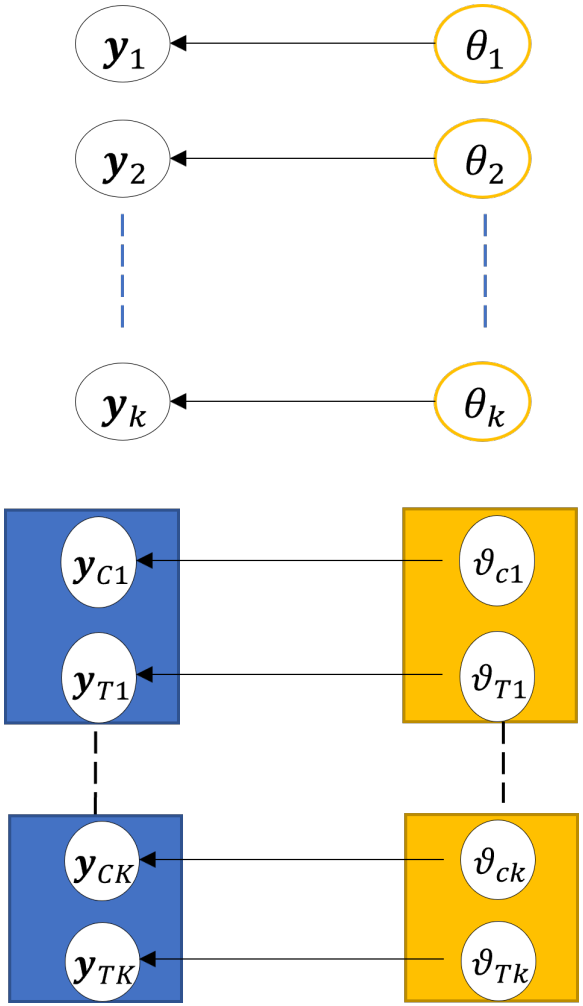
$$\boldsymbol{\beta_k} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_{\beta_k})$$

Table: Summary of the four probability models

Model	**Hierarchical** α_k	**Hierarchical** β_k	β_k **constrained**
M1: Full hier, constrained	Yes	Yes	Yes
M2: Full hier, unconstrained	Yes	Yes	No
M3: α_k-only hier, constrained	Yes	No	Yes
M4: α_k-only hier, unconstrained	Yes	No	No



Randomised basket trial design



- Our design can be visualised in two ways:
  - define a 'basket' as the cross-classification of indication and biomarker stratum, yielding up to 2K baskets in total.
  - define a 'basket' by indication, and within each basket there are 2 biomarker strata - simplifies model setup, similar to TRB approach in basket trials.

Simulation setting

1. Simulate stage 1 data under different scenarios for each of the K subtrials.
2. Undertake interim analysis using the observed stage 1 data - evaluate enrichment and futility decision rules.
3. Next, simulate data for subsequent stages based on decision at the previous stage.
4. Conduct final analysis - maximum sample size reached or the accrual has been stopped for all indications due to futility.

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5. Evaluation metrics: enrollment, power, proportion of enrichment & futility, bias, RMSE.

Basic trial setting,

- Indications/Subtrials: $K = 4$
- Outcome: $y_{ij} \sim bernoulli()$
- Simulation scenarios: 9;
- Sample size: $n_k = 40$, each strata has $n_k/2$.

Results

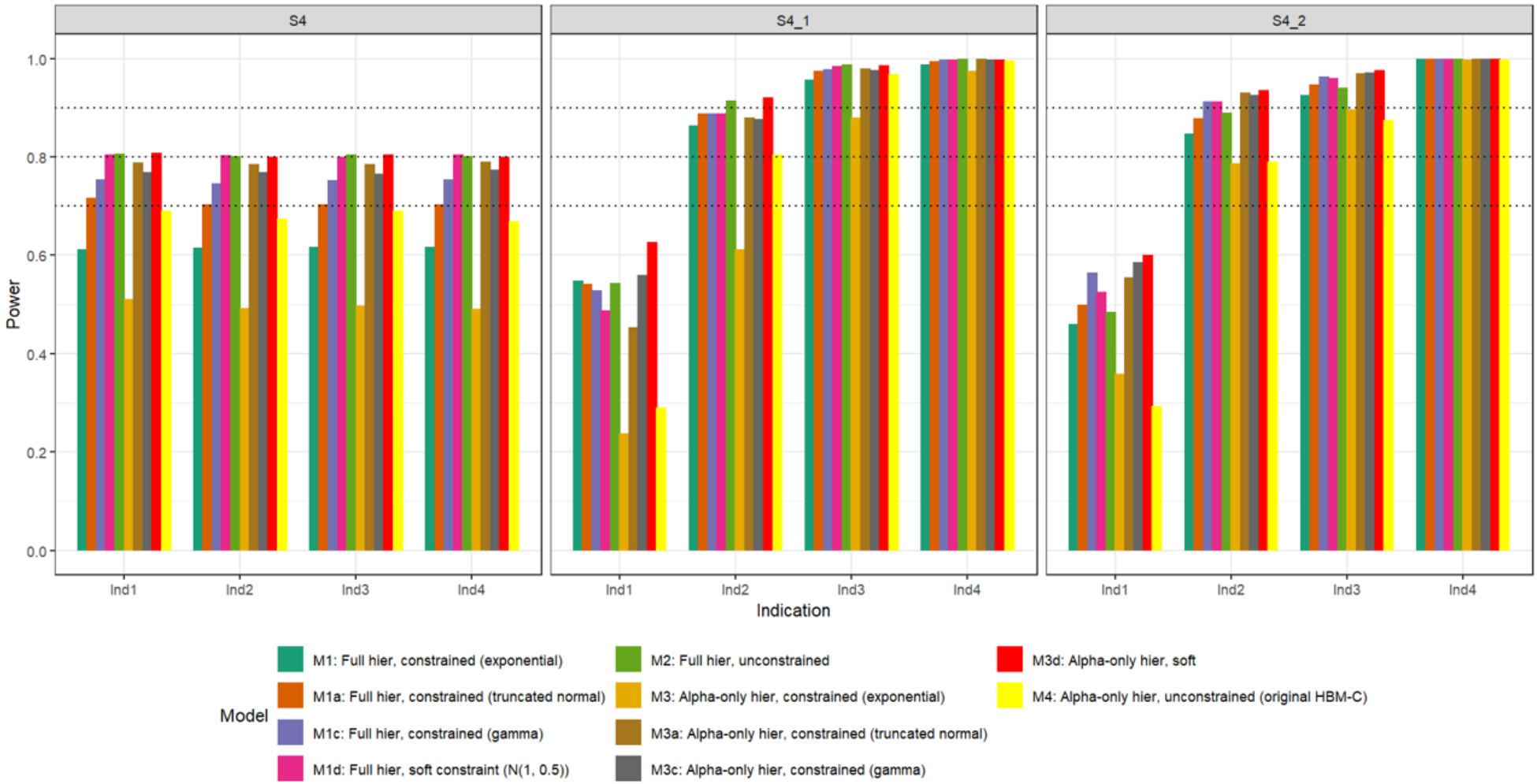
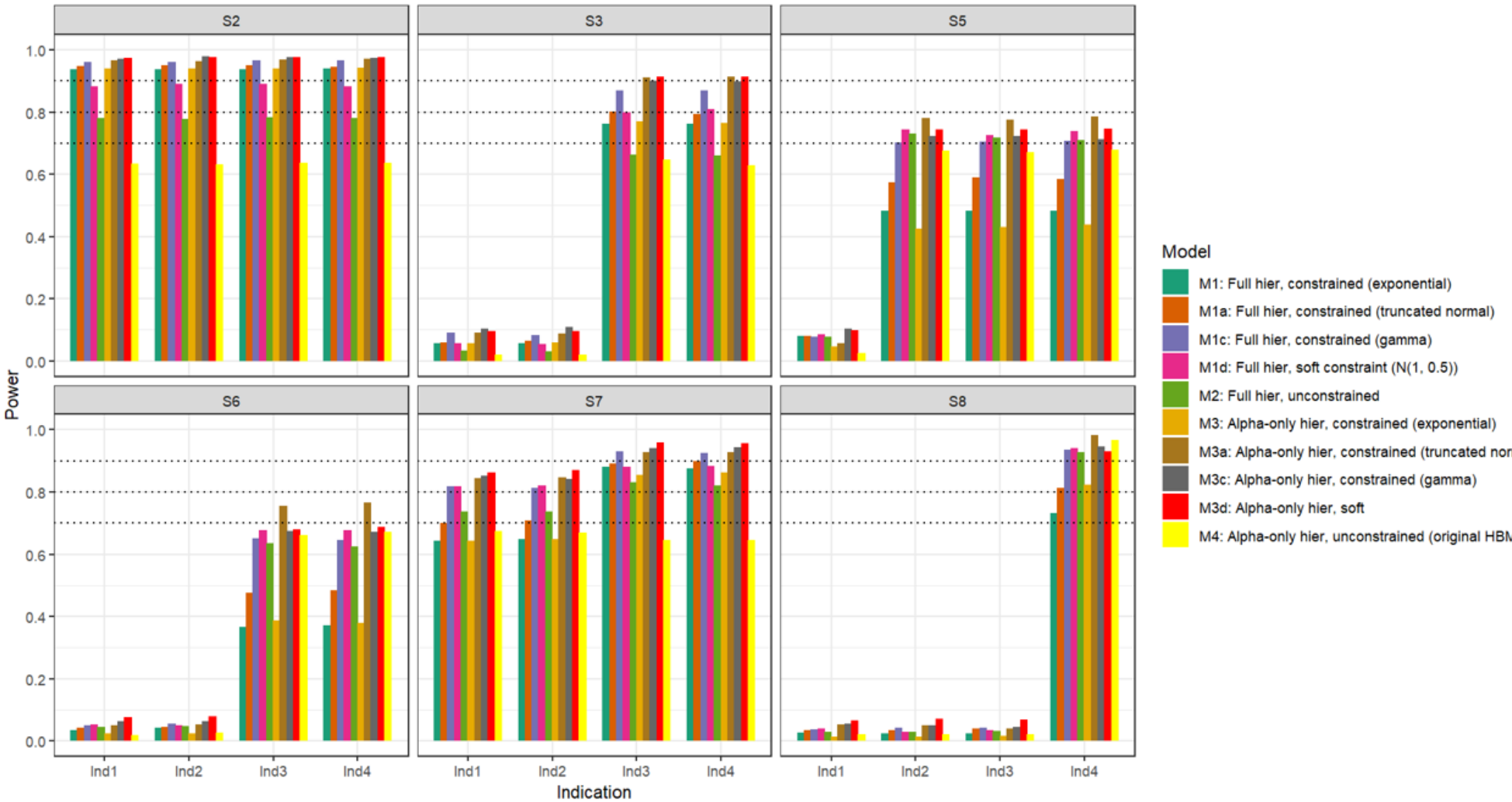


Figure: Statistical power - Scenario: Biomarker +ve respond better in all indications, under varyling levels of heterogeneity.

Results



- S2: All active baskets. S3: Partial S2. S5: S4-BM effect in all except Ind1.

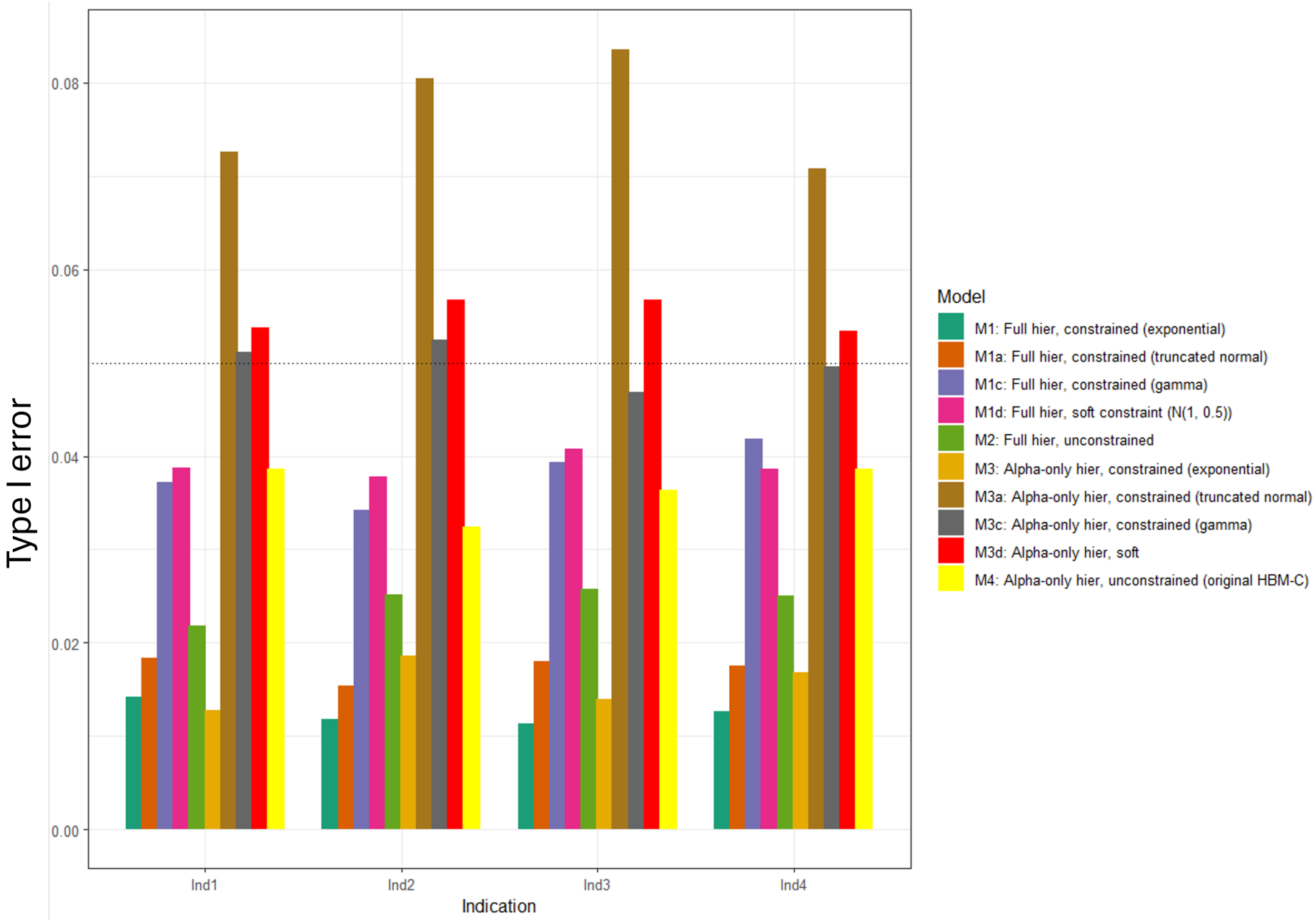


Figure: Type I error comparison

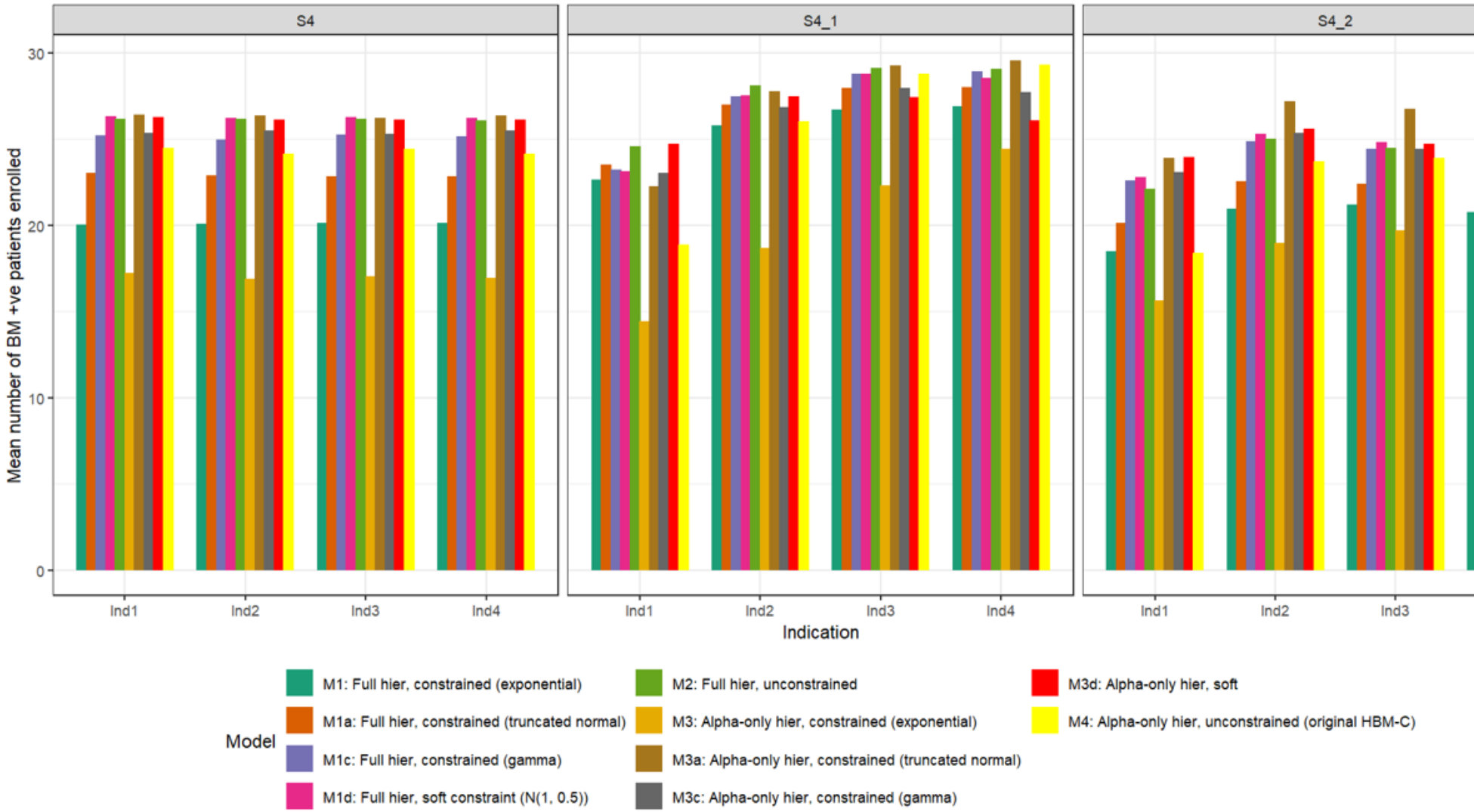


Figure: Average number of BM +ve patients enrolled

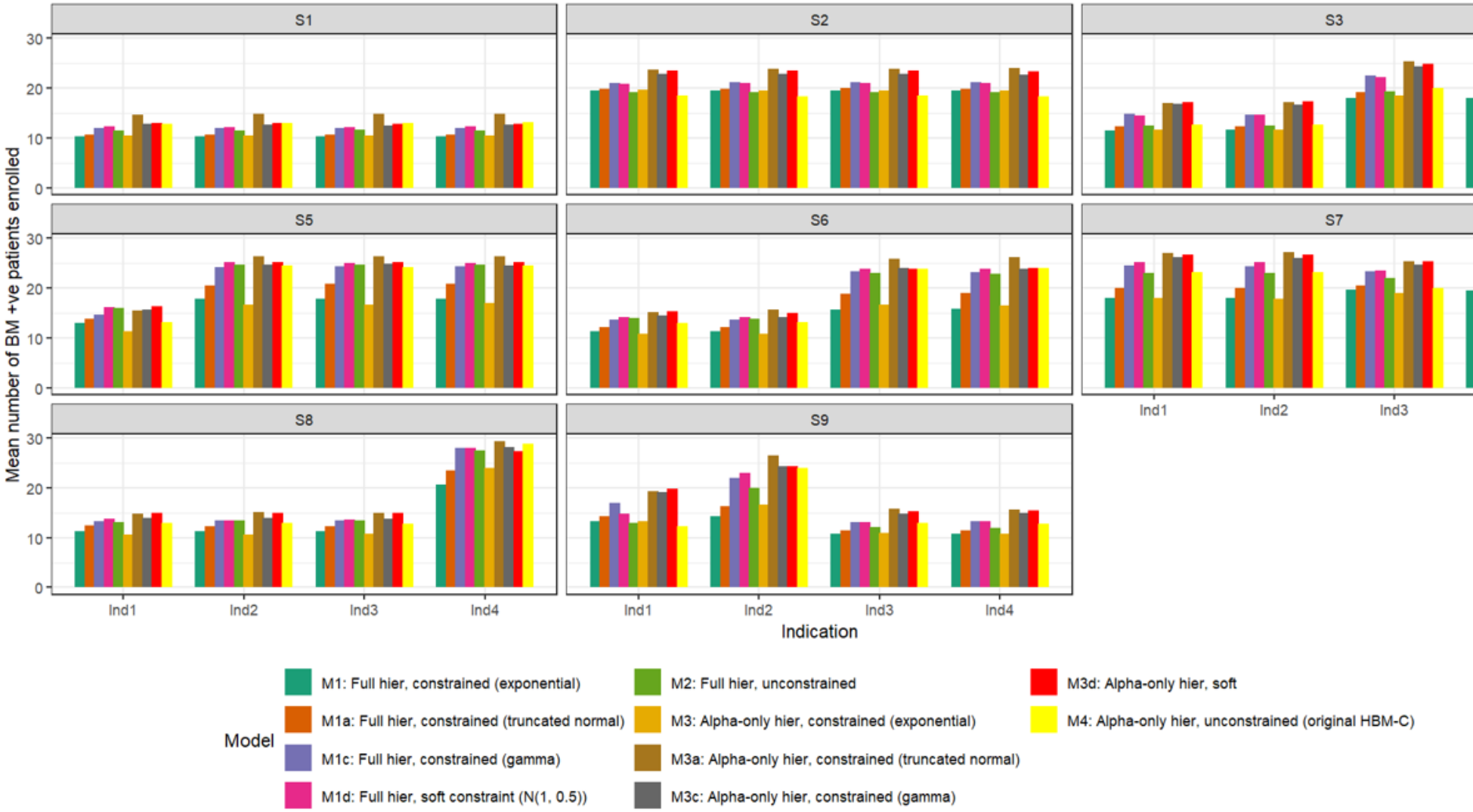


Figure: Average number of BM +ve patients enrolled

Conclusion & future work

- Enrichment basket designs feasible and offer important advantages.
- Full hierachical models not always beneficial.
- Constrained models have poor performance when misspecified,
- Fully explore other advanced Bayesian borrowing methods - EXNEX, commensurate prior approach et al.

Acknowledgements

Thank you for listening!

luke.ouma@astellas.com