Designs for Basket Clinical Trials and the Exploratory/Confirmatory Paradigm

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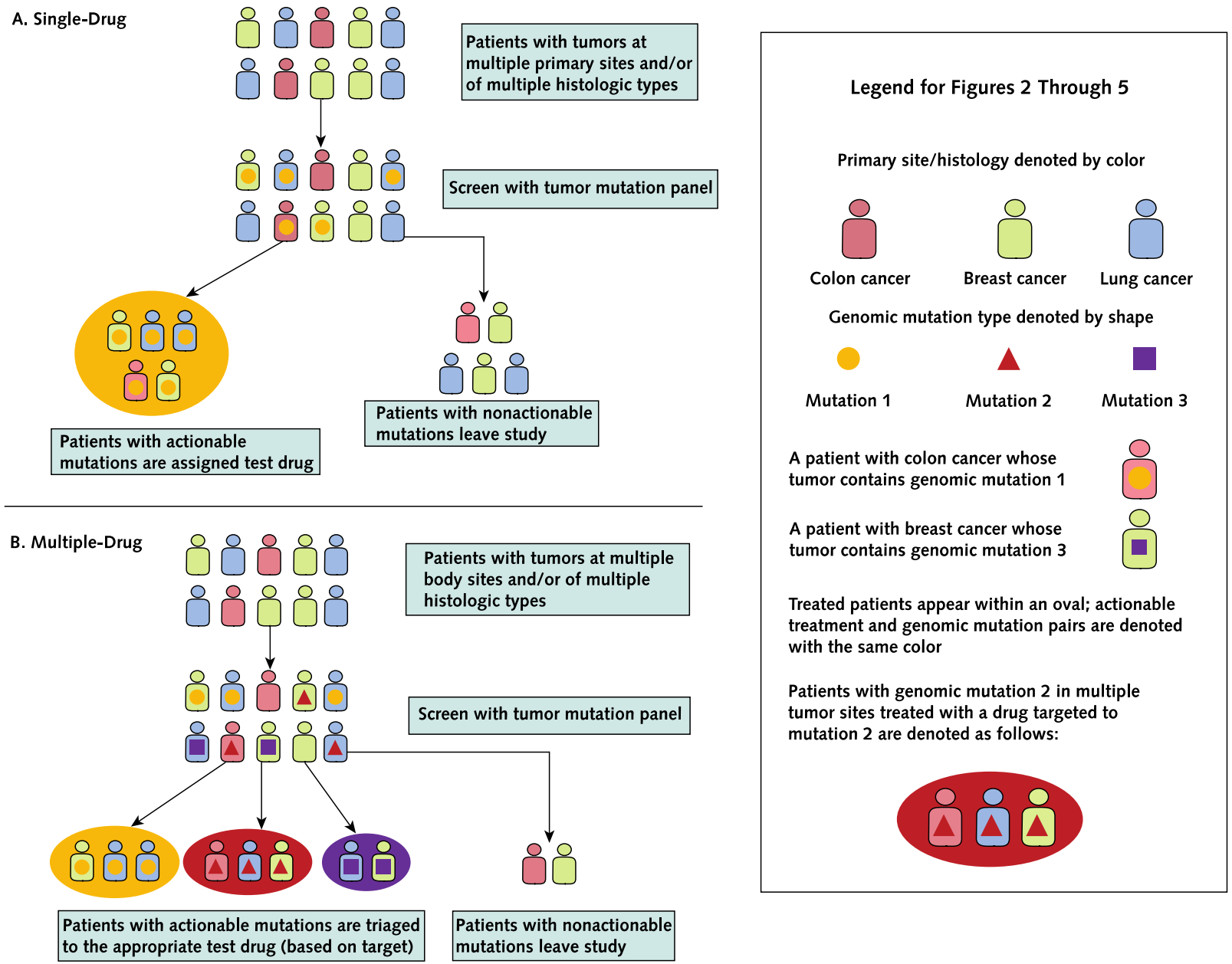
What is a basket design?

- Phase II
- Multiple histologic types of cancer
- Eligibility based on common genomic alteration
- One treatment regimen
- No control group

Variations

- Basket designs for different drugs embedded in common tumor characterization infrastructure
  - Each drug has a different genomic alteration for patient selection
  - Patient triaged to drug based on genomic alteration
- In addition to histologic differences in patients, there may be variants of the genomic alteration used for eligibility
- Randomization to control group

Figure 2. Nonrandomized basket designs.



Objective

- Identify the histologic types for which the drug is active in patients with the genomic alteration

For drugs targeted to altered or amplified target

- Basket designs make more sense than the traditional histologically specific phase II designs for exploratory trials

Endpoint

- Tumor response
- Stable disease > 6 months
- Durable tumor response

Current basket trials are sized

- As single phase II trial ignoring the multiple histological types
- As a separate phase II trial for each histological type
- Newer designs

New Designs for Basket Trials

- Leblanc et al. (2009)
  - Separate Simon 2-stage designs for each histology.
  - Interim futility analysis for pooled population.
- Cunannan (2017)
  - Two-stage design. Interim analysis uses test of interaction to decide whether to pool histologies or to have adequate separate accrual for each histology
- Simon et al. (2016)
  - Bayesian basket design
  - Prior and posterior probabilities of H_0 that all histologies are similar in sensitivity vs H_1 that histologies are independent in their sensitivities.
  - Continual re-assessment of activity of each histology weighted by posterior probabilities

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

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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.

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 separate 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, $p_k \geq p_{hi}$ 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_{hi} or p_{lo} as has been used previously in phase two clinical trials [4].

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Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Genomic Alteration–Driven Clinical Trial Designs in Oncology

Richard Simon, DSc

The established molecular heterogeneity of human cancers necessitates the development of new paradigms to serve as a reliable basis for precision medicine. The assumptions underlying some of the conventional approaches to clinical trial design and analysis are no longer appropriate because of the molecular heterogeneity of tumors of a given primary site. This article reviews some clinical trial designs that have been actively applied in the codevelopment of therapeutics and predictive biomarkers to inform their use in oncology. These include the enrichment design, the basket design, and the umbrella design. Oncology leads most other therapeutic areas in development of personalized or precision medicine. Personalized or precision medicine is practiced daily in oncology on the basis of tumor genomics and may evolve in other therapeutic areas as it has in oncology, rather than according to inherited polymorphisms as so often imagined. Consequently, some of the clinical trial designs described here may serve as a possible blueprint for therapeutic development in fields other than oncology.

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For author affiliation, see end of text.

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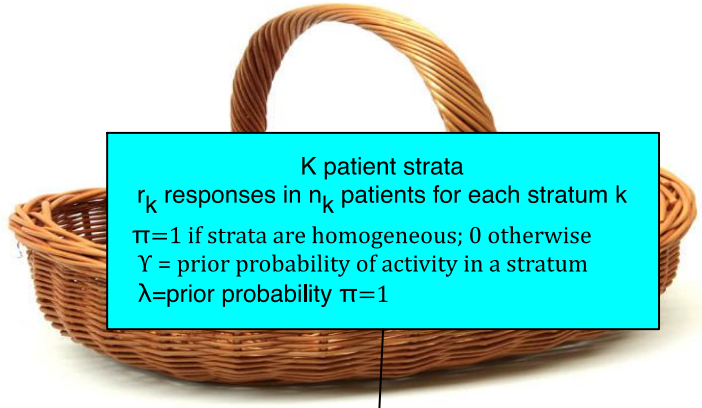
- K strata
- p_k = response probability in stratum k (k=1,…,K)
- $p_k \in \{p_{lo}, p_{hi}\}$
- H_0: $p_1=p_2=\ldots=p_K$ & all equal p_{hi} with probability γ
- H_1: $p_1=p_2=\ldots=p_K$ independent selections from $\{p_{lo}, p_{hi}\}$ with Bernoulli parameter γ



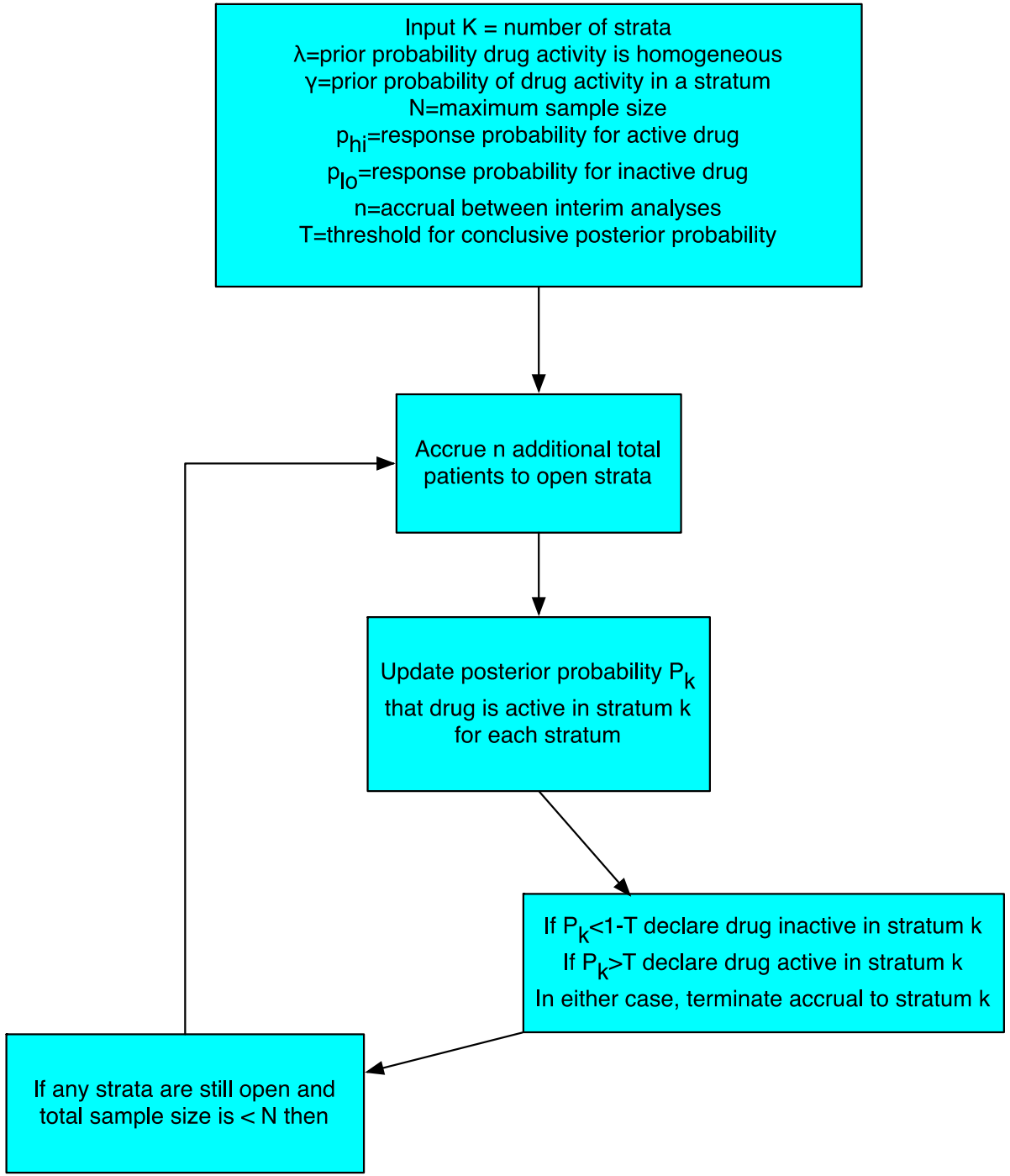
K patient strata
r_k responses in n_k patients for each stratum k
$\pi=1$ if strata are homogeneous; 0 otherwise
Υ = prior probability of activity in a stratum
λ=prior probability $\pi=1$

Compute ν = posterior probability $\pi=1$

Compute P_0=probability drug is active in all strata assuming strata are homogeneous

Compute for each k=1,2,...K
$P_{k,ind}$ = probability drug is active in stratum k assuming strata are independent

Posterior probability drug is active in stratum k equals
$P_k = \nu P_0 + (1-\nu) P_{k,ind}$


Input K = number of strata
λ=prior probability drug activity is homogeneous
γ=prior probability of drug activity in a stratum
N=maximum sample size
p_{hi}=response probability for active drug
p_{lo}=response probability for inactive drug
n=accrual between interim analyses
T=threshold for conclusive posterior probability
Accrue n additional total patients to open strata
Update posterior probability P_k that drug is active in stratum k for each stratum
If P_k<1-T declare drug inactive in stratum k
If P_k>T declare drug active in stratum k
In either case, terminate accrual to stratum k
If any strata are still open and total sample size is < N then

Shiny Baysian Basket Design App

- https://brpnci.shinyapps.io/main/

Observed response rate			Posterior prob of homogeneity	Posterior prob of activity		
Stratum 1	Stratum 2	Stratum 3		Stratum 1	Stratum 2	Stratum 3
6/20	3/10	1/5	.67	.99	.97	.83
6/20	3/10	0/5	.35	.99	.95	.44
1/20	3/10	0/5	.08	.04	.86	.13
1/20	3/10	1/5	.09	.07	.89	.49
1/20	3/10	2/5	.10	.11	.92	.86

λ=.33, γ=.33, p_{lo}=.05, p_{hi}=.25

Table 2
Bayesian basket design with three strata.

No. of active strata	Expected no. of true discoveries	Expected no. of false discoveries	Average total sample size
0	0	.12	23.8
1	.61	.14	27.3
2	1.42	.15	27.5
3	2.61	0	22.4

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

λ=.33, γ=.5,
p_{lo}=.05, p_{hi}=.25

Table 3
Bayesian basket design with interim analysis after every 5 patients.

No. of strata K	True positive rate	False negative rate	False positive rate	True negative rate	Average total sample size
3	.85	.15	.10	.90	25.4
5	.84	.16	.14	.86	35.8
10	.83	.17	.19	.81	54.3

A stratum was closed when posterior probability of activity was < 0.2 or > 0.8.

λ=.5, γ=.33,
p_{lo}=.05, p_{hi}=.25

Basket clinical trial of vemurafinib in non-melanoma tumors with V600 BRAF mutations

	NSCLC	Colorectal	Colorectal With Cetuximab	Cholangio Ca	ECD/LCH	Anaplastic thyroid	Glioma	MM	PXA	Other
Response rate	8/19	0/10	1/26	1/8	6/14	2/7	0/8	0/5	3/4	3/14
Posterior prob of activity	.97	.063	.003	.26	.95	.58	.10	.21	.90	.40

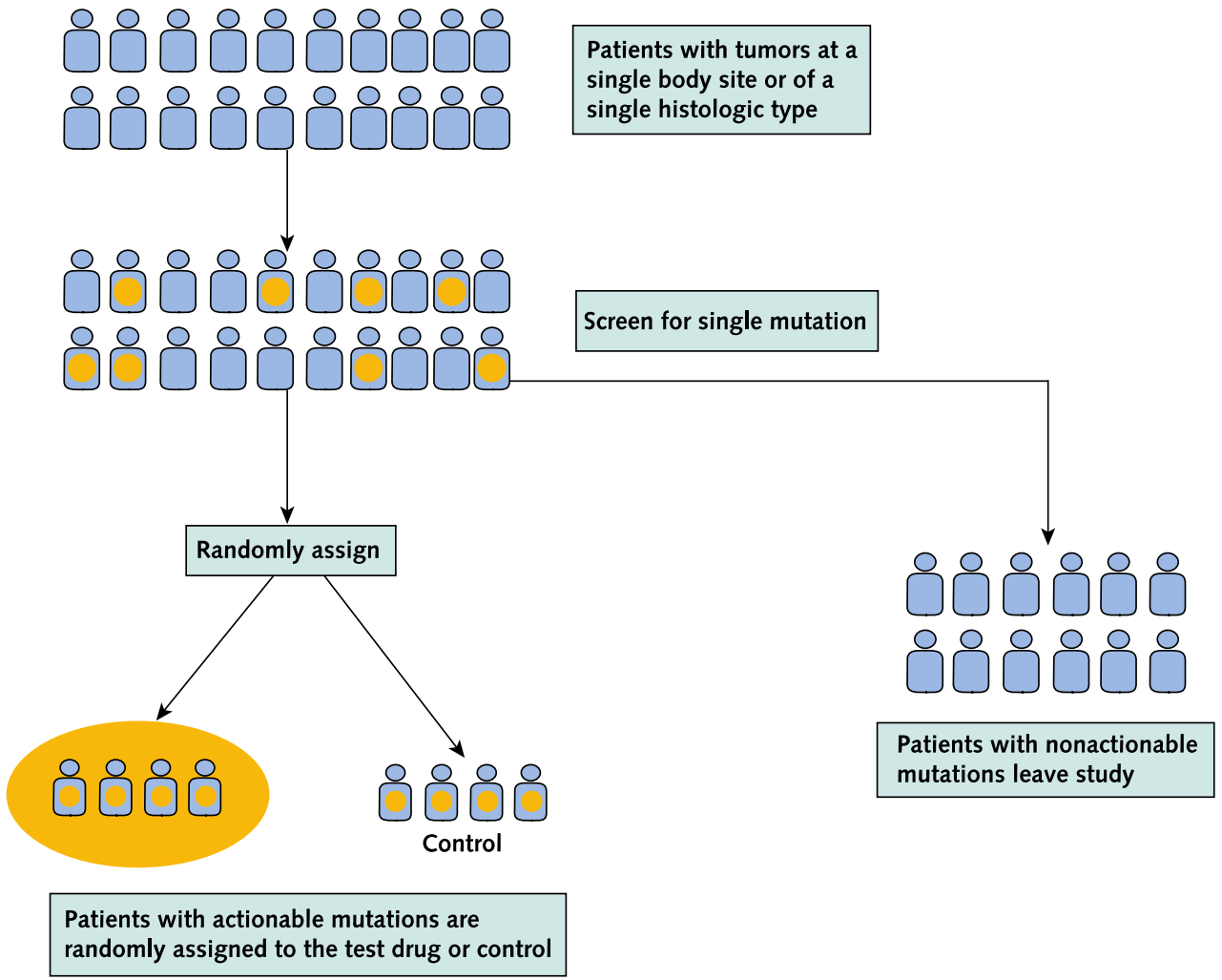
ECD=Erdheim-Chester disease; LCH=Langerhans cell histiocytosis
PXA=Anaplastic pleomorphic xanoastrocytoma

λ=.33, γ=.5, p_{lo}=.15, p_{hi}=.35

Options for Exploratory → Confirmatory Transition

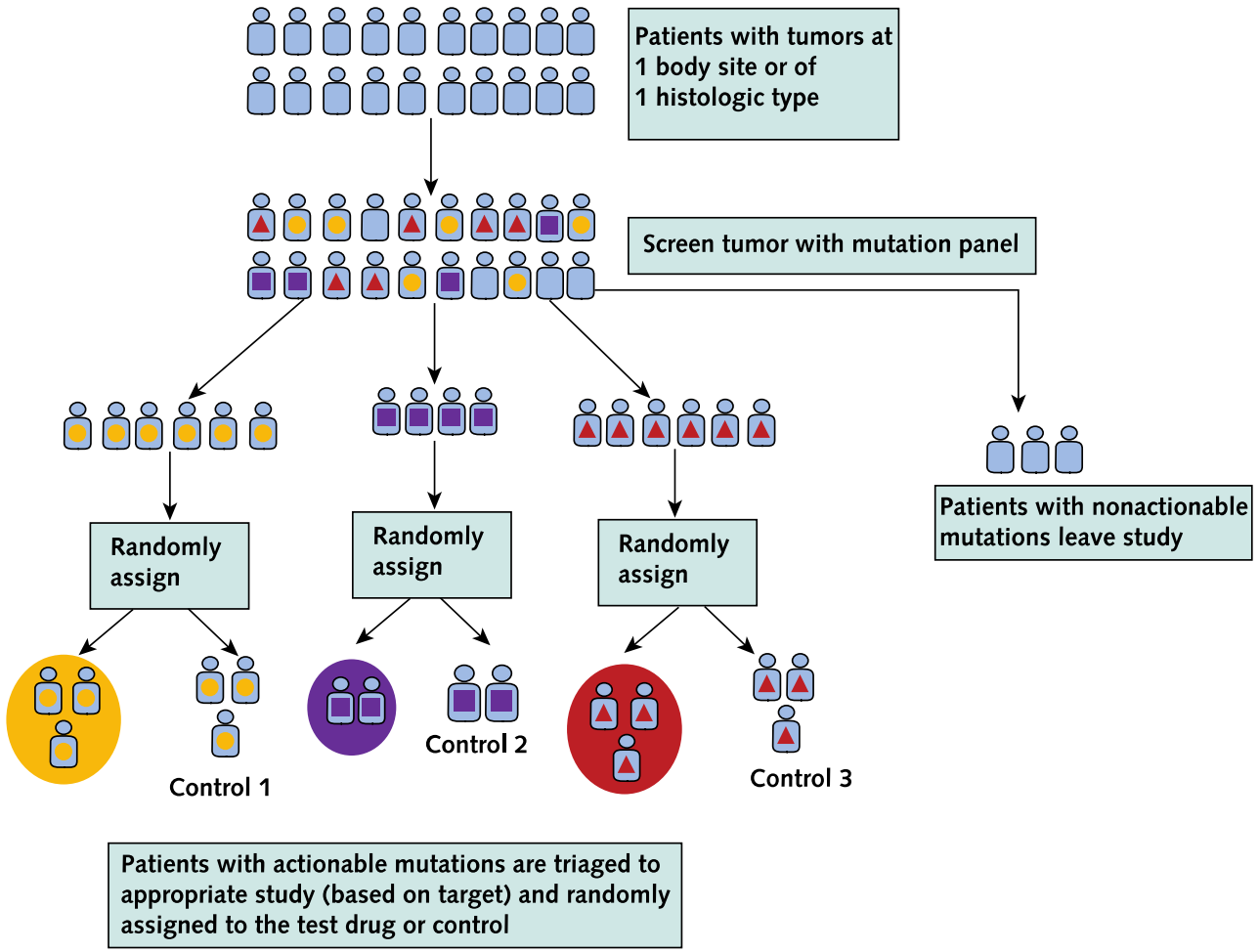
1. For active histologies with high prevalence, conduct separate enrichment trials

Figure 4. Phase 3 enrichment design.



Color denotes primary site/histologic type of tumor, and shape represents genomic mutation type. See **Figure 2** for legend.

Figure 5. Phase 3 umbrella design.



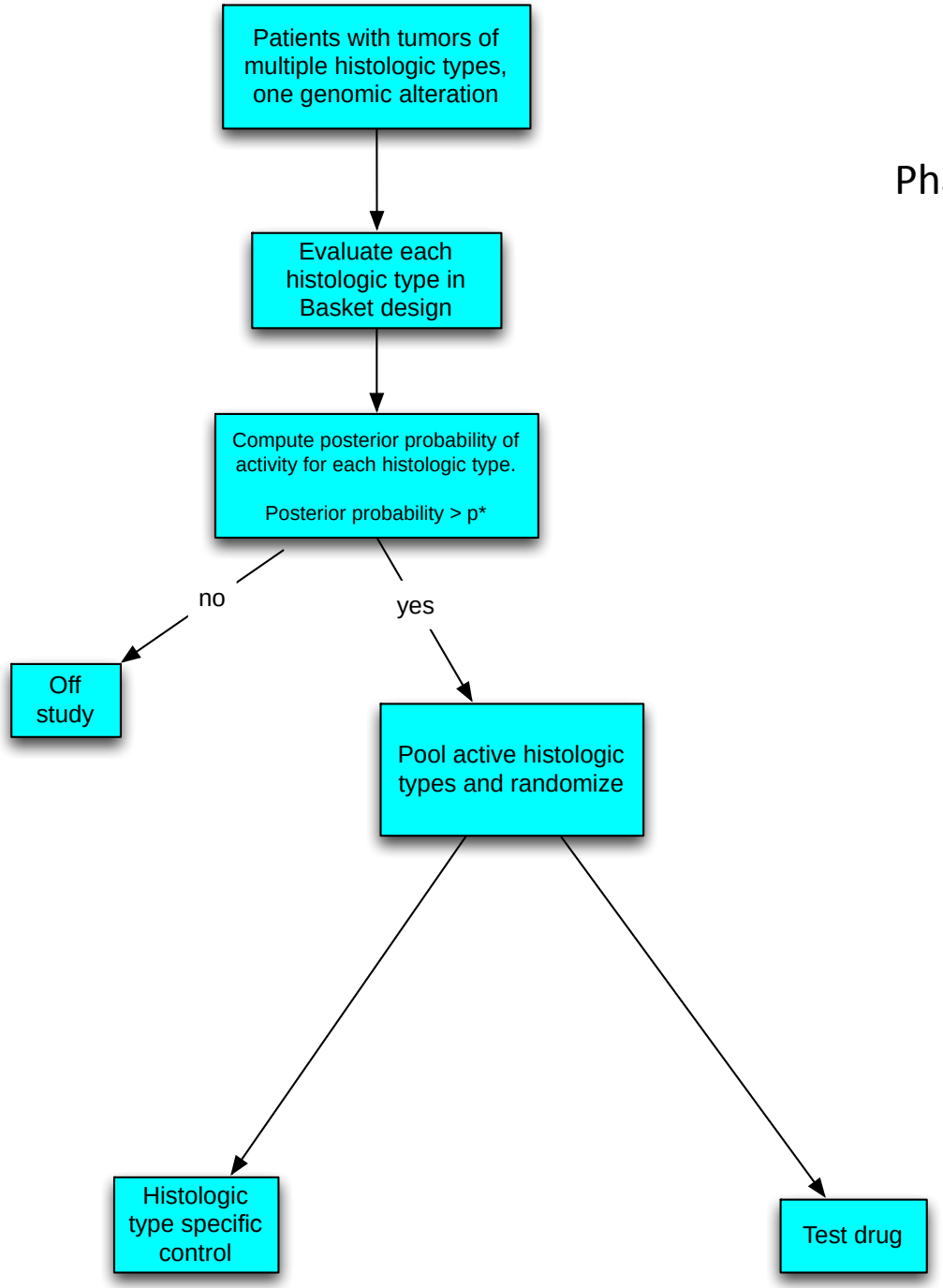
Color denotes primary site/histologic type of tumor, and shape represents genomic mutation type. See **Figure 2** for legend.

Options for Exploratory → Confirmatory Transition

2. Pool active histologies with low prevalence and conduct single multiple histology phase III trial

- Possibly histology specific control arms or physicians' choice control arm
- Trial sized and analyzed in histology pooled manner

Phase II/III Basket Design



Options for Exploratory → Confirmatory Transition

3. If drug sensitivity is homogeneous across histologies and drug is approved for some histology, consider extending indication to all histologies for which no effective treatment exists

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Articles

The role of nonrandomized trials in the evaluation of oncology drugs

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Abstract

Although randomized trials provide the most reliable evidence of a drug's safety and efficacy, there are situations where randomized trials are not possible or ethical. In this article we discuss when and how single-arm trials can be used to support full approval of oncology drugs. These include situations in which an unprecedented effect on tumor response is observed in a setting of high unmet medical need, clinical trial patients have been well characterized, enabling a target population to be clearly defined, experience exists in a sufficient number of patients to allow adequate assessment of the risk:benefit relationship, and a proper historical context can be provided for analysis. We also discuss how response rates might be considered predictive of long-term outcomes or clinically meaningful in and of themselves in certain contexts.