A basket trial design based on constrained hierarchical Bayesian model for latent subgroups

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ABSTRACT

It is well known a basket trial consisting of multiple cancer types has the potential of borrowing strength across the baskets defined by the cancer types, leading to an efficient design in terms of sample size and trial duration. The treatment effects in those baskets are often heterogeneous and categorized by the cancer types being sensitive or insensitive to the treatment. Hence, the assumption of exchangeability in many existing basket trials may be violated, and there is a need to design trials without this assumption. In this paper, we simplify the constrained hierarchical Bayesian model for latent

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Agenda

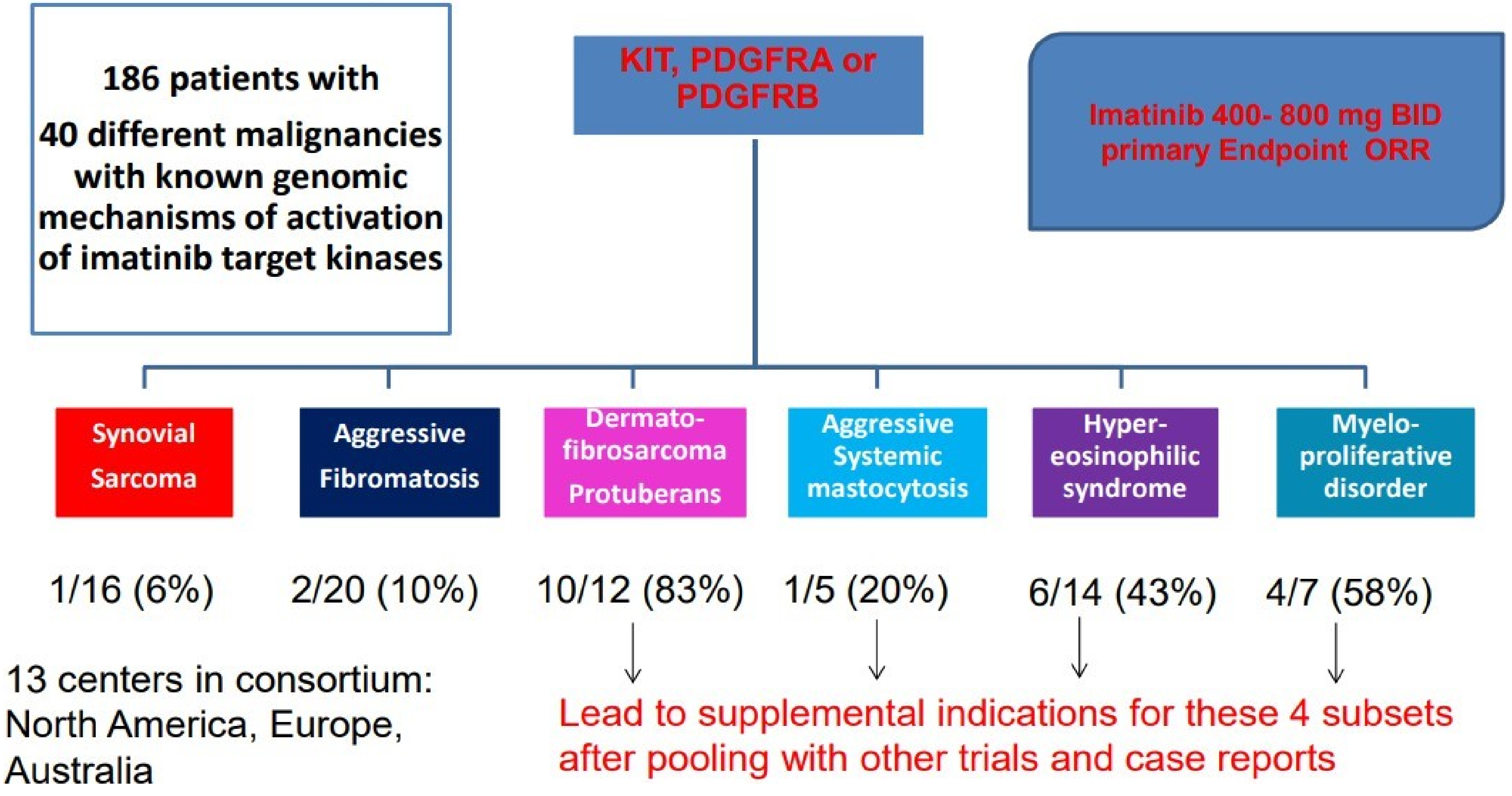
Introduction

- Cancer types are traditionally defined based on the original location of the tumors, such as breast cancer or lung cancer.
- In traditional phase II clinical trial design (Simon’s two-stage design is often used), a new treatment is evaluated for one cancer type in a single trial at a time.
- Due to advancements in precision medicine and scientific discovery of cancer mechanisms, the treatment has shifted to targeted therapies and immunotherapies, which fight tumors based on the disruption of the aberrations, regardless of the location of the tumor.
- This implies that clinical trial designs may allow multiple cancer types to be investigated for a new treatment at the same time within a single trial, which is called a **basket trial**.

Basket Trials

- Usually, it is more efficient to combine the clinical data of all cancer types for statistical analysis.
- However, sometimes heterogeneity may present in the treatment effects across cancer types.
- For example, Vemurafenib was highly efficacious for BRAF V600E mutated melanoma and hairy cell leukemia, but not for colorectal cancer with the same mutation (Hyman et al., 2015).
- The heterogeneous treatment effects across cancer types impose challenges for statistical modeling and designs.
- There is increasing statistical interest in the design and analysis of basket trials.

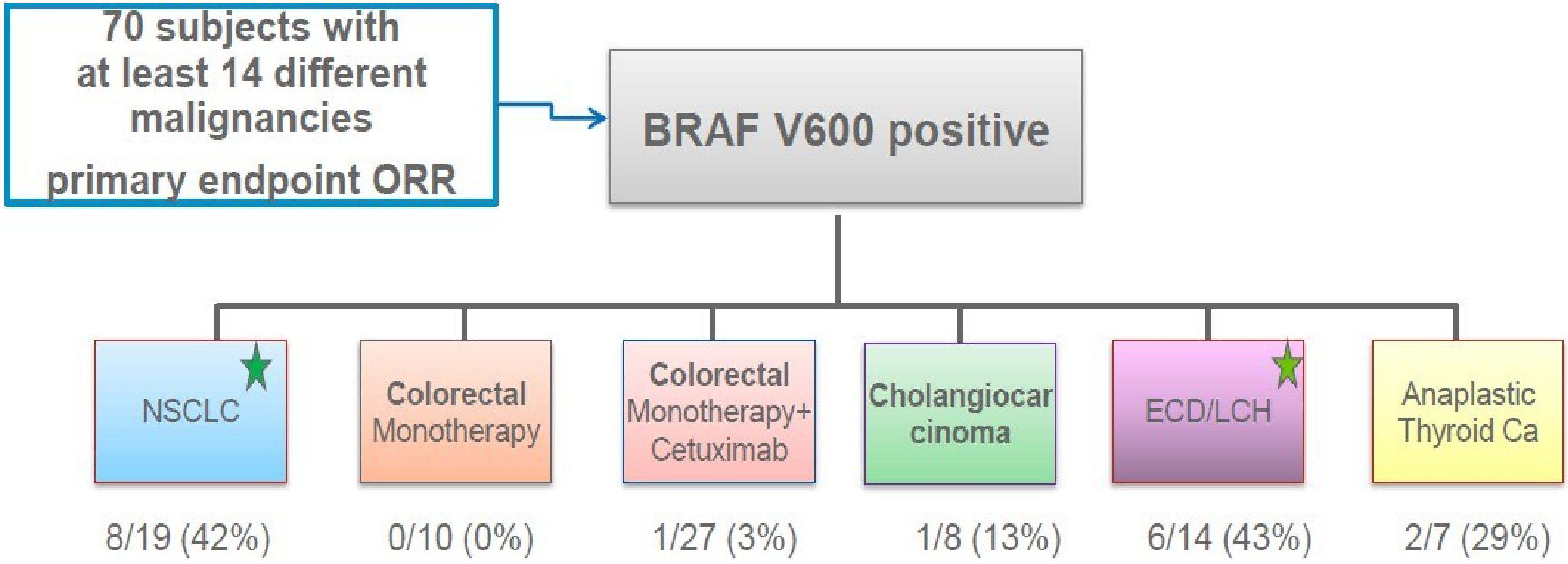
Imatinib (Chugh et al., 2009)



- The trial was initially designed based on a fully exchangeable hierarchical Bayesian model (Thall et al. 2003)
- The response rates are quite different among cancer types

Blumenthal. Innovative trial designs to accelerate the availability of highly effective anti-cancer therapies: an FDA perspective, AACR 2014.

Vemurafenib (Hyman et al., 2015)



- The trial was initially designed based on Simon's two-stage design (Simon, 1989) for each of the six cancer types
- Ignores the commonality among cancer type with same genetics mutation

Constrained HBM for latent subgroup

- To consider the reality of non-exchangeability across baskets, Takeda et al. (2022) have proposed a constrained hierarchical Bayesian model for latent subgroups (CHBM-LS) for basket trials where baskets are defined by two classifiers; they are the cancer types as the most common classifier, and the multiple levels of another classifier which could be common for complex basket trials.

- However, the majority of the basket trials have baskets defined only by the single classifier, i.e., cancer type

- We propose simplifying CHBM-LS for two classifiers to deal with the potential heterogeneity of treatment effects due to the single classifier of the cancer type.

Classifier and Latent Subgroups

Classifier:

- j: classifier (cancer types), $1, \ldots, J$.

Latent subgroups for the classifier:

- l: latent subgroup, $1 \leq l \leq L$ and $L \leq J$.

Latent subgroup membership indicator:

- C_j: the latent subgroup membership indicator. $C_j = l$ denoting that the j^{th} basket belongs to the classified latent subgroup l
- $C_j \sim \text{multinomial}(\pi_1, \ldots, \pi_L)$, where π_l is the probability that the j^{th} basket belongs to the classified latent subgroup l, with $\sum_{l=1}^{L} \pi_l = 1$.

Constrained HBM for latent subgroup (CHBM-LS) (1/4)

Model specification:

- Y_{ij}: the binary response of the i^{th} patient in the j^{th} basket, where $Y_{ij} = 0,1$ represents a non-responder and a responder
- $Y_{ij} = I(\xi_{ij} > 0)$, where $I(A)$ denotes the indicator function for event A, i.e., $Y_{ij} = 1$ if $\xi_{ij} > 0$ and $Y_{ij} = 0$ if $\xi_{ij} \leq 0$.
- ξ_{ij}: a latent variable for the i^{th} patient in the j^{th} basket
- Assuming the latent variable ξ_{ij} follows a normal distribution with a mean that varies with basket j as

$$\xi_{ij} \sim N(\mu_j),$$

for $i = 1, \ldots, n_j$, where n_j denotes the number of patients in the j^{th} basket.

Constrained HBM for latent subgroup (CHBM-LS) (2/4)

Parameters with latent subgroups:

- Conditionally on C_j, μ_j follows a normal distribution with η_l and σ^2 denoting the mean parameter and the variance parameter, respectively,

$$\mu_j | C_j = l \sim N(\eta_l, \sigma^2).$$

- Therefore, the response rate, defined as the number of responders divided by the number of patients in the baskets, are generally similar in the same latent subgroup l but different across the latent subgroups
- Thus, the response rates in a basket trial with the latent subgroups can be modelled by the hierarchical Bayesian model.

Constraint:

- $\eta_1 \leq \cdots \leq \eta_L$ for each latent subgroup in the cancer type

Constrained HBM for latent subgroup (CHBM-LS) (3/4)

The proposed CHBM-LS with single classifier:

- The constraint is formalized as

$$\eta_l | \eta_{-l} \sim N(\eta_l | \xi, \tau^2) I\left(\eta_{(l-1)} \leq \eta_l \leq \eta_{(l+1)}\right)$$

- Denote $\boldsymbol{\eta}$ by the vector of all η_l and $\boldsymbol{\eta}_{-l}$ by the subvector with η_l being deleted, for $l = 1, \dots, L$.
- $N(\xi, \tau^2)$ denotes the hyperprior normal distribution with mean ξ and variance τ^2, with the truncated support of η_l given by the indicator function.
- The ordered constraint can be achieved at each MCMC step by generating the proposals $\boldsymbol{\eta} = (\eta_1, \dots, \eta_L)$ and subjecting to $\eta_1 \leq \cdots \leq \eta_L$.

Constrained HBM for latent subgroup (CHBM-LS) (4/4)

Likelihood:

- The individual likelihood of the i^{th} patient in the j^{th} basket with the outcome Y_{ij} is given by

$$p\left(Y_{ij}|C_{ij},\boldsymbol{\eta},\sigma^2\right) = \left[\Pr\left(\xi_{ij} > 0|\boldsymbol{\eta},\sigma^2\right)\right]^{Y_{ij}}\left[\Pr\left(\xi_{ij} \leq 0|\boldsymbol{\eta},\sigma^2\right)\right]^{1-Y_{ij}}$$
$$= \left[\int_0^{\infty} N\left(\xi_{ij}|C_{ij},\boldsymbol{\eta},\sigma^2\right)\right]^{Y_{ij}}\left[\int_{-\infty}^{0} N\left(\xi_{ij}|C_{ij},\boldsymbol{\eta},\sigma^2\right)\right]^{1-Y_{ij}}$$

- $C_{ij} = 1, \dots, L$ is the latent subgroup membership indicator of the i^{th} patient in the j^{th} basket.

The number of latent subgroups

- In principle, the selection of the number of latent subgroups L can be made by fitting the model with $L = 1, \dots, J$, and then selecting the value of L that yields the smallest value of DIC.
- However, it is usually sufficient to restrict the search space of L to $\{1,2\}$ in practice, because the number of cancer types in a basket trial is typically small and all enrolled patients have the same genetic or molecular aberration.
    - 1 = (all basket being either insensitive or sensitive)
    - 2 = (some basket being insensitive, the others being sensitive)
- The restriction is also beneficial for intuitively interpreting the clinical trial results.

Trial design based on CHBM-LS (1/2)

Hypothesis:

- $H_0: p_j < q_0$ versus $H_a: p_a > q_1$ for $j = 1, \dots, J$
  - p_j: the response rate in the j^{th} basket
  - q_0: the null response rate that the treatment is deemed futile
  - q_1: the alternative response rate that the treatment is considered promising

Interim data:

- $D_t = \{Y_{ij}, i = 1, \dots, n_{jt}, j = 1, \dots, J\}$: the interim data at the t^{th} look.
- Assume that n_{jt} patients in the j^{th} basket have been enrolled at the t^{th} interim look for $t = 1, \dots, T$.

Trial design based on CHBM-LS (2/2)

The proposed CHBM-LS design procedure:

1. Enroll n_{jt} patients in the j^{th} basket.
2. Given the t^{th} interim data D_t, estimate p_j using the CHBM-LS.
   a) Futility stopping: if $\mathrm{Pr}\left[p_j > (q_0 + q_1)/2 \,|D_t\right] < Q_f$, suspend the accrual for the j^{th} basket, where Q_f is a probability cut-off for futility termination.
   b) Otherwise, continue to enroll patients until the next interim look.
3. Once the maximum sample size has been reached or the accrual has been stopped for all baskets due to futility, evaluate the treatment efficacy based on the final data D:
   a) If $\mathrm{Pr}\left[p_j > q_0|D\right] > Q$, declare that the treatment is efficacious for the j^{th} basket, where Q is a probability cut-off for efficacy;
   b) Otherwise, declare that the treatment is not efficacious for this basket.

Simulation Study (1/2)

Target for comparison:

- Independent model (Independent)
- Hierarchical Bayesian model (HBM, Thall et al., 2003; Berry et al., 2013)
- Exchangeability–non-exchangeability model (EXNEX, Neuenschwander et al., 2015)
- CHBM-LS with a single classifier (Takeda et al., 2025)

Design:

- 2-stage design with 12 subjects per stage per basket, where early stopping for futility is allowed.

Simulation Study (2/2)

Simulation setting:

- Classifier: 4 cancer types ($J = 4$)
- Maximum numbers of latent subgroups for the classifier is $L = 2$
- $q_0 = 0.1, q_1 = 0.3$
- Rejecting H_0 criterion: $\Pr(P > 0.10|\text{data}) \geq 0.90$
- Futility criterion: $\Pr(P > 0.20|\text{data}) \leq 0.10$

Summarized results:

- Percentage of times that each basket rejects H_0 (%reject)
- Percentage of times that each basket stopped for futility (%stop)
- Average total sample size (avgN)

Simulation Scenarios

Scenario	Cancer type			
	1	2	3	4
1	0.10	0.10	0.10	0.10
2	0.30	0.30	0.30	0.30
3	0.10	0.10	0.30	0.30
4	0.10	0.10	0.10	0.30
5	0.10	0.30	0.30	0.30
6	0.10	0.30	0.30	0.50
7	0.10	0.30	0.50	0.70

- Scn 1: Global null scenario
- Scn 2: Global alternative scenario
- Scn 3-7: Heterogeneous

Simulation Results (1/2)

Scenario	Design	Parameter	Cancer type				avgN
			1	2	3	4	
1		Response rate	0.10	0.10	0.10	0.10	
	Independent	%reject (%stop)	6.2 (65.4)	8.1 (65.4)	7.0 (66.3)	7.1 (63.5)	64.7
	HBM	%reject (%stop)	3.8 (60.8)	5.1 (59.0)	4.3 (60.2)	4.2 (57.8)	67.5
	EXNEX	%reject (%stop)	6.0 (59.9)	4.0 (60.4)	5.5 (59.6)	4.2 (61.1)	67.1
	CHBM-LS	%reject (%stop)	7.8 (37.4)	7.9 (35.1)	8.7 (35.3)	8.2 (35.1)	78.9
2		Response rate	0.30	0.30	0.30	0.30	
	Independent	%reject (%stop)	84.5 (7.8)	85.4 (7.2)	84.8 (7.6)	83.2 (10.7)	92.0
	HBM	%reject (%stop)	90.9 (1.4)	91.1 (1.0)	91.0 (1.4)	89.4 (2.1)	95.3
	EXNEX	%reject (%stop)	75.7 (1.6)	74.6 (2.0)	74.6 (1.8)	74.0 (1.4)	95.2
	CHBM-LS	%reject (%stop)	88.8 (1.7)	86.9 (2.1)	87.7 (1.3)	88.7 (1.8)	95.2
3		Response rate	0.10	0.10	0.30	0.30	
	Independent	%reject (%stop)	6.4 (66.1)	7.0 (65.0)	83.5 (9.2)	82.9 (10.2)	77.9
	HBM	%reject (%stop)	7.1 (35.0)	8.4 (33.4)	84.1 (5.3)	83.2 (6.4)	86.4
	EXNEX	%reject (%stop)	11.6 (34.1)	10.1 (33.8)	73.5 (5.3)	70.3 (4.3)	86.7
	CHBM-LS	%reject (%stop)	8.8 (33.7)	7.9 (30.9)	87.8 (1.6)	87.3 (3.2)	87.7
4		Response rate	0.10	0.10	0.10	0.30	
	Independent	%reject (%stop)	7.3 (65.5)	6.8 (66.5)	8.2 (66.7)	85.4 (8.4)	71.1
	HBM	%reject (%stop)	7.0 (48.7)	7.0 (48.4)	8.6 (48.0)	79.3 (6.8)	77.8
	EXNEX	%reject (%stop)	11.3 (43.2)	11.3 (46.5)	11.7 (45.6)	58.4 (7.1)	78.9
	CHBM-LS	%reject (%stop)	8.4 (29.6)	9.9 (32.6)	9.0 (33.3)	88.4 (3.0)	84.2

Simulation Results (2/2)

Scenario	Design	Parameter	Cancer type				avgN
			1	2	3	4	
5		Response rate	0.10	0.30	0.30	0.30	
	Independent	%reject (%stop)	6.2 (68.9)	85.5 (8.4)	86.4 (8.3)	85.4 (8.4)	84.7
	HBM	%reject (%stop)	12.0 (31.6)	87.9 (3.1)	89.9 (2.0)	88.7 (3.0)	91.2
	EXNEX	%reject (%stop)	10.6 (29.9)	75.7 (2.2)	75.4 (1.3)	73.2 (2.8)	91.7
	CHBM-LS	%reject (%stop)	6.6 (32.8)	87.6 (2.4)	88.7 (2.0)	88.7 (2.2)	91.3
6		Response rate	0.10	0.30	0.30	0.50	
	Independent	%reject (%stop)	5.3 (68.5)	83.5 (9.3)	84.2 (9.0)	99.7 (0.3)	85.5
	HBM	%reject (%stop)	15.6 (28.0)	89.3 (1.0)	88.6 (2.5)	99.8 (0.2)	92.2
	EXNEX	%reject (%stop)	10.3 (27.7)	75.6 (1.9)	75.8 (2.5)	98.1 (0.0)	92.1
	CHBM-LS	%reject (%stop)	9.6 (30.3)	88.6 (1.7)	88.1 (2.5)	99.9 (0.0)	91.9
7		Response rate	0.10	0.30	0.50	0.70	
	Independent	%reject (%stop)	7.6 (65.7)	85.2 (7.7)	99.5 (0.5)	100.0 (0.0)	87.1
	HBM	%reject (%stop)	21.5 (23.8)	91.2 (1.0)	100.0 (0.0)	100.0 (0.0)	93.0
	EXNEX	%reject (%stop)	10.8 (27.4)	74.3 (3.6)	98.1 (0.1)	100.0 (0.0)	92.3
	CHBM-LS	%reject (%stop)	9.3 (31.3)	87.5 (1.5)	100.0 (0.0)	100.0 (0.0)	92.1

Conclusion

- We have simplified the CHBM-LS for two classifiers by Takeda et al. (2022) to the most commonly used simple basket trials where baskets are defined only by the cancer types.
- The CHBM-LS approach assumes that baskets might belong to different underlying latent subgroups, and the baskets within a latent subgroup have similar treatment effects.
- The simulation results show that the CHBM-LS approach can outperform the other approaches with higher statistical power and better control of type I error rates under various scenarios with heterogeneous treatment effects across baskets.
- CHBM-LS can be a valuable approach in oncology early phase trial to search for sensitive cancer types which respond to the new treatment better than others while identifying insensitive cancer types.

Primary Reference

- Takeda K, Liu S, Rong A. Constrained hierarchical Bayesian model for latent subgroups in basket trials with two classifiers. Stat Med. 2022;41:298-309.

- Takeda K, Hashimoto A, Liu S, Rong A. A basket trial design based on constrained hierarchical Bayesian model for latent subgroups. Journal of Biopharmaceutical Statistics 2025;35(2):271-282.

- Thall P, Wathen J, Bekele B, Champlin R, Baker L, Benjamin R. Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes. Stat Med. 2003;22:763-780.

- Berry S, Broglio K, Groshen S, Berry D. Bayesian hierarchical modeling of patient subpopulations: efficient designs of phase II oncology clinical trials. Clin Trials. 2013;10:720-734.

- Neuenschwander B, Wandel S, Roychoudhury S, Bailey S. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceutical Statistics 2015;15(2):123–34

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