Published in final edited form as:

Cancer J. 2019 ; 25(4): 254–263. doi:10.1097/PPO.0000000000000384.

Biostatistical and Logistical Considerations in the Development of Basket and Umbrella Clinical Trials

Laura M. Yee, PhD*, Lisa M. McShane, PhD*, Boris Freidlin, PhD*, Margaret M. Mooney, MD*, Edward L. Korn, PhD*

*Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD.

Abstract

Oncology clinical trials are undergoing transformation to evaluate targeted therapies addressing a wider variety of biologically defined cancer subgroups. Multi-arm basket and umbrella trials conducted under master protocols have become more prominent mechanisms for the clinical evaluation of promising new biologically driven anti-cancer therapies that are integral to precision oncology medicine. These new trial designs permit efficient clinical evaluation of multiple therapies in a variety of histologically and biologically defined cancers. These complex trials require extensive planning and attention to many factors, including choice of biomarker assay platform, mechanism for processing clinico-pathologic and biomarker data to assign patients to substudies, and statistical design, monitoring, and analysis of substudies. Trial teams have expanded to include expertise in the interface between biology, clinical oncology, bioinformatics, and statistics. Strategies for the design, conduct, and analysis of these complex trials will continue to evolve to meet new challenges and opportunities in precision oncology medicine.

Keywords

basket trials; umbrella trials; master protocols; biostatistics; study design; study implementation; biomarkers; interim monitoring

INTRODUCTION

Development of a multitude of targeted anti-cancer agents has fueled progress in precision oncology medicine and dramatically influenced the design, conduct, and analysis of oncology clinical trials. Precision medicine relies on interrogation of host (patient) and disease (tumor) characteristics to best match them to the target or mechanism of action of a therapy. Oncology clinical trials have evolved historically from empirical assessments to biologically driven precision medicine trials. Relevant tumor biology is typically characterized by measurement of biomarkers, which represent molecular alterations or variants associated with genes at the level of DNA (e.g., alteration), RNA (e.g., aberrant

Correspondence: Laura M. Yee, PhD, Division of Cancer Treatment and Diagnosis, National Cancer Institute. Address: 9609 Medical Center Dr. Rockville, MD 20850. Telephone: 240-276-5654. laura.yee@nih.gov.

Conflicts of Interest and Source of Funding: No conflicts of interest are declared. The views presented in this article are those of the authors and should not be viewed as official opinions or positions of the National Cancer Institute, National Institutes of Health, or U.S. Department of Health and Human Services.

copy number, splicing or fusions), or protein (e.g., under- or over-expression). Altered expression of a gene may additionally reflect actions of other genes in the same biological pathway or other mechanisms such as epigenetic processes. Germline DNA variants such as those in genes that control metabolism of drugs can also be useful in precision medicine, but the focus of this article is tumor biomarkers - specifically those that reflect molecular alterations in the tumor that could serve as potential targets for anti-cancer therapy. For simplicity of discussion, the terms (molecular) alteration and targeted therapy will be used throughout to denote aberrant biological characteristics (biomarkers) of tumors and anti-cancer therapies directed against them.

Clinical evaluation of targeted therapies requires trials that simultaneously evaluate efficacy of the therapy and ability of a biomarker assay to identify patients who are most likely to benefit from it. This presents numerous challenges in designing, conducting, and analyzing clinical trials of targeted therapies. Trial logistics must accommodate obtaining tumor specimens and performing assays to characterize each patient's tumor for presence or absence of the target molecular alterations. Depending on feasibility and comparability of available methods to assess the biomarkers, assays may be performed at local clinical sites or in a central laboratory; they may be performed outside of the trial prior to registration, or following, depending on the trial design. The proportion of patients with cancer whose tumor exhibits the target molecular alteration may be small, the prevalence of the alteration may vary by tumor histology, and varying biological background or concomitant or prior therapies for different tumor histologies may have an impact on a targeted therapy's efficacy. These factors must be considered together to assess feasibility and select an appropriate design and analysis strategy for the trial.

Basket and umbrella trials, and hybrids, have emerged as feasible and efficient approaches for the evaluation of multiple targeted anti-cancer agents and/or for the evaluation of one or more agents in potentially multiple tumor histologies. In the sections that follow, these concepts will be defined and discussed in the context of illustrative examples of completed and ongoing clinical trials. Due to their underlying multi-arm or multi-subgroup structures, basket and umbrella trials are typically managed in the context of master protocols¹, for which logistical and administrative issues are also discussed in this paper. Discussion focuses on trial feasibility, strategies for obtaining biomarker assay results, appropriate statistical design, monitoring, and analysis plans, and logistical and administrative considerations.

BASKET TRIALS

A basket trial is a trial for patients whose tumors have a specific molecular alteration and who are treated with an agent specifically targeted for that alteration. Basket trials are generally histology agnostic, i.e., tumors of varying histologies are grouped together in a "basket" defined by a shared molecular alteration (Figure 1A). An example of a basket trial was the trial of larotrectinib, a TRK inhibitor, which enrolled patients with tropomyosin receptor kinase (TRK) fusion-positive cancers, regardless of histology². More typical is a basket trial with multiple baskets; a multi-basket trial enrolls multiple subgroups of patients, each corresponding to a basket defined by different tumor alterations, and treated with a

matched targeted agent. Such alterations for which there are matched targeted agents are often referred to as “actionable” alterations. To identify patients whose tumors have one of the specified alterations, the trial design may include a screening protocol, which serves as a front door where patients have their tumor alterations identified and are then assigned to the appropriate molecular basket; patients without a protocol-defined actionable alteration go off the study (Figure 1B). Alternatively, the trial design may require patients to have tumor assay results documenting an actionable alteration, already in-hand, to be eligible for the trial (Figure 1C). The NCI-MATCH trial³ initially incorporated a screening protocol but then switched to requiring patients to be pre-screened (from a set of prequalified laboratories) when it became more common for patients to have their tumors molecularly assessed in the community. A multi-basket trial can include a varying number of baskets over time, as baskets are closed when their accrual is complete and new ones are opened when new target-agent opportunities arise. Other notable basket trials include the BRAF-vemurafenib trial⁴, CREATE⁵, TAPUR⁶, DART⁷, NCI-Pediatric-MATCH⁸, NCI-MPACT⁹, Genentech MyPathway¹⁰, and Novartis Signature¹¹.

It is also possible to have a randomized basket trial, where patients within each basket are randomized to a control or experimental treatment^{11,12}. For example, in the SHIVA trial¹² patients with any kind of metastatic solid tumor were eligible if they had a targetable molecular alteration from a specified set with available matched therapies. Eligible patients were then randomized to an experimental treatment (determined by their molecular alteration) or to physician choice of standard treatment.

When screening is not available or commonly performed in the community, the great advantage of a multi-basket trial over a single basket trial is that a much higher proportion of patients can be assigned an experimental treatment. This is especially advantageous when the prevalences of the individual alterations are relatively low. For example, NCI-MATCH has 35 baskets, with the number still increasing. During the period when patients were still being centrally screened as part of the trial, more than 35% of the patients screened were found to have an actionable alteration in their tumor, with the prevalences of the alterations specific to individual arms ranging from 0.03% to 3.47%¹³. (However, not all of these patients enrolled on a subtrial and received treatment, for reasons including application of additional clinical and molecular exclusion criteria at the subtrial level, patient refusal, or availability of subtrials which opened and closed to accrual at different times.)

The sample size for each basket of a multi-basket trial is determined by its predefined goals. Typically, response rate is used as the endpoint for a (nonrandomized) basket for trials enrolling patients with advanced disease. For example, NCI-MATCH (where the primary analysis in each basket was pooled across the different histologies) specified a samples size of 31 eligible patients for each basket, targeting response rates of 5% versus 25%³. That is, the null response rate of 5% was considered likely to indicate an uninteresting level of activity; whereas, a response rate of 25% was felt to represent a promising level of activity deeming the agent worthy of further study. Other trials use various histology-based designs that are discussed below in CONSIDERATIONS FOR POOLING. There was no interim monitoring in each basket in NCI-MATCH; possibilities for interim monitoring in basket trials are discussed below in INTERIM MONITORING. Although the primary analysis for

each basket in NCI-MATCH pooled across the different histologies; there are other possibilities for basket trials discussed below in CONSIDERATIONS FOR POOLING. Interestingly, the very positive results of the larotrectinib basket trial² (75% response rate) led to the USA FDA granting tissue-agnostic accelerated approval for larotrectinib for patients with TRK-fusion-positive solid tumors¹⁴.

UMBRELLA TRIALS

An umbrella trial is designed to enroll patients with a specific histology, and any of multiple potential tumor molecular alterations, who are assigned to different subtrials based on those alterations. As with a basket trial, the tumor molecular screening can be performed as part of the trial (Figure 2A) or in the community (Figure 2B). Any subtrial can be a single-arm trial designed to evaluate the efficacy of a targeted agent, or a randomized trial with a standard-treatment control arm (which could be observation). Unlike basket trials, patients without a target match in an umbrella trial can easily be put on a randomized subtrial of two relevant treatments for the histology. However, since patients with the designated alterations have been excluded from the non-match subtrial, there may be some question as to what population the results will generalize¹⁵.

An example of an umbrella trial is the ALCHEMIST trial for early-stage non-small cell lung cancer patients¹⁶: Patients with EGFR mutant tumors can participate in a phase III trial of erlotinib versus observation; patients with ALK rearranged tumors can participate in a phase III trial of crizotinib versus observation; and patients with neither tumor alteration can participate in a trial of nivolumab versus observation. An example of an umbrella trial with some single-arm subtrials is the Lung-MAP trial for advanced non-small cell lung cancer patients^{17,18}. Other notable umbrella trials include FOCUS4¹⁹, TCA Ovarian Cancer Trial²⁰, and TRIUMPH²¹.

The sample size for each subtrial of an umbrella trial will depend on its objectives. For example, the phase III subtrial of ALCHEMIST for EGFR mutant tumors has a required sample size of 410, targeting an improvement in median overall survival from 5 to 7.5 years, whereas some of the single-arm phase II subtrials of Lung-MAP have required sample sizes of 40, targeting response rates of 15% versus 35%. Standard interim monitoring of the subtrials of an umbrella trial can be used; this is discussed below in INTERIM MONITORING.

BIOMARKER ISSUES

Basket and umbrella trials use biomarker assays to determine whether patients' tumors possess the molecular alterations required to be eligible for a specific basket of a basket trial or for a specific substudy of an umbrella trial. The term biomarker, the analyte or characteristic that is being measured (e.g., BRAF V600E mutation), is distinguished from the assay that is used to measure it (e.g., a next generation sequencing panel assay performed at a specified central lab using scrolls from a formalin fixed paraffin embedded tissue block containing tumor specimen collected at baseline). The terms biomarker and tumor molecular alterations will be used somewhat interchangeably in the discussion that follows, even

though biomarker is a more general term that encompasses more than tumor molecular alterations. While the choice of biomarker is critical from a scientific perspective, the choice of assay to measure that biomarker is also important to ensure that an appropriate patient population is being identified.

Analytical Validation

Biomarker assays undergo analytical validation to describe the performance of the assay including its sensitivity, specificity, accuracy, and precision, among other characteristics²². Assays that include multiple assay components, such as multiplex assays and variants within next generation sequencing (NGS) assays, are commonly used for screening in multi-arm basket and umbrella trials. In these settings, each biomarker component may need to be separately assessed for its analytical performance. Analytical validation methods are described in detail elsewhere^{23–27}. In general, the level of assay validation required will be determined by how the assay will be employed in the study.

Investigators must decide whether a single, well-validated assay should be used, several assays harmonized across laboratory sites should be used, or several locally performed assays with minimal harmonization can be used. The choice of assay(s) may be guided by assessment of the agreement of the assay across sites, even when assays are commercially available. For example, recent studies demonstrated that commercially available circulating tumor DNA (ctDNA) NGS sequencing assays had moderate levels of discordance²⁸, while studies comparing FDA-approved companion and complementary diagnostic PD-L1 immunohistochemistry assays showed good agreement except for one discordant assay^{29,30}.

Local Versus Centralized Screening

Several issues should be considered in deciding whether the screening assay will be performed at a central lab, at local labs, or both. In the ALCHEMIST umbrella trial, a centralized assay was used in a screening protocol to assign patients to arms based on tumor EGFR alterations, ALK rearrangements, or neither¹⁶. In a collaboration involving several trials testing pembrolizumab in patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, investigators pooled five separate single arm trials to create a basket trial^{31,32}. In this setting, local MSI-H/dMMR PCR or IHC tests from each patient's local treatment facility were employed in three arms while central PCR tests were employed in two arms.

Centralized screening requires more upfront planning and resources. A central screening lab (or network of labs) needs to be accessible to a large number of potentially eligible patients and be able to process a sufficiently large volume of specimens in a timely fashion to meet study accrual goals and clinically acceptable turnaround times for assay results. In addition, the assay may need to undergo additional harmonization (if a network of labs is running the centralized assay) and analytical validation. However, a central assay has many benefits including that the assay analytical validation results are known in advance (e.g., the assay is adequately precise and yields few false positives and false negatives). The NCI-MATCH trial used a centralized targeted NGS panel assay that was harmonized across four testing labs to screen patients in the early phases of the trial³⁴. Additional advantages of using a

central assay are that specifics such as assays reagents and equipment (e.g., sequencing platform), technical protocol (e.g., RNA extraction procedures for RNAseq), and computational methods (e.g., bioinformatic pipeline in a next generation sequencing assay) are pre-specified and well controlled, thus paving the way for regulatory approval and swifter translation to clinical use of the assays and drugs if the trial is successful.

Local screening, if widely available in the community, may facilitate faster accrual because patients have direct access through their local clinical sites. A drawback to using local assays is that there could be substantial variability across different assays relative to a gold standard assessment, which could lead to enrolling many patients with false positive test results or excluding patients with false negative test results. Therefore, local screening has the potential to create difficulties in the long run if the trial may be used to support regulatory approval of a drug indication. For example, in the pembrolizumab basket trial for MSI-H solid tumors, FDA approved the drug for MSI-H solid tumors but required post-marketing development of a companion diagnostic test for this use³¹.

Investigators sometimes use local screening for trial enrollment but use centralized screening to confirm results. To accrue patients with rare genetic variants more quickly, the NCI-MATCH trial began using local testing at a series of pre-qualified academic and commercial labs to enroll patients, followed by retrospective centralized testing when specimens were available³⁵. Enrolling only patients who have positive local *and* centralized tests can bias the patient population when assessing the clinical utility of the drug using the centralized test³⁶. Because such a study does not include patients with local negative but centralized positive test results, the primary analysis may be more likely to show benefit of therapy than an analysis of patients who are enrolled solely on the centralized assay. Therefore, implications of this “prescreening bias” need to be considered if the trial may be used to support an FDA-cleared or approved test.

Multiple Biomarkers in Master Protocols

For trials that incorporate multiple biomarker-directed arms, it is important to pre-specify how patients will be assigned to a trial arm when a patient has multiple actionable tumor alterations (or biomarkers)¹. Two common ways of handling assignment of patients with multiple actionable biomarkers include prioritizing the biomarkers in some way and using a pre-specified randomization scheme to assign therapy. In the NCI-MATCH trial, patients with multiple actionable biomarkers were assigned to the biomarker-selected arm for which there was the highest level of preliminary evidence for potential therapeutic benefit^{3,37}. In the LUNG-MAP trial, investigators used a pre-specified algorithm to randomize patients with multiple actionable biomarkers to a trial subgroup¹⁷. This algorithm randomized patients so that they were more likely to be assigned to the trial subgroup with the lower prevalence biomarker^{1,17}.

CONSIDERATIONS FOR POOLING RESULTS

When the level of clinical activity in all (or some) of the patient subgroups (e.g., defined by tumor histology or other characteristics) is expected to be similar it may be appropriate to use various statistical approaches to pool results across the subgroups. The advantage of

pooling of results is the larger sample size for inference, which can be especially important when the numbers of patients in the subgroups are small. Pooling methods can range from complete pooling (where all subgroups are analyzed together) to various partial pooling methods, in which estimates of outcome in each subset are influenced by the outcomes in the other subsets (“borrowing information”). However, it is important to remember that the borrowing of information comes at a price of the need to adjust the design to account for the possible heterogeneity of the subgroup effects. Without such adjustments pooling may dramatically increase the possibility of subjecting some future patient subgroups to ineffective potentially toxic therapies or the possibility of missing agents with promising activity in some subgroups. Post hoc pooling simply based on observed outcomes in the absence of a pre-planned statistically valid approach is not appropriate. Pooling will be discussed separately for basket and umbrella trials.

Basket Trials

In a basket trial, the opportunity for pooling is across histologies, and it may be appropriate if there is reasonably strong scientific rationale that the activity of the agent would be similar in the different histologies. For example, each arm (basket) of the multi-basket NCI-MATCH trial³ used complete pooling in that the primary analysis examines the response rate in each arm regardless of histology. On the other hand, the BRAF-Vemurafenib trial⁴ used no pooling and analyzed patients in each histology-specific cohort separately. It should be noted that analyzing each histology-specific cohort separately in a basket increases the probability of falsely declaring that the agent works for some histology (unless a multiple comparison adjustment is made)³⁸.

The simplest type of partial pooling estimates the response rate for a specific histology as a weighted mean of the response rate for that histology and the overall response rate (regardless of histology); the weights determine the amount of pooling of information across the histologies. The challenging issue is the choice of the weights. The most common framework for choosing weights is to use Bayesian hierarchical modeling³⁹, which uses the spread of the observed histology-specific rates to determine data-driven weights. In particular, if the observed rates are close to each other, then the estimated rate for each histology is taken to be close to the overall response rate, whereas if the observed rates are far apart, the estimated rate for each histology is taken to be close to its histology-specific rate. Unfortunately, simple implementations of this approach do not work, leading to inflated probabilities of incorrectly declaring as effective an agent that does not work in a histology and incorrectly declaring as ineffective an agent that does work in a histology⁴⁰. Although methodologic work continues to improve data-driven pooling⁴¹, no rigorous methods for reliably using the observed data to determine when to borrow across subgroups without inflating the design error rates is currently available. Given current understanding of statistical performance of available pooling approaches, it is advisable to restrict use of data-driven pooling to secondary analyses. It should be noted that that some pooling methods can still be effectively used in interim futility monitoring; see INTERM MONITORING below.

Umbrella Trials

In an umbrella trial, the opportunity for pooling is across substudies defined by different biomarkers. At first glance, pooling seems to make no sense, as why would one expect the activity of different targeted agents being used to treat patients in their respective biomarker subsets to be similar? However, there is one special case of an umbrella trial where such pooling is used, namely the biomarker strategy design. A strategy design is a randomized comparison of a strategy treatment arm that uses biomarkers to determine the treatment versus a treatment arm that is standard of care (with no use of biomarkers). For example, in the TCA Ovarian Cancer Trial²⁰ in the biomarker-strategy arm a chemosensitivity assay was used to choose from a panel of 12 chemotherapy regimens; in the control arm patients received physician's choice of chemotherapy. Note that a strategy design involves a complete pooling of the results across the biomarker-defined substudies.

(A strategy design can also be used for a randomized basket trial, where the results of all the targeted experimental treatments are compared to the results of all the control treatments. Note that in this case the design involves complete pooling over both the biomarker subgroups and histologies. For example, in the SHIVA trial¹² the primary analysis was pooled over the three molecular pathways and 26 histologies.)

The strategy design is appealing in that it directly addresses the clinical question of interest: Does using biomarkers to direct treatment improve outcomes? However, there are several potential problems with the strategy design. The first problem is that the pooling across patient subsets can make the results of the trial difficult to interpret: If some alteration-agent subsets are effective and others are not, a trial may be (overall) positive even though some agents are ineffective in their targeted subsets, or a trial may be (overall) negative even though some agents are very effective in their targeted subsets. For example, it has been suggested that the overall results for the SHIVA trial may have been negative because the patients with molecular alterations in the hormone receptor pathway may not have benefited¹².

A second problem with strategy designs is that there may be a large proportion of patients receiving the same treatments on both arms, which can dilute any between-arm treatment differences⁴². For example, in the TCA Ovarian Cancer Trial, 70% of the patients in the standard-treatment arm received agents that they could have received in the strategy-treatment arm²⁰. An approach to lessen the treatment overlap between the randomized arms is to only enroll patients who have an actionable alteration; this avoids treating patients with standard therapy on the strategy arm. Additionally, overlap can be completely eliminated in some situations by only using experimental agents that are not generally available outside of the trial, in the strategy arm; this was the approach used in the SHIVA trial¹².

Finally, a third potential problem with strategy designs is that the strategy arm may look better than the standard treatment arm only because agents being used in the strategy arm are more effective than the standard treatment, and not because the biomarkers are providing any useful information. To avoid this problem, one could randomize patients in the "standard-treatment" arm to receive the same set of agents being used in the strategy-treatment arm⁴³. This approach was used in the MPACT study⁴⁴ where patients were

randomized between the experimental arm (where the agents patients received were selected based on their tumor biomarkers) and the control arm (where patents received one of the non-matched drugs with the non-match drug assignment determined to closely follow the agent distribution on the experimental arm). However, this approach can be logistically challenging, especially with a large number of biomarker-agent combinations (which is the only situation where one should consider using a strategy design).

INTERIM MONITORING

Interim monitoring of an ongoing clinical trial allows for the possibility of stopping a trial early when the accruing outcome data become sufficiently convincing to answer the study question. Trials can be stopped for efficacy when it becomes clear that the experimental treatment has the design-specified level of activity. For a phase II trial that means the activity is sufficient to warrant further development of the therapy, and for a phase III trial the activity should be sufficient to change clinical practice. Interim monitoring should also generally include monitoring for futility/inefficacy, which allows stopping the trial when it becomes clear that the experimental treatment does not have sufficient activity (so that continuing the trial would not be useful)⁴⁵. Because an undisciplined approach to interim monitoring can lead to trials having inflated type 1 errors and reduced power, trial designs including formal interim monitoring plans have been developed, as will now be briefly described.

In the single-arm trial setting, two-stage designs evaluate the outcomes in an initial set of patients, to decide whether to continue on to a second stage of accrual. There are many such two-stage designs⁴⁶. For example, a Simon optimal two-stage design⁴⁷ targeting a 20% response rate as clinically interesting and a 5% response rate as uninteresting is as follows: Accrue 12 patients at the first stage. If there is at least one response, accrue an additional 25 patients to the second stage. The therapy is deemed worth pursuing if there are at least four responses out of the 37 patients treated. Note that this design does not consider stopping at the first stage for efficacy. The reason for this is that one would want to gain more experience with a new therapy than just a small cohort of first-stage patients. However, with biomarker-specified eligibility the patient population may be quite small with the trial slowly accruing, in which case it may be reasonable to consider early efficacy results. In these situations, we would recommend using a two-stage design that accommodates an early analysis for efficacy as well as futility, but reporting the results early for efficacy instead of stopping early. For example, a Fleming design⁴⁸ similar to Simon design accrues 12 patients at the first stage and 25 at the second stage, but allows for first-stage stopping for efficacy (three or more responses) as well as for futility (zero responses). We would modify this design not to stop at the first stage (for planning purposes), but to allow public release of the positive results at the first stage while continuing to accrue to the second stage of the trial. Continuation provides more experience with the drug's activity and safety profile.

In the randomized trial setting, there are many different approaches to interim futility monitoring⁴⁹. A particularly simple rule is to perform the analysis when one-half the information on the trial becomes available (which corresponds to one-half the required number of events specified by the trial design), and stop the trial for futility if the

experimental treatment arm is doing worse (by any amount) than the standard treatment arm⁵⁰. For a randomized phase III trial, efficacy interim analyses are typically done at specified information times, e.g., 33%, 50%, and 75% information, and require strong evidence to stop, e.g., p-values less than 0.00001, 0.0014, and 0.0092, respectively, for a trial with a one-sided type 1 error of 0.025⁵¹. For randomized phase II trials, interim analyses for efficacy are generally not included in order to minimize the possibility of stopping the study before sufficiently mature efficacy/safety data is available. Note that, unlike the single-arm designs, the reporting-early-for-efficacy-without-stopping option is not generally available in randomized designs since it would be inappropriate to keep randomizing patients to the control arm after the experimental arm has been shown to be definitively better.

Nonrandomized Basket Trials

The interim monitoring of a basket trial is generally related to the analysis strategy for the trial: If the study is designed to analyze patients with different histologies separately at the end of the trial, then one could use interim monitoring for patients in each histology. For example, in the BRAF Vemurafenib trial a two-stage design with futility monitoring was used for each of the histology-specific cohorts⁵². On the other hand, if the primary analysis is to include all patients in the basket regardless of histology, one might perform futility monitoring on all the patients in the basket regardless of histology⁵³. The potential problem with this approach is that one may stop a basket for futility (e.g., with 0 responses in the first 15 patients treated) because the basket happens to be dominated by one or a few histologies in which the therapy does not to work (while the histologies where the treatment works happen to be underrepresented). To avoid this problem, sometimes no futility monitoring is specified. For example, there is no futility monitoring specified in the NCI MATCH trial. If in a particular basket of a multi-basket trial it is expected that a high proportion of patients will be of a specific histology, then one should include futility monitoring for these patients. An example is found in the multi-basket NCI-COG Pediatric Match trial⁸ where the subgroup (basket) of patients whose tumors harbor IDH1 mutations is expected to be comprised almost exclusively of patients with glioma. For this reason, futility monitoring was added for this particular basket. In addition to specifying histology-specific futility rules, one may specify histology-specific accrual caps to ensure that the trial is representative of the entire histology spectrum.

Randomized Basket Trials

It can be challenging to include formal histology-specific interim analysis guidelines for a randomized basket trial because of the mix of histologies enrolled. For example, because there were 26 different histologies enrolled in SHIVA with the largest being 20% of the enrollment¹², it would have been problematic to have histology-specific futility rules. However, similarly to the non-randomized basket trials, if a randomized basket study is expected to enroll a high proportion of patients with a specific histology/biomarker combination, then the study should include futility monitoring for this subpopulation. Interim futility monitoring for the overall comparison of randomized arms regardless of histology does introduce a risk of stopping the trial early when the experimental treatments are working for some, but not all, of the histologies; this mirrors the interpretation problems at the final analysis of randomized basket trials (as described in CONSIDERATIONS FOR

POOLING RESULTS above). However, in contrast with nonrandomized basket trials (where the response analyses of small histologic subgroups may still provide a meaningful signal of the treatment activity in that subgroup), in randomized trials interpreting relative treatment effects over multiple small biomarker/histologic subgroups is extremely challenging. Given these interpretational concerns and the higher resource burden of randomized studies, one should consider including futility monitoring for the overall randomized comparison.

Umbrella Trials

In umbrella trials, standard interim guidelines (appropriate for the type of study, single arm or randomized) can be used for each substudy, as they are analyzed independently. The only additional monitoring that is necessary is to ensure that the numbers of patients being screened into the different substudies is sufficient to support feasibility of trial continuation to reach the planned sample sizes.

Feasibility monitoring

Biomarker-driven trials often involve rare biomarker subgroups. In order to ensure that subgroup-specific questions can be answered within an acceptable time frame, feasibility monitoring rules may be required to monitor the accrual rates to the individual subgroups. Enrollment of patients onto the subgroup-specific treatment arms will depend not only on the prevalence of the qualifying tumor biomarkers in the study patient population, but also on percentage of acquired specimens that meet minimal acceptance criteria for quality and quantity, percentage of successful assays, and the proportion of patients who agree to enroll on the treatment arm when found to be eligible based on tumor molecular characteristics. Furthermore, in some cases involving recently developed assays, feasibility rules may be needed to be included to ensure that the biomarker screening procedures can be accommodated within the accepted standard of care. For example, in some diseases like acute myelogenous leukemia, treatment cannot be delayed by more than a few days, thus making biomarker assays with longer turnaround times impractical.

IMPLEMENTATION OF MASTER PROTOCOLS

Management of basket and umbrella trials with their inherent complexity due to inclusion of potentially several tumor histologies, experimental therapies, and biomarker-defined subgroups requires careful coordination and oversight. Master protocols have proven useful for this purpose. Like the trial designs, the structure of master protocols continue to evolve¹. Some master protocols incorporate multiple histologies and experimental agents such as NCI-MATCH while others such as ALCHEMIST involve a set of independent treatment trials that share a common molecular/biomarker screening protocol within a specific disease area, patient population and/or clinical setting. The major design and operational characteristics of a master protocol are selected to ensure enhanced coordination and efficiency compared to what can be achieved in single trials conducted independently. Such design efficiencies are supported by innovations in the infrastructure underlying the trials, including common screening platforms, governance committees, central institutional review boards, trial networks, and shared processes for data management⁵⁴. This section will

elaborate on several master protocol designs and their impact on infrastructure and administrative components.

The NCI National Clinical Trials Network (NCTN) is an example of a national trial network consisting of both academic and community medical centers with an infrastructure that includes many of the innovations needed to conduct master protocols effectively⁵⁵. This infrastructure provides a common enrollment and data management system for all trials conducted in the network, an NCI Central Institutional Review Board (CIRB), an NCI informed consent template, and shared processes for tissue collection, data monitoring and safety reporting. For the NCI-MATCH and NCI Pediatric MATCH master protocols, the NCI established a network of Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories to screen tumor tissue from patients using validated assays and standard operating procedures (with inter-laboratory proficiency testing) in order to assign patients to appropriate targeted therapy treatment trials⁵⁵. The NCI also negotiated collaborative agreements with numerous pharmaceutical and biotech companies to provide agents for evaluation in several of its master protocol clinical trials with the NCI Division of Cancer Treatment Diagnosis, Cancer Therapy Evaluation Program as the IND sponsor. As sponsor, NCI requested pre-IND meetings with the FDA to reach agreement on the design and conduct of these master protocols, especially on issues related to the common molecular/biomarker screening component and conduct of the master protocol under a single IND. Governance committees including steering committee and agent selection and monitoring committees were also established for these master protocol as needed.

Even with an established infrastructure with many of the innovative components needed to conduct complex master protocols, there are numerous administrative challenges in the design and implementation of these types of master protocols at the both the national and individual site/investigator level⁵⁶. The development of a complex master protocol involving agreements with multiple pharmaceutical/biotech company partners must address issues related to budgeting and cost-sharing for the common molecular/biomarker screening component, instituting a level of standardization across substudies, providing communication on individual substudy conduct to appropriate company partners, and ensuring regulatory compliance for assays required for different types of targeted agents with possible need for bridging studies for specific company developed assays if a common platform is used¹⁵. The increased complexity of these types of protocols also impose significant workload issues at the local site level (e.g., opening multiple treatment substudies and processing a higher number of protocol amendments when only a few may patients at a site may be assigned to any substudy) despite the efficiencies of some trial components (e.g., a common screening component, use of a CIRB).

There are a number of administrative choices in developing a master protocol that can ease the management of the master protocol at local sites as well as within the Coordinating Center for the master protocol and at the CIRB. NCI's initial experience with its master protocols illustrate the advantages and disadvantages of particular approaches.

The NCI-MATCH master protocol, which evaluates whether patients with diverse types of advanced cancer and tumors containing certain molecular alterations derive clinical benefit

when treated with single-agents targeted against those alterations, was initially designed as a single protocol document under a single IND. This single protocol consists of an overarching, integrated molecular/biomarker screening component and multiple single-arm phase 2 substudies, each testing a different targeted agent or combination (Figure 3A). The administrative choice of a single protocol document proved cumbersome over time to the institutional review board, regulatory agency, and local sites as all these entities were faced with managing the entire protocol document of all substudies every time there was an amendment that only affected 1 or 2 of the substudies or the master screening component. This became especially problematic as the number of substudies increased.

In order to address the issues that arose with the conduct of NCI-MATCH as a single protocol document, the NCI Pediatric MATCH master protocol, which had the same general scientific trial design as NCI-MATCH, was designed in a more modular format. A master version control document was instituted for NCI Pediatric MATCH (Figure 3B) that provided overall management of the screening component and individual substudies in a more independent manner. The master version control document is used to briefly describe the overall objectives of the master protocol and to list/index and track the activation, amendment history, and closure of the individual substudies. If an amendment only involves 1 substudy, then the amendment is processed with just a change in the master version control document (i.e., showing the date of the amendment for that specific substudy) and the appropriate changes in the individual substudy. In a similar manner, when a new substudy is added to NCI Pediatric MATCH, the amendment is processed showing the addition of the substudy to the index in the master version control document and the submission of the new substudy protocol. Managing NCI Pediatric MATCH using this administrative format has simplified processing at the local site as well as at the CIRB and FDA. In addition, this format simplifies appropriate reporting to clinicaltrials.gov for each individual substudy and to company partners on their specific substudy. Some aspects of this modular format have now been incorporated into NCI-MATCH as well to help manage that master protocol.

The ALCHEMIST initiative was designed in a distinct administrative format from that of NCI-MATCH and NCI Pediatric MATCH. The ALCHEMIST master protocol also involves a very different clinical setting and a single disease. ALCHEMIST is evaluating new adjuvant therapies in early-stage non-small cell lung cancer (NSCLC) in definitive, randomized phase 3 trials as opposed to the evaluation of new investigational agents in small single-arm phase 2 studies in advanced disease in NCI-MATCH and NCI Pediatric MATCH⁵⁷. The design of ALCHEMIST consists of a completely separate master screening protocol which tests tumors with appropriate NSCLC histologies first for EGFR alterations and ALK rearrangements with assignment of patients to appropriate treatment trials evaluating whether therapies targeting those alterations are more efficacious than the current standard of care (Figure 3C). If those molecular alterations are not found or patients have other types of NSCLC histologies, the patients are assigned to a treatment trial evaluating immunotherapy versus the current standard of care. Each of the ALCHEMIST randomized treatment trials is a completely independent trial. In this administrative format, each of the randomized treatment trials is covered by a trial-specific IND. Since the master screening component and the individual treatment trials are separate protocols, there is maximum flexibility in the administrative management of each protocol/trial; however, increased

coordination is required to ensure that changes in the master screening protocol are reflected as needed in the individual treatment trials.

As new master protocols are designed to address new combination therapies across various cancer types and other disease-specific evaluations of diverse investigational therapies in earlier phase randomized trials, alternative administrative formats have been proposed. One such format involves combining administrative elements of the NCI-MATCH master protocols with those of ALCHEMIST (Figure 4). This format involves a completely separate master molecular/biomarker screening protocol (similar to ALCHEMIST) combined with multiple cassettes of substudies under distinct master version control documents (similar to NCI Pediatric MATCH). An administrative format like this could be used to evaluate major categories of therapies (e.g., a cassette for biomarker-driven targeted agents versus a cassette for non-matched therapies) or distinct cancer types (e.g., a cassette for biomarker-driven targeted combinations in breast cancer versus another disease type) or other scientific themes (e.g., cassette for various agents or agent combinations targeting a specific molecular pathway in various disease types). One potential advantage of this type of administrative format is that particular cassettes of substudies might be under different INDs (if appropriate) and could be managed by different clinical trials groups within the NCTN; however, this variation would require additional high-level coordination for regulatory compliance with the FDA and for trial protocol and data management across clinical trials groups.

There is no perfect administrative format for the conduct of complex master protocols. The advantages and disadvantages of any particular approach must be weighed in light of the specific scientific objectives of the master protocol.

DISCUSSION

Precision medicine has prompted a paradigm shift for the design, conduct, analysis, and management of oncology clinical trials. Master protocols for clinical trials such as multi-basket and umbrella trials have proven useful to achieve an economy of scale by coordinating access to multiple biologically driven clinical trials through a central system that allows streamlining of regulatory, administrative, and data management processes. Flexibility is maintained so that subprotocols within a master protocol can have statistical design, monitoring and analysis plans tailored to the clinical question being addressed in their eligible subcohorts, yet, when appropriate, cross-cohort analyses can be facilitated by the master protocol structure.

Substantial resources are required for successful conduct of precision medicine trials conducted as master protocols. Because many of these trials rely on collection of large-scale genomic data, traditional clinical trial teams must expand to include laboratory scientists and bioinformaticians with specialized expertise in the processing and management of these data. Data management needs go beyond conventional clinical databases to those with capabilities to handle large scale genomic data. Informatics systems may be needed to serve as decision tools to guide interpretation and visualization of large-scale molecular data to

guide treatment eligibility determination and assignment. This added expertise and data infrastructure can be leveraged across the trials within a master protocol.

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Figure 1:

Basket trials. (A) Basket trial with one basket. (B) Multi-basket trial with screening as part of the protocol. (C) Multi-basket trial with eligibility restricted to patients with tumor molecular alterations for which treatments are being tested.

Figure 2. Umbrella trials. (A) Trial with screening as part of the protocol. (B) Trial with eligibility restricted to patients with tumor molecular alterations for which treatments are being tested.

Figure 3.

Examples of NCI master protocol administrative designs. (A) NCI-MATCH designed as a single protocol document with integrated master screening and multiple substudy components. (B) NCI Pediatric MATCH designed with an overarching master control document that manages the master screening and multiple substudy components as separate protocols. (C) The ALCHEMIST initiative is designed with a separate screening protocol and independent treatment trials that are coordinated with the screening master.

Figure 4.
Potential administrative design for complex master protocol initiatives with separate sets ("cassettes") of multiple substudies.