The Bayesian basket design for genomic variant-driven phase II trials

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\textbf{ARTICLE INFO}

\textbf{Keywords:}
Basket clinical trials
Genomic clinical trials
Actionable mutations

\textbf{ABSTRACT}

Basket clinical trials are a new category of early clinical trials in which a treatment is evaluated in a population of patients with tumors of various histologic types and primary sites selected for containing specific genomic abnormalities. The objective of such studies is generally to discover histologic types in which the treatment is active. Basket trials are early discovery trials whose results should be confirmed in expanded histology specific cohorts. In this report, we develop a design for planning, monitoring, and analyzing basket trials. A website for using the new design is available at https://brbnci.shinyapps.io/BasketTrials/ and the software is available at GitHub in the "Basket Trials" repository of account brbnci.

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1. Introduction

A major focus of oncology drug development involves use of tumor genomics to guide the use of molecularly targeted drugs. When the action of a drug is mediated by a de-regulated molecular target whose role in the pathophysiology of the tumor is well understood, then development of the drug and a companion diagnostic in a histologic type of cancer is relatively straightforward [1]. However, activity of a drug against tumors of a histologic type bearing a genomic alteration does not always imply that the drug will be active against tumors of other histologic types bearing the same alteration. Also, even for a single histologic type, there may be multiple alterations in the same pathway (or gene) of interest and performing a single clinical trial for each alteration may not be feasible. Because phase III clinical trials generally test a single hypothesis about the effectiveness of a drug in a prespecified population of patients, these uncertainties must generally be resolved in earlier phase clinical trials. For this reason, a new type of early phase clinical trial has arisen, the "basket trial" [2].

The basket trial represents an early phase II discovery trial in which patients with defined genomic alterations but multiple histologic types of tumors are selected to discover in which histologic types of tumors the targeted drug is active. If the selection includes a variety of types of genomic alterations or a variety of mutated genes, the basket trial may also be designed to determine which alterations in which genes sensitize the tumor to the drug. To perform a standard phase II trial in each histologic type of tumor or for each genomic alteration is often not feasible. Basket trials are discovery trials rather than hypothesis testing trials; promising results of drug activity for a subset should be confirmed in an expanded phase II where possible. Although basket trials are ongoing in many major cancer centers [3], new statistical designs that address the special features of basket trials have not been previously reported. Here we describe such a design. We have also developed a website https://brbnci.shinyapps.io/BasketTrials/ so that others can consider using this design for their studies.

2. The model

2.1. Prior distribution

Assume that there is one treatment and $K$ strata of patients. If all of the patients have a common genomic alteration in their tumors, then the strata will represent different histologic types of patients. However, in some cases, eligibility may include tumors with different alterations of the same gene or alterations in different genes in the same signaling pathway. In those cases the strata may represent subsets with different alterations or different alterations and histologic types. Let $p_k$ denote the response probability for stratum $k$. We are interested in determining whether the treatment is active or not, ie, $p_k \geq p_{th}$ for each stratum $k$. We take a Bayesian approach with a two point parameter space for each stratum; that is $p_k$ is either $p_{th}$ or $p_0$ as has been used previously in phase two clinical trials [4].
At the start of the clinical trial we need to specify the prior probabilities \( Pr(p = x) \) where \( p \) denotes the vector \((p_1, \ldots, p_K)\) and \( x \) denotes a vector of \( K \) components each of which is either \( p_{\text{hi}} \) or \( p_{\text{lo}} \). This represents the specification of \( 2^K \) quantities, which must sum to 1. The approach we will describe, however, requires the elicitation of only two parameters in addition to \( p_{\text{hi}} \) and \( p_{\text{lo}} \). Our model incorporates two hypotheses. One hypothesis is that the response probabilities in the strata are identical, ie, the activity of the drug does not depend on histologic type of the tumor. In this case either the drug is active in all strata or in none. \( \lambda \) denotes the prior probability that the strata are completely correlated. The other hypothesis is that drug activity in different strata are independent. \( \gamma \) denotes the prior probability that the drug is active in any specific stratum.

### 2.2. Interim analysis

At any point in the trial, we can compute the posterior probabilities \( Pr(p = x) \) for all of the \( 2^K \) \( x \) vectors. The posterior probabilities depend on the numbers of responses and sample sizes in each of the \( K \) strata at that time. Let those numbers be denoted by the vectors \( r \) and \( n \) respectively. That is, for stratum \( k \) there are \( r_k \) responses in \( n_k \) patients. The posterior probability can be written:

\[
Pr(p = x | r, n) = \frac{Pr(p = x) \prod_{k=1}^{K} x_k^r (1 - x_k)^{n_k - r_k}}{\sum_{x} \prod_{k=1}^{K} x_k^r (1 - x_k)^{n_k - r_k}}
\]

where \( Pr(p = x) \) is the prior probability that \( p_k = x_k \) for \( k = 1, \ldots, K \) and each element of the \( x \) vector is either \( p_{\text{hi}} \) or \( p_{\text{lo}} \). The posterior probability for a given \( x \) is the product of a normalizing constant \( c \) times the prior probability, \( \text{times the likelihood of the response data observed up to that point if the response numbers are given by the } r \text{ vector and the sample sizes are given by the } n \text{ vector. The normalizing constant } \frac{1}{c} \text{ can be determined to make the } 2^K \text{ posterior probabilities sum to 1.}

To compute the posterior probability of activity for a specific stratum \( k \) \( Pr(p_k = p_{\text{hi}} | r, n) \), we sum all of the \( 2^{K-1} \) terms \( Pr(p = x) \) \( r \text{ and } n \text{ corresponding to } x_k = p_{\text{hi}} \).

We may compute these posterior probabilities for each stratum at fixed interim analysis times to determine which strata to close. We would close a stratum if \( Pr(p_k = p_{\text{hi}} | r, n) \) is too small. If the posterior probability of activity is very large for a specific stratum, we might also close that stratum as the activity question has been answered for that stratum. Early positive results can be used to prompt initiation of a subsequent expanded phase II study of that particular stratum. Particularly if accrual to that particular stratum was fairly rapid, closing accrual to it after it exceeds a threshold for particular stratum. Posterior probability of success can facilitate use of limited resources which can be utilized for the treatment of patients in less prevalent strata. The design is illustrated in Figs. 1 and 2.

### 3. Results

Table 1 provides some examples of how the posterior probabilities of activity depend on the response experience in all of the strata. The examples are illustrated for a trial with three strata. The prior probabilities were specified using the parameters \( \gamma = 0.33 \) and \( \lambda = 0.5 \) indicating the prior probability that the drug is active in any particular stratum is 0.33 and the probability that the activities are perfectly correlated across strata is 0.5. We used \( p_{\text{hi}} = 0.25 \) and \( p_{\text{lo}} = 0.05 \). The first three columns of the table show the response data at the time of the interim analysis. The final three columns show the posterior probabilities of activity for the three strata. The strata are ordered by prevalence. For the first two rows of the table, the response rates observed for strata 1 and 2 are equal to 0.30, ie, 6/20 and 3/10, respectively. The posterior probabilities of drug activity for the first two strata are large. The strong inference in stratum 2 is based on borrowing information from the activity seen in stratum 1, the prior probability of 0.5 that the strata are perfectly correlated, and that 3/10 is more consistent with a response rate of 25% than one of 5%. In the first row the response rate for stratum 3 is 0/5 and the posterior probability of activity for stratum 3 is surprisingly large at 0.90. Clearly, information is being borrowed from strata 1 and 2. In the second row the response rate for stratum 3 is 0/5 and the posterior probability of activity in stratum 3 drops substantially in spite of the activity seen in strata 1 and 2. The next three rows of the table show cases in which the response rate for the dominant stratum 1 is only 1/20 at the interim analysis but remains 3/10 for stratum 2. In this case, the posterior probability of activity for stratum 2 is large, in spite of the lower response rate.
of the low response rate seen in the dominant stratum 1. So the analysis is not locked in to assuming that activity is correlated across the strata. Whether the posterior probability of activity for stratum 2 is large enough to trigger shutdown of accrual to the stratum depends on the threshold used. The BATTLE I clinical trial promoted treatments if the posterior probability of activity exceeded 0.80. The posterior probability of activity for the most prevalent stratum 1 is low [5]. That probability of activity ranges from 0.04 to 0.18 depending on the number of responses seen in the less prevalent stratum 3. Accrual to stratum 1 might be curtailed following this interim analysis depending on what threshold for closing down a stratum is used.

### Table 1
Illustration of how strata-specific posterior probability of activity depends on response rates in all strata.

<table>
<thead>
<tr>
<th>Stratum 1</th>
<th>Stratum 2</th>
<th>Stratum 3</th>
<th>Posterior probability of activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/20</td>
<td>3/10</td>
<td>1/5</td>
<td>0.99 0.98 0.90</td>
</tr>
<tr>
<td>6/20</td>
<td>3/10</td>
<td>0/5</td>
<td>0.99 0.96 0.58</td>
</tr>
<tr>
<td>1/20</td>
<td>3/10</td>
<td>0/5</td>
<td>0.04 0.80 0.13</td>
</tr>
<tr>
<td>1/20</td>
<td>3/10</td>
<td>1/5</td>
<td>0.11 0.86 0.50</td>
</tr>
<tr>
<td>1/20</td>
<td>3/10</td>
<td>2/5</td>
<td>0.18 0.91 0.86</td>
</tr>
</tbody>
</table>

### 4. Expected number of discoveries

Table 2 shows the results of computer simulations with three strata as a function of the number of strata in which the drug was active. In these simulations, interim analyses to update the posterior probabilities of activity for each stratum are conducted after every group of five evaluable total patients. We assumed that the strata were equally prevalent and that accrual to a stratum was closed if the posterior probability of activity was either less than 0.2 or greater than 0.8. Otherwise, accrual continued for that stratum. The trial was also terminated after 50 total patients if previously all of the strata had not already been closed. Results of 1,000 simulations with $p_{h0} = 0.05$, $p_{h1} = 0.25$, $\lambda = 0.33$ and $\gamma = 0.5$ are shown in Table 2. With zero or three active strata the homogeneity hypothesis is true and activity decisions are achieved early. With one or two active strata, the homogeneity hypothesis is false and there is less sharing of information among strata.

Table 3 shows results as a function of the number of strata using the same parameters as in Table 2 and thresholds less than 0.2 or greater than 0.8 for closing accrual to a stratum. Here we computed the average error rates per positive and negative strata when the activity status of the drug in each stratum is averaged over the prior distribution. The average false positive rate is the number of false positives divided by the expected number of strata in which the drug was inactive; similarly for false negatives.

Fig. 2. Graphical representation of the specification of initial parameters and the interim analyses.
were 1,000 simulated replications for K = 3 and 5, but only 100 for K = 10 because the computations become more time consuming. For K = 3 or 5 we used nmax = 50 but for K = 10 we used nmax = 70. The average total sample size till all strata were closed increased from 25.4 for three strata, to 35.8 for five strata and 54.3 for 10 strata. An optimum two-stage design [6] for distinguishing a rate of 0.20 would have a response probability of 0.05 from 0.25 with type I and type II error rates of 0.20 would have a first stage of 6 patients and a total sample size of 16 patients. Using this type of design separately for each stratum could require substantially more patients than the Bayesian designs used in Table 3 although their operating characteristics are quite different. The simulation we performed can be conducted in planning a basket trial using the relative prevalence across the strata expected for the trial instead of assuming the strata are equally prevalent as for the simulations reported here. The website we provide permits unequal prevalence to be specified. The parameters \( p_{lo}, p_{hi}, \lambda \) and \( \gamma \) and the frequency of interim analyses can be tailored to the specific trial.

5. Examples

Table 4 shows response rates for 10 strata of cancer types in a basket trial of the BRAF inhibitor vemurafenib reported by Hyman et al [7]. For our model, we used the parameters \( p_{lo} = 0.15, p_{hi} = 0.35 \) indicated by the authors as of interest to them with \( \lambda = 0.33 \) and \( \gamma = 0.5 \). With these parameters we computed that the posterior probability of homogeneity of treatment effects among the strata was only 0.008. Because the posterior probability of homogeneity is so small with these 10 strata, there is little borrowing of information among strata. The posterior probabilities of activity of the drug in each of the 10 strata are shown in the table. The drug is very likely to be active for patients with BRAF V600E mutations in NSCLC, Erdheim-Chester disease or Langerhans’ cell histiocytosis, and PXA with posterior probabilities of activity at the 35% level of 0.95, 0.90 and 0.82, respectively. The drug is clearly not active in the colorectal cancer strata or in glioma with posterior probabilities of activity of 0.03, 0.01, and 0.05. Activity in cholangio cancer, anaplastic thyroid carcinoma, multiple myeloma and the “other” category is less certain with posterior probabilities of activity of 0.15, 0.41, 0.11 and 0.24, respectively.

As a second example, we consider the design of a basket trial of a PARP inhibitor for solid tumor malignancy patients with relapsed/refractory advanced stage disease for whom no other treatment options are available. Patients with genomic alterations in one or more DNA repair genes are eligible and tumors are categorized based on results from a DNA repair panel as complex 1 versus complex 2 vs. all other repair-related genes. An overall response rate assessed at 8 weeks of at least 0.20 would be considered promising for this advanced group of patients and no activity was considered a response rate less than 0.05. The cancer center considering this study expects to accrue approximately 3 patients per month. It was considered desirable to limit the total sample size to 50 patients.

An interim analysis was planned after evaluation of the first 20 subjects. At interim analysis, the posterior probability of activity for each stratum is computed using the pre-specified prior probability parameters. Accrual to a stratum is terminated if the posterior probability of activity becomes greater than 0.80 or less than 0.20.

Sample size planning for this Bayesian basket trial was guided through simulations using the interactive web based program. Table 5 shows the expected values of the sample size, true positive rate, false negative rate, false positive rate and true negative rate where the number of active strata is averaged with regard to the prior distribution. Since we could not determine in advance the prevalence of each of the complex subgroup strata, we evaluated this design in several different settings but held fixed the values of \( \lambda = 0.50, \gamma = 0.33 \). We constrained the maximum sample size to 50 evaluable patients.

Table 5 indicates that average power for identifying truly positive effects for this drug seem adequate. The average probability of false positive rates fall somewhat above 0.20 when a stratum has prevalence < 0.30; however, these rates are still close to 0.20 and our focus is to identify promising regimens to evaluate further in an expanded cohort in subsequent studies. An optimal two-stage design in each stratum would require 9–16 patients per stratum or 27–48 patients total. When the strata are homogeneous with regard to drug activity, the expected time to complete the optimal two-stage designs will be longer. The comparison among designs becomes more favorable to the Bayesian basket design as the number of strata increases.

For this study, posterior probabilities of activity could be computed as a function of histologic subset although the study would not be powered for any formal evaluation within a histologic type. Still, these would be used as valuable preliminary data for hypothesis generation and planning future trials with this regimen and/or this treatment approach. Posterior probability of activity provides a convenient summary of data that reflects both observed response rate and sample size. Even in the event of insufficient clinical activity, these findings along with correlative measures of biomarker activity and targets would be useful in designing future studies.

6. Discussion

We have introduced a statistical model for planning, monitoring and analyzing early phase basket discovery trials involving one drug hypothesized to target tumors with specific genomic or molecular characteristics. These types of discovery trials are useful in the setting where eligibility is “histology agnostic” and focused on those with the specific molecular target instead of the standard paradigm of focusing on a given histology. In this setting, the targeted patient population can consist of patients having multiple histologic types and/or multiple genomic variants thought to make

![Table 2](image)

<table>
<thead>
<tr>
<th>No. of active strata</th>
<th>Expected no. of true discoveries</th>
<th>Expected no. of false discoveries</th>
<th>Average total sample size</th>
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<tr>
<td>0</td>
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<td>23.8</td>
</tr>
<tr>
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<td>.6</td>
<td>.14</td>
<td>27.3</td>
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<td>22.4</td>
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</table>

Interim analysis was performed after every five patients. A stratum was closed when posterior probability of activity was < 0.2 or > 0.8.

![Table 3](image)

<table>
<thead>
<tr>
<th>No. of strata K</th>
<th>True positive rate</th>
<th>False negative rate</th>
<th>False positive rate</th>
<th>True negative rate</th>
<th>Average total sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>.85</td>
<td>.15</td>
<td>.10</td>
<td>.90</td>
<td>25.4</td>
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<tr>
<td>5</td>
<td>.84</td>
<td>.16</td>
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<tr>
<td>10</td>
<td>.83</td>
<td>.17</td>
<td>.19</td>
<td>.81</td>
<td>54.3</td>
</tr>
</tbody>
</table>

A stratum was closed when posterior probability of activity was < 0.2 or > 0.8.
them candidates for the drug. Such trials are of increasing importance in this era of ‘omics’ technologies and personalized medicine [3] but when the number of patient strata increases, the traditional phase II trial designs become less attractive. Especially in the histology agnostic setting, it is not necessarily valid to assume that the activity of the drug will be the same in all strata. In the standard phase II trial setting, assessing different patient groups requires separate adequately powered hypothesis testing in each stratum based on the assumption that there is no relationship among the strata; the corresponding sample size requirements can be logistically challenging to achieve and the results may demonstrate that the response rates for different strata were in fact concordant.

The model we developed accommodates a-priori uncertainty about how correlated the stratum-specific drug activities are and borrows information across strata when the data indicates it is warranted. The model is relatively easy to apply. The investigator must prospectively specify the strata and the usual levels of response probability corresponding to clinical or biologic activity $\gamma_h$ and inactivity $\gamma_o$. The investigator also specifies two additional parameters, the prior probability $\lambda$ that the activity levels are completely correlated across the strata, and the prior probability $\psi$ that for any particular stratum the drug is active. A larger $\gamma$ results in a larger posterior probability of activity for the same data although the effect of $\gamma$ decreases with increasing sample size. Studies of very promising treatments corresponding to a large $\gamma$ can sometimes provide large posterior probabilities of activity with smaller sample sizes than would be required by frequentist planning with the standard type I and type II error criteria. This relates to the so called “type III error”, the error we make by failing to discover an effective treatment because we do not perform the relevant clinical trial.

The monitoring of the trial using the model introduced here amounts to just computing the posterior probability of activity for each stratum. Although Bayesian posterior probabilities do not require pre-specification of interim analysis times, for purposes of data quality it is generally best to have pre-specified interim analyses either based on calendar time or total number of patients evaluable. At each interim analysis, the posterior probabilities are computed and decisions are made about which strata to continue and which not to continue. These decision rules need not be pre-specified for the validity of Bayesian posterior probabilities, but it will generally be useful to establish such rules prospectively so that issues of trial management and interpretation can be considered from the outset. In this process, it will be useful to conduct clinical trial simulations as described above and giving the operating characteristics shown in Table 3. Such simulations can be performed using the web-based interactive program at https://brbnci.shinyapps.io/BasketTrials/. These operating characteristics do require specification of the interim analysis interval and the decision rule for closing accrual to a stratum based on interim results. Control of the average true and false discovery rates should determine the maximum sample size, decision rules for declaring activity or inactivity, and the monitoring plan. This design does not provide strong control of the type I and type II error rates for each stratum under all possible configurations of drug activity among the strata [4]. If such control is deemed necessary, a standard phase II design for each stratum separately should be used [6]. We believe that such strong control is not necessary for many basket discovery trials, however, and that the expected number of true and false discoveries with regard to the prior distribution is an appropriate criterion for a screening trial when separate phase II studies are not feasible or where there is a substantial a-priori probability that the strata are homogeneous with regard to drug activity.

Previously developed statistical methods for phase II trials with multiple strata could be used for the design and analysis of basket trials. Leblanc et al [8] proposed a method which is similar to conducting a traditional phase II trial within each stratum. It differs however, in that a futility analysis of the pooled strata is performed and stratum specific futility analyses are conducted more frequently than with the optimal two-stage clinical trials [6].

Thall et al [9] developed a hierarchical Bayesian design for a phase II design with strata consisting of subtypes of sarcoma. Freidlin et al [4] evaluated these designs in simulations, however, and found that the hierarchical prior resulted in minimal sharing

<table>
<thead>
<tr>
<th>Complex 1</th>
<th>Complex 2</th>
<th>Others</th>
<th>Expected sample size</th>
<th>True positive rate</th>
<th>False negative rate</th>
<th>False positive rate</th>
<th>True negative rate</th>
<th>Probability of no false positives when all strata are negative</th>
</tr>
</thead>
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<tr>
<td>0.33</td>
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<td>0.16</td>
<td>0.17</td>
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<td>0.81</td>
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<td>0.45</td>
<td>0.45</td>
<td>0.10</td>
<td>34</td>
<td>0.86</td>
<td>0.14</td>
<td>0.24</td>
<td>0.76</td>
<td>0.82</td>
</tr>
</tbody>
</table>
of information across strata. Our priors clearly do provide for sharing, the amount determined by the parameter $\lambda$ and by the data.

The design we have introduced is flexible, for example modifications can be imposed where we set minimum sample sizes for the strata to ensure sufficient clinical experience before classifying a given stratum as having insufficient probability of drug activity. The design does have limitations, however. It is limited to non-randomized basket trials with a binary endpoint.

In non-randomized clinical trials it is difficult to properly interpret time to event outcomes because of the variable nature of the pace of disease and the dependence on ascertainment. Some phase II trials use disease control rates at a landmark time, eg, 8 weeks, as a binary endpoint. The Bayesian priors utilized here could be generalized to priors on hazard ratios for use with randomized basket trials. Such trials, however, would require substantial increases in sample size to support within stratum inference and this would not be consistent with the screening objective.

The method described here requires the specification of four design parameters. Two of the parameters, $p_{lo}$ and $p_{hi}$ are analogous to the parameters specified in standard phase II trial designs. The parameter $\lambda$ indicates the prior probability that the true response probabilities are concordant among strata. A value of 0.5 means there is no preliminary evidence favoring the concordance of activity hypothesis over the independence hypothesis. We recommend that the value of $\lambda$ generally be set somewhat less than 0.5, however, to avoid having excessive sharing of information among strata early in the clinical trial when sample sizes are small. In many cases the test drug will have been previously active in another histologic type of tumor and the basket trial will be screening for off-label use as in Hyman et al [7]. In such cases, we recommend setting the value of $\gamma$ to 0.5.

The approach described here can be generalized to settings where we do not expect there to be complete symmetry among the strata. For example, there may be four histology groups and two types of genomic alterations for each histology group, eg, point mutation or amplification. There are eight strata and the $\gamma$ values may be different for the point mutation strata and the amplification strata. Also, the prior probability that the two mutation groups within a histology group have the same activity level may be greater than the prior probability that the histology groups have the same activity level for a given mutation type. The given model is easily modified to accommodate such modifications.

Conflicts of interest

None.

References