REVIEW ARTICLE

Biomarker Clinical Trials in Lung Cancer: Design, Logistics, Challenges, and Practical Considerations

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Received 21 May 2018; revised 10 August 2018; accepted 15 August 2018
Available online - 4 September 2018

ABSTRACT

Treatment for lung cancer has evolved in the past 3 decades starting with platinum-based chemotherapy as the standard of care, regardless of histology, in the early 1990s to the current age of biomarker-driven therapy. Consequently, clinical trials in lung cancer have evolved in response to this new shift of paradigm, leading to novel approaches that simultaneously shorten the development process and allow evaluation of multiple patient cohorts. Herein, we provide an overview of the landscape of lung cancer clinical trials in the era of targeted therapies, precision medicine, and biomarkers. Specific trials are given as examples to illustrate the design paradigms. The paper is organized by drug development phases starting with early-phase biomarker discovery to proof-of-concept trials to definitive trials. We also present some thoughts on future directions.

Keywords: Biomarker designs; Clinical trials; Lung cancer; Practical considerations; Logistical challenges

Introduction

Lung cancer accounts for an estimated 13% of cancer cases in the United States but is responsible for 26% of cancer deaths, making it one of the most deadly cancers.[1] Lung cancer is a disease with multiple histologic types.[2] Approximately 57% of patients are diagnosed with metastases; therefore, prognosis is often poor at diagnosis.[1] Treatment for lung cancer has evolved in the past 3 decades starting with the early 1990s when lung cancer was treated as a single disease with a combination of platinum-based chemotherapy as the standard of care, regardless of histology.[3] With the recognition of biological differences among histologic subtypes in the early 2000s, the standard of care in advanced NSCLC shifted to histology-focused chemotherapy such as cisplatin + gemcitabine for squamous histology or cisplatin + pemetrexed for nonsquamous NSCLC. The addition of a number of kinase inhibitors such as sorafenib or motesanib did not improve outcomes beyond platinum-based combination regimens.[4-7] However, the addition of bevacizumab, a vascular endothelial growth factor (VEGF)–specific antibody, to carboplatin + paclitaxel showed a survival benefit compared to carboplatin + paclitaxel alone in recurrent or advanced NSCLC.[8] A comprehensive summary of histology-driven treatments of advanced NSCLC is provided by Langer et al.[9]

Further understanding of cancer biology led to modern therapy options that target specific signaling pathways such as the EGFR pathway that is targeted by the EGFR tyrosine kinase inhibitors (TKIs), erlotinib, gefitinib, and afatinib.[10-14] The increased recognition of specific genetic mutations driving some tumors or responsible for resistance to certain TKIs further marked a paradigm shift where treatments are tailored to target

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Disclosure: Dr. Dahlberg has received grants from the National Institutes of Health; has received personal fees from Astra Zeneca; and has a patent pending regarding volumetric tumor growth in advanced NSCLC patients with EGFR mutations. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2018.08.2019

specific genetic mutations. A recent example is the AURA3 trial which showed that osimertinib (designed to inhibit the T790M resistance mutation to earlier EGFR TKIs) is superior to platinum therapy plus pemetrexed after first-line EGFR-TKI therapy for T790M-positive patients with advanced NSCLC in terms of response, progression-free survival (PFS), and patient-reported symptoms.[15] Another example of successful mutation-specific targeted therapy is the identification of dabrafenib plus trametinib as effective treatment for patients with $BRAF^{V600E}$-mutant metastatic NSCLC.[16,17] This combination is also approved for treatment of BRAF-mutated melanoma.[18] With additional genetic mutations that continue to be identified coupled with the explosive growth of targeted agents, the old paradigm of clinical trials, evaluating treatments for one mutation at a time, is not efficient. Novel approaches that simultaneously shorten the development process and allow evaluation of multiple patient cohorts are needed.

We provide an overview of the landscape of lung cancer clinical trials in the era of targeted therapies, precision medicine, and biomarkers. Specific trials are given as examples to illustrate the design paradigms. The paper is organized by drug development phases starting with early-phase biomarker discovery, followed by proof-of-concept trials including adaptive phase II designs and a discussion of tissue-agnostic and molecularly-defined trial designs (known as basket trials). Definitive phase II/III and phase III trials are also described. The objective, advantages, challenges, and practical considerations for the designs are summarized in Table 1. Finally, we present thoughts on future directions.

Early-Phase Biomarker Discovery Trial Designs

Drug development for populations of patients whose tumors harbor relatively rare abnormalities can be a challenge because inferences regarding the efficacy of drug-biomarker pairing rely on small sample sizes. The historical drug development paradigm in oncology has featured a series of stages from phase I through phase III clinical trials, where phase I studies evaluate toxicity and establish recommended phase II doses. In more recent years, however, phase I trials have enrolled more patients than would traditionally be required for a definitive randomized phase III trial. The rationale for such large phase I trials is to assess efficacy endpoints in specific subsets of patient populations identified by biomarkers. This phenomenon, known as seamless drug development, blurs the lines between phase I, phase II, and phase III trials in such a way that the phase I trial data can be used to file for accelerated approval with the United States Food and Drug Administration (FDA).

One of the first agents approved in such a manner in thoracic oncology was crizotinib, which received accelerated approved in 2011 for the treatment of patients with locally advanced or metastatic NSCLC harboring the ALK receptor tyrosine kinase (ALK) rearrangement as detected by a test that was also FDA approved. The route to approval was the result of disparate observations, starting with the identification of the ALK fusion protein in 1994 in non-Hodgkin's lymphoma, the oncogenic driver identified in 6.7% (5 of 75) of NSCLC patients studied in 2007.[19,20] Accelerated approval was based on the results from the single-arm trial which showed a best objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) of 61% (95% confidence interval [CI]: 52%–70%) and a median duration of response in excess of 11 months.[21] A supporting additional single-arm trial showed a 50% response rate and efficacy of crizotinib was confirmed in a randomized phase III trial of 347 patients (PFS hazard ratio [HR]: 0.49, 95% CI: 0.37–0.64), leading to regular approval of this agent for the treatment of ALK-positive NSCLC.[21]

This example highlights the fact that the intention of the expansion cohort has evolved into an opportunity to estimate efficacy endpoints, such as response with more precision, by enrolling more patients to a trial after only a handful of initial responses are observed. Providing statistical justification for such increase in sample sizes in the form of a power calculation for a pre-specified hypothesis test is usually lacking.[22] Because the probability of response on phase I trials tends to be low on average, and the probability of an adverse event is usually high, it is acknowledged that every drug entering seamless drug development is not a success story. As expansion cohorts become more common and larger, such as the phase I pembrolizumab trial which enrolled more than 1200 patients, the concern of phase I trials potentially committing too many resources and enrolling too many patients has become a reality.[23] These concerns and potential solutions are to be addressed in draft guidance to industry being drafted by the FDA Office of Hematology and Oncology Products.[24] Meanwhile, there are several considerations to be made when designing phase I clinical trials with samples sizes that exceed what has been traditionally expected. Beyond having a good biological rationale for the drug-marker pairing, statistically, the sample size should support the objectives of the trial. It is important to recognize that even with the exceedingly large sample sizes, expansion cohort studies are not designed as confirmatory trials, thereby lacking rigorous design criteria needed to evaluate the safety and efficacy of investigational agents. The

Table 1. Trial Design by Development Phase

Development Phase (Objective)	Design	Advantages	Challenges	Practical Considerations
Biomarker discovery (Identify potential biomarker subgroup that may respond to new therapy)	Phase I with expansion cohort	Opportunity to assess efficacy in rare biomarker subsets Possibility of accelerated approval	Lack of statistical power Lack of stopping rules for toxicity or futility No clear metrics of success	Have good rationale for drug-marker pairing Sample size should support objectives of trial
Proof of concept (Provide early read of efficacy in target population)	Adaptive trial	Flexible design Use of accumulating data to guide study conduct Potential increase in efficiency Attractive for rare tumors or cohorts with low marker prevalence	Requires more planning to ensure trial integrity Requires validated, short-term endpoint for adaptation Outcome-adaptive trial may have some concerns with biased results	Transparent design and randomization algorithm needed to minimize bias and to improve reproducibility
	Basket trial	Assess treatment effect of biomarker on multiple tumor types simultaneously Logistical efficiency through the use of "master protocol" Flexibility to add/remove sub-studies Attractive option for rare tumor subsets	Logistically demanding Trial can be large and duration can be long Control arm can be obsolete with rapid changes in standard of care Heterogeneous responses across tumor groups may lead to bias or inflation of false positive rates	Careful evaluation of prevalence of biomarker is needed to ensure enough patients are screened to achieve required sample size. Consistency of biomarker assay across sites is important Planning requires well-coordinated efforts among members of multidisciplinary team
Definitive trial (Confirm efficacy of new therapy in target population)	Umbrella	Opportunity to assess treatment effect on multiple biomarker subgroups Attractive options for rare marker subgroups Logistical efficiency through the use of "master protocol" Flexibility to add/remove sub-studies	Logistically demanding Trial can be large and duration can be long Control arm can be obsolete with rapid changes in standard of care	Consistency of biomarker assay across sites is important Planning requires well-coordinated efforts among members of multidisciplinary team Often needs international partnerships to make it feasible
	Randomized Phase II or Phase III	Minimal selection bias More statistical power Opportunity to include stopping rules for toxicities, futility, or efficacy Clearer metrics of success	Requires larger sample size May take time to accrue patients Resource intensive to plan and coordinate Scientific question may become irrelevant by time of trial completion	Planning requires well-coordinated efforts among members of multidisciplinary team International partnership provides potential solution to accrual challenges

design concerns include the lack of stopping rules for toxicity, lack of sample size justification, and often no clear definition of metrics of success. Additionally, these studies are often designed based on a presumption of success and do not include plans for interim analysis to allow for early stopping for futility (lack of efficacy).

Proof-of-Concept Trials

Following initial discoveries, proof-of-concept (POC) clinical trials are designed to provide an early read of efficacy of new therapeutic regimens in the target population. As a result, the putative therapeutic benefit of a new treatment can be quickly supported or refuted. The trial must show whether the new treatment is efficacious gauged by easy-to-measure, short-term clinical endpoints or surrogate endpoints such as biomarker modulation. The goals of POC trials are primarily exploratory rather than confirmatory.

POC trials often take place in the early phase of drug development. Typically, these trials are smaller in size, aiming to screen for treatments with a large effect size. The allowable error rates tend to be larger than phase II or III trials and the sample size is typically smaller than phase II or III trials. Hence, the study can be completed

in a short duration of time. However, an early strong signal can sometimes lead to accelerated approval as in the example of crizotinib discussed earlier. Another type of POC trials include biomarker credentialing trials seeking to document that a drug can successfully inhibit a target such as in "window-of-opportunity" studies, although this is rarely done in oncology. POC studies can also be designed further in the drug development process such as in phase II trials. They can be designed taking into consideration the "cost" or "utility" of various decisions by incorporating the true-positive, true-negative, false-positive, false-negative decisions, the cost and time of running the trials into considerations.[25]

Phase II Trials

The primary goal of phase II trials is to obtain a better understanding of the efficacy of a new treatment which helps determine whether the treatment is promising to warrant a confirmatory phase III trial. There are single-arm phase II trials and randomized phase II trials. In single-arm phase II trials, all patients are assigned to receive the same treatment. Efficacy of the new treatment is measured against a historical control. In randomized phase II trials, patients are randomly assigned to receive the treatment prescribed to the arm they are assigned. A promising new treatment can be determined by comparing the efficacy between treatment arms or by comparing each arm to a historical control. Phase II trials are typically designed to look for large treatment effects but, at the same time, controlling for both type I and type II errors. Compared to phase III trials, a larger type I error rate is tolerated because false-positive findings can be refuted later. On the other hand, a smaller type II error is desired such that we do not miss the opportunity to identify an effective treatment (a small false-negative rate). To improve the success upon a positive finding of a phase II trial, that is, to yield a large positive predictive value, type I and type II error rates need to be calibrated by assessing the prior probability of success in each specific context.[26]

An example of phase II POC trial in lung cancer includes the dabrafenib plus trametinib trial for patients with $BRAF^{V600E}$-mutant metastatic NSCLC.[16,17] This was a phase II trial with multiple cohorts. One cohort included patients with previously treated metastatic NSCLC. A single-arm two-stage Green-Dahlberg design with one interim analysis for futility was used for this cohort of patients.[16,27] The planned enrollment was 40 patients (20 per stage) which provided 92% power with a type I error of 3.2% to detect a 55% overall response rate against the null hypothesis of 30%. Fifty-nine patients were enrolled in this cohort between December 2013 and January 2015. Another cohort of this trial targeted patients with $BRAF^{V600E}$-mutant previously untreated metastatic NSCLC.[17] The design for this cohort was a single-arm one-stage study. The planned enrollment was 25 patients to achieve 92% power with a type I error of 4.4% to detect a 60% overall response rate against the null hypothesis of 30%. The study enrolled 36 patients to this cohort between April 2014 and December 2015. This study was the first to evaluate the combination of BRAF and late endosomal/lysosomal adaptor, MAPK and MTOR activator 3 (MEK) inhibition in NSCLC leading to FDA approval of this combination for $BRAF^{V600E}$-mutant NSCLC.

Adaptive Trial Design

With their exploratory nature, adaptive designs are suitable choices for POC trials. By definition, adaptive designs allow the use of interim data to guide the study as it progresses. This is in contrast with traditional trial design where the sample size, the treatment allocation, and the study duration are fixed at the onset. There are different types of adaptive designs, for example, adaptive dose finding, adaptive estimation for treatment's toxicity and efficacy, adaptive stopping for toxicity, futility and/or efficacy, outcome adaptive treatment assignment, adding or dropping treatments, and adaptive sample size re-estimation.

Compared to traditional designs, adaptive designs continue to learn about the effect of the new treatment to make interim decisions for early stopping based on treatment's toxicity and efficacy and assign treatments to patients. Therefore, conclusions are made based on real-time data continuously updated during the course of the trial. Adaptive designs have the potential to increase the study efficiency by making a decision based on current data which can lead to smaller trials and shorten the drug development time.[28] However, continuous adaptation can also lead to larger trials in some cases. From a statistical perspective, Bayesian inferential framework is inherently suitable for adaptive designs. In this framework, the prior information of the unknown parameter, the observed data, and the formation of the posterior distribution of the parameter are all used such that the posterior distribution becomes the new prior distribution for subsequent learning. The new prior coupled with new data generate a new posterior distribution and the iterative learning process continues.[29,30]

An example of Bayesian adaptive design in lung cancer research is the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) program.[31] The BATTLE program consists of two trials: BATTLE-1 and BATTLE-2. Both are Bayesian adaptive phase II trials. The BATTLE-1 trial was the first biopsy-mandated, biomarker-based, adaptively

randomized clinical trial in patients with previously treated NSCLC.[32] Eligible and consented patients underwent a core-needle biopsy to acquired tissues for molecular analysis. Depending on the biomarkers, a patient was classified into one of the five biomarker groups: 1) EGFR group, 2) KRAS/BRAF group, 3) VEGF group, 4) nuclear receptor binding factor 2 (RXR)/cyclin D1 group, or 5) none of the above group. The four treatment arms were erlotinib, sorafenib, vandetanib, and the combination of erlotinib and bexarotene. Although the target for each agent was not completely understood at the time of the trial development, each treatment was chosen to target the closest molecular aberrations in each of the four corresponding marker groups respectively. The primary endpoint, the 8-week disease control rate (DCR), was chosen as an early efficacy endpoint which correlated with the overall survival (OS) time in patients with advanced lung cancer.[33] A Bayesian hierarchical probit model was applied to estimate the DCR.[34] Within each treatment arm, the model allowed for borrowing information across the five marker groups to improve the accuracy for estimating DCRs. The DCRs of the four treatments in different marker groups were continuously updated as the trial progressed. Eligible patients were first equally randomized to the four treatment arms. Then, as the data became more mature, patients were adaptively randomized into one of the four treatment arms with the randomization probability being proportional to the updated DCR estimate for someone with their biomarker profile. If a treatment was found not to be promising in a certain marker group, assignment for the patient with that biomarker profile to the treatment will be suspended. Conversely, if a treatment was highly efficacious in a certain marker group, more patients with that biomarker profile were assigned to that treatment. This is an example of outcome-adaptive randomization where the ultimate goal is to have more patients assigned to the treatments deemed more efficacious based on their biomarker profiles and, at the end of the trial, identify all the efficacious treatment-biomarker combinations.[35]

The BATTLE-1 trial showed the feasibility of implementing an adaptive design in lung cancer and established the paradigm of requiring pre-treatment biopsy in relapsed NSCLC patients for molecular profiling to guide treatment (Fig. 1). Tam et al.[36] reported a high success rate (82.9%) using the image-guided percutaneous transthoracic core-needle biopsy for acquiring tissue for biomarker analysis. This trial led to the discoveries of potential predictive biomarkers in lung cancer.[37-40] One example was that Ihle et al.[37] found that patients who had either mutant KRAS-Gly12Cys or mutant KRAS-Gly12Val had worse PFS compared with patients who had other mutant KRAS proteins or wild-type KRAS.

The MATRIX trial is another example of a phase II Bayesian adaptive trial. In this trial, treatment is assigned based on a patient's molecular profile with no randomization. Response rate is the primary endpoint for most of the substudies in the trial and PFS is the primary endpoint for some substudies. Having a set of common primary endpoints allows the trial enough flexibility to address appropriate mechanism of effect across therapies. The trial opened in March 2015 with a plan to enroll 620 patients (NCT02664935).[41] It includes 18 molecular biomarker cohorts and seven treatments (eight drugs). Detailed rationale for biomarker and treatment selections is given by Middleton et al.[42] A unique design feature of the MATRIX trial is that different mechanisms of activation/deregulation of a pathway are treated as separate cohorts to allow assessment of response for each specific mechanism. This trial also includes a substudy where patients enrolled without an actionable mutation are offered an anti–programmed death ligand 1 (PD-L1) monoclonal antibody whose evidence of activity has been shown in patients with NSCLC.[43]

Adaptive Bayesian trial designs are more flexible than traditional trial designs. However, because of this flexibility, adaptive Bayesian trials require more careful planning to ensure the design is well thought out and to preserve the integrity of trial conduct. Another challenge with adaptive Bayesian designs is the lack of standard software for design implement. A collection of useful software for Bayesian designs from the BATTLE program is made available at the University of Texas MD Anderson Cancer Center software download site (https://biostatistics.mdanderson.org/SoftwareDownload/) and the software online site (https://biostatistics.mdanderson.org/SoftwareOnline/).

Tissue Agnostic or Molecularly Defined Rather Than Organ-Defined Trials

The discovery of common genetic aberrations across tumor types and the importance of genetic aberrations to therapeutic responses have now led to a shift in drug development strategy. Novel agents are now developed to target genetic aberrations across tumor types rather than targeting specific tissues/sites.[44] In May 2017, the FDA granted accelerated approval to pembrolizumab for microsatellite instability-high (MSI-H) or mismatch repair deficient tumors. This was the agency's first tissue/site-agnostic approval.

Basket trials aid in the design of tissue agnostic and molecularly targeted studies. These are mostly early POC trial designs that aim to identify a signal, which are subsequently followed by randomized phase II and phase III trials. A lot of the same concerns as expansion

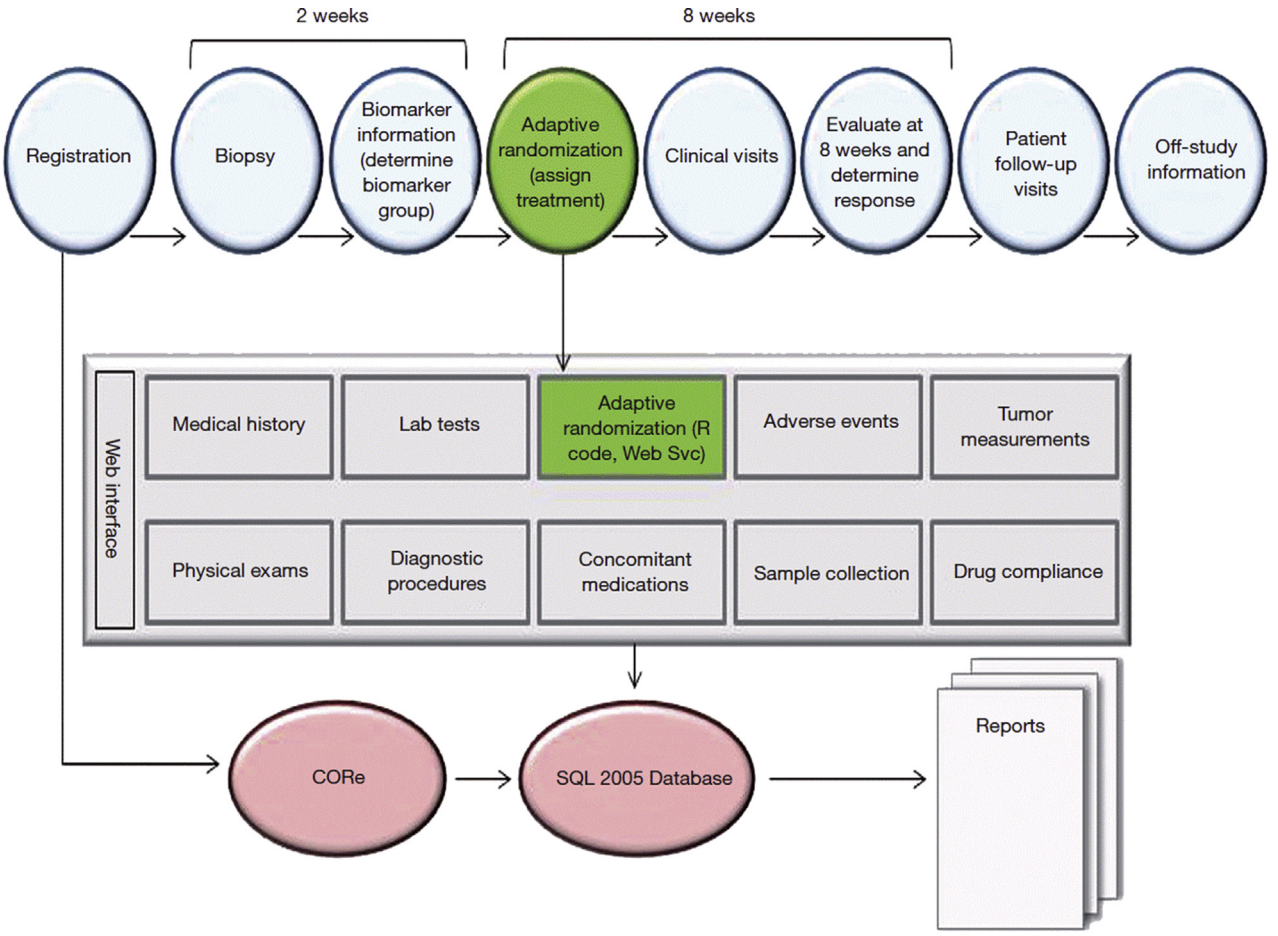

Figure 1. Schematic diagram of BATTLE-1 trial conduct via web-interfaced database application. Reprinted from Liu and Lee[31] with permission.

cohorts, discussed earlier, and accrual issues that will be expounded in later, also apply to these trials.

Basket Trial Design

Basket trial design is a novel biomarker-based design that includes patients with different histologic or tumor subgroups who carry the same molecular aberrations.[45,46] Each of these histologic/tumor subgroups, called a "basket," forms a substudy of the overall trial (Fig. 2). The substudies within a basket trial can have the same type of design or different designs or a combination of both. The goal of a basket trial design is to efficiently identify effective treatment targeting a particular molecular aberration which is associated with multiple tumor types. The logistical efficiency of a basket trial is achieved by the use of a single "master" protocol.[46] A "master protocol" is a platform document that governs the conduct of all substudies within a basket trial. It also contains the subprotocols for the substudies within the overall trial. Substudies can be added or removed from a master protocol during the life of the overall trial. This platform allows investigators the flexibility to respond to new discoveries either by adding new disease cohorts or by removing substudies that are shown not promising for future development.

The SCRX001-006 trial (NCT02709889) is an example of a basket trial which includes a cohort of lung cancer patients.[47] This is a phase 1/2, open-label study of Rova-T as second-line or later therapy for delta like canonical Notch ligand 3 (DLL3)–expressing advanced solid tumors. The study includes eight tumor cohorts: malignant melanoma, medullary thyroid cancer, glioblastoma, large-cell neuroendocrine carcinoma, neuroendocrine prostate cancer, high-grade gastroenteropancreatic neuroendocrine carcinoma, other neuroendocrine carcinoma, and other solid tumors. The primary endpoint for the phase I component is the maximum tolerated dose and the primary endpoint for dose expansion phase is overall response rate. The trial is currently recruiting patients with a total planned enrollment of 378 patients for both phases. Another example of ongoing basket trial that includes lung cancer is the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) (NCT02465060) which has expanded to 24 cohorts.[48]

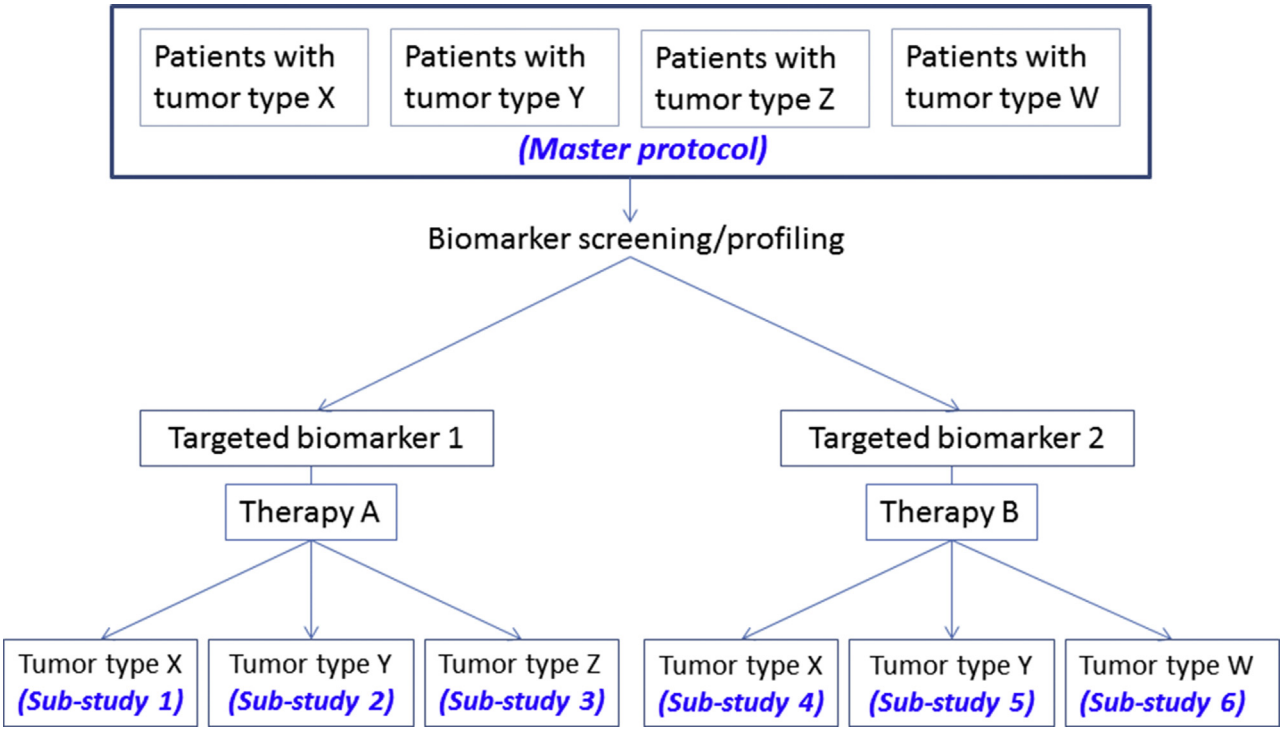

Figure 2. Schema of basket trial design.

Feasibility and complexity are major challenges with large-scale basket trials. For example, the numbers of screened patients that matched the criteria to be included in the some of the NCI-MATCH cohorts were lower than expected; therefore, slow accrual is a concern. From a statistical perspective, the efficiency of basket trials comes from pulling data across all tumor subgroups to estimate the treatment effect. However, this pooled approach only works well when response to the therapy is relatively homogeneous across all tumor subgroups. Heterogeneous responses across tumor subgroups may lead to potential bias and/or inflation of the false-positive rates. A new calibrated Bayesian hierarchical model has recently been proposed to better control the type I error rate in basket trials.[49]

Definitive Trials

The new era of targeted therapies not only influences the design of earlier phase trials, as discussed in above, but also impacts the designs of later phase confirmatory trials. Most therapeutic developments in NSCLC have focused on patients with advanced and metastatic disease or on the more common histology subtype of NSCLC such as adenocarcinoma. Development and acceptance of more innovative designs in recent years provide opportunities to expand therapeutic development to other underrepresented histologies or early stage of NSCLC. The Southwest Oncology Group (SWOG) Master Lung Protocol (Lung-MAP; SWOG S1400) (NCT02154490) and the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) (NCT02194738) are examples of such efforts. Both of these trials use the umbrella design, described below.[50-53]

Umbrella Trial Design

In an umbrella trial design, patients are first screened for and assigned to a specific biomarker subgroup (Fig. 3). Patients in each subgroup are then assigned to one of the therapies specifically targeting the biomarker they harbor.[45] Some umbrella trials allow inclusion of a subgroup of patients with no actionable biomarker. Each of these biomarker subgroups forms a substudy of the overall trial. Similar to basket trials, each overall umbrella trial is governed by a "master protocol" and the substudies within the overall trial can have the same and/or different designs. As a consequence, umbrella trials benefit from the same logistical efficiencies described for basket trials. Specifically, new substudies can be added in response newly discovered biomarkers or testing new therapies while completed substudies or those substudies that shown to be harmful or not promising for further development can be removed. Another advantage of umbrella trial design is that the effect of a new agent can be assessed in rare genetic subgroups by pooling across cohorts of patients that exhibit similar response to the therapy.

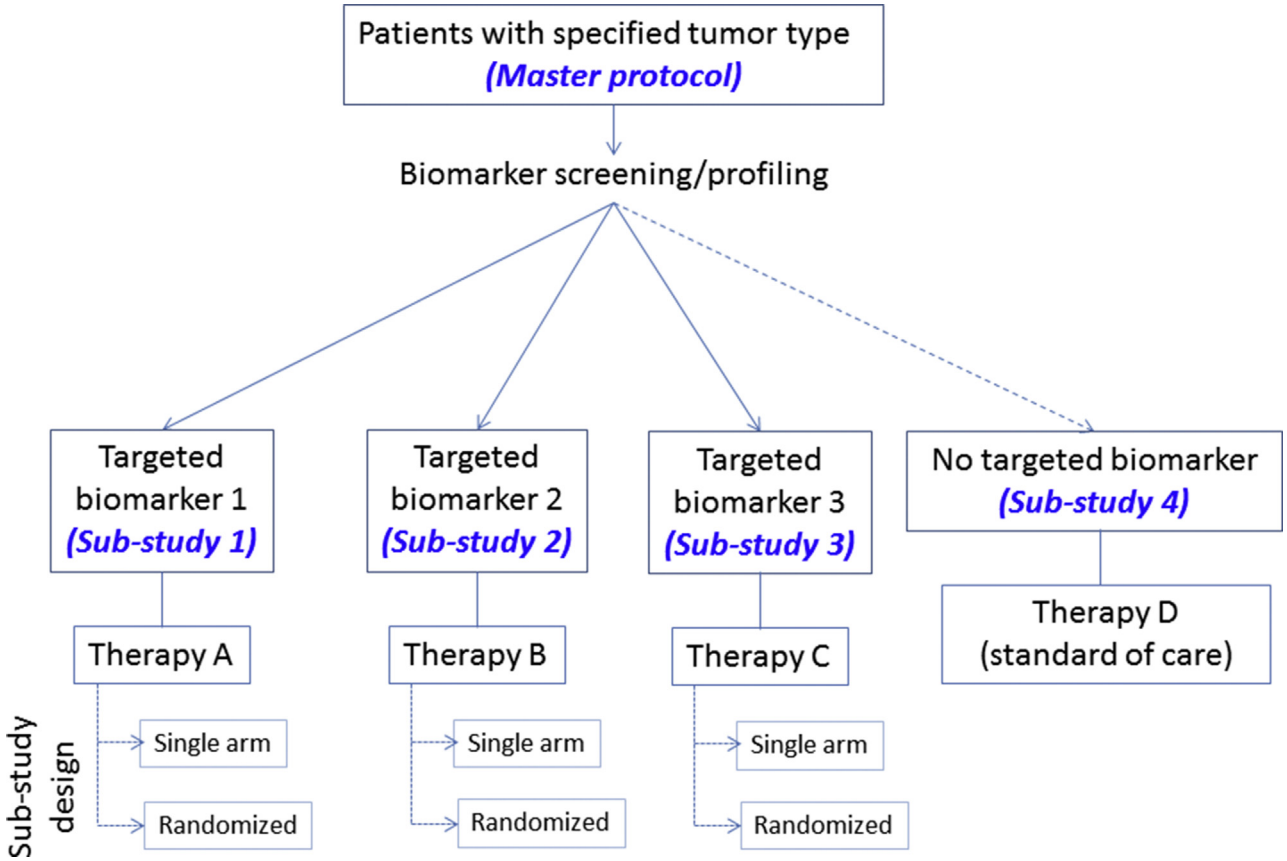

Figure 3. Schema of an umbrella trial design.

Phase II/III Design

The SWOG Lung-MAP is a biomarker-driven phase II/III umbrella trial designed to evaluate second-line treatments of metastatic squamous cell carcinoma (SCC).[50,51] This study was designed as an umbrella trial with five initial substudies. Each substudy was designed as a randomized phase II/III trial with docetaxel as the standard of care except for substudy E where erlotinib was the standard of care. Substudy A consists of a cohort of patients without matched mutations. Substudies B through E consist of patients with PI3KCA gene mutation; CCND1, D2 CDK4 amplification; FGFR gene amplification, mutation, or fusion; and MNNG HOS transforming gene (c-MET) mutations, respectively. A phase II/III design was used to shorten the drug development process. The phase II of the trial serves as an interim analysis evaluating the futility (lack of efficacy) of the experimental therapy. The primary endpoint for the phase II component is PFS (evaluated at 55 events). The primary endpoints for phase III component include OS and PFS (analysis occurred after 256 deaths).[54] The planned sample sizes range from 112 to 170 patients for the phase II and 302 to 400 for the phase III, including patients from the phase II.[54] A protocol amendment is currently underway to expand enrollment to patients with non–squamous cell lung cancer and to evaluate immunotherapy combinations.

Although the statistical designs for these studies have been refined and remain efficient, a major problem has been the lack of target validation before assigning patients with particular aberrations to specific agents. For example, at the time the Lung-MAP trial was developed, there were emerging data suggesting that PIK3CA mutations and FGFR fusions in NSCLC were not necessarily predictive of responses to available PI-3–kinase inhibitors and FGFR inhibitors, respectively. Similarly, there were no data indicating that CCND1 and CDK4 mutations or amplification were predictive of response to cyclin dependent kinase 4/6 (CDK4/6) inhibitors. Future investigators are urged to seek initial data of the efficacy of targeted agents that can then be validated in umbrella designs. Such an approach will yield more positive results that justify the resources and effort put in the design and conduct of these complex studies.

Phase III Design

The ALCHEMIST trial is another example of an umbrella confirmatory trial in NSCLC.[52,53] This is one of the few large studies focusing on early-stage high-risk NSCLC. The ALCHEMIST trial is a National Clinical Trials

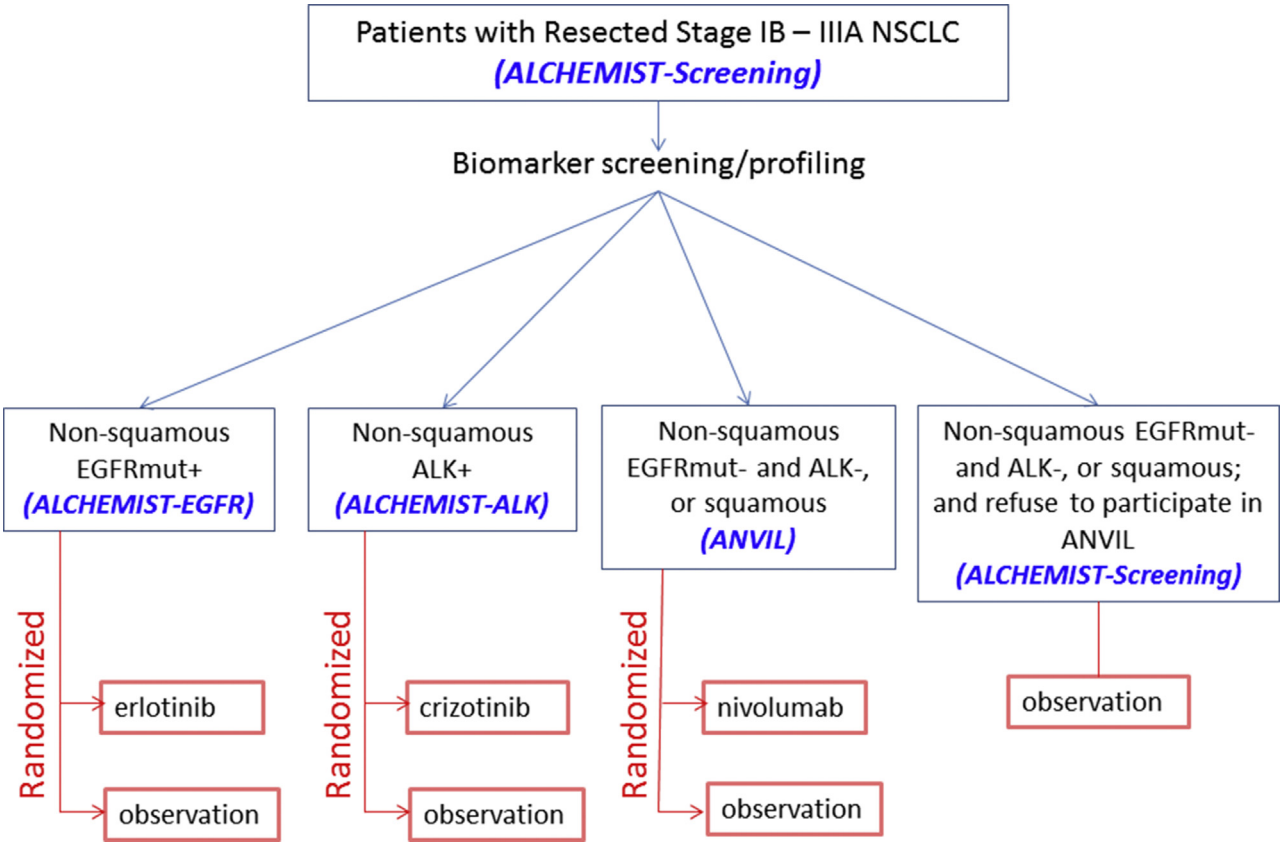

Figure 4. Schema of ALCHEMIST trial.

Network (NCTN) initiative that originally consisted of three integrated protocols including ALCHEMIST SCREENING, ALCHEMIST-EGFR (NCT02193282), and ALCHEMIST-ALK (NCT02201992) which work across NCTN groups.[53,55,56] As of May 2, 2016, the ALCHEMIST PD-L1 (NCT02595944) substudy was added to the initiative and eligibility was expanded to include patients with early stage squamous cell lung cancer.[57] All patients in the ALCHEMIST screening trial must be consented to this study to be screened for EGFR, ALK, and PD-L1 before being enrolled into the therapeutic trial corresponding to the biomarker they harbor (Fig. 4).[53] Non–squamous cell patients with EGFR mutations or ALK rearrangements who are eligible are enrolled and treated under the ALCHEMIST-EGFR or the ALCHEMIST-ALK protocol, respectively, as described below.[55,56] Non–squamous cell patients with neither EGFR mutations nor ALK rearrangements and squamous cell patients are screened for PD-L1 expression and are offered participation in the Adjuvant Nivolumab in Resected Lung Cancers (ANVIL) substudy, regardless of their PD-L1 status.[57] Patients not eligible for one of the adjuvant treatment trials under the ALCHEMIST umbrella or those who choose not to enroll on the adjuvant therapy trials are followed for recurrence and survival for 5 years on the ALCHEMIST SCREENING protocol.[53] It is estimated that more than 8000 patients must be enrolled onto ALCHEMIST SCREENING to sufficiently meet the accrual requirements for the therapeutics trial.

The ALCHEMIST-EGFR (A081105) is a randomized phase III trial. Patients with completely resected stage IB–IIIA nonsquamous NSCLC with centrally confirmed EGFR mutations are randomized to receive either erlotinib or placebo for 2 years.[55] This substudy was originally designed as a double-blind placebo controlled trial. As of June 15, 2017, the study was modified to be an open-label trial with the placebo arm becoming an observational arm.[55] The primary endpoint for ALCHEMIST-EGFR is OS with an estimated sample size of 410 patients with the final analysis planned after 183 events have occurred. One interim analysis for futility was planned for this trial.

The ALCHEMIST-ALK (E4512) is also a randomized open-label phase III trial in patients with the same disease and stage as the other ALCHEMIST trials but with ALK rearrangements.[56] In this trial, patients are randomized to receive crizotinib for 2 years or to the observation arm. The primary endpoint for this substudy is OS. The estimated samples size for ALCHEMIST-ALK is 360 patients with the final analysis planned after164 events have occurred. Ten interim analyses for efficacy were planned for this study.

The third therapeutic protocol for the ALCHEMIST trial is the ANVIL substudy (EA5142).[57] This is a randomized trial where patients, regardless of their PD-L1 expression status, are randomized at a 1:1 ratio to either the nivolumab arm or the observation arm. The co-primary endpoints for this substudy are OS and disease-free survival (DFS) where the events for DFS include primary tumor recurrence, new lung lesion, or death due to any cause. The total expected sample size is 714 patients to achieve 293 events for the OS endpoint and 315 events for DFS.[46] These trials set the stage and precedence for large national coordinated trials. These coordinated efforts provide an efficient platform for trials targeting patients with histology and early disease stage that may be logistically prohibitive in a more traditional clinical trial paradigm.

Although at first sight the designs of these definitive trials seem similar to typical phase II/III (Lung-MAP) and phase III (ALCHEMIST) trials, planning these trials requires well-coordinated efforts among members of a multidisciplinary research team. This can be resource- and time-intensive, making the scientific question likely irrelevant by the time the trial is ready for patient enrollment. ALCHEMIST ALK and EGFR trials include crizotinib and erlotinib as the experimental agent. However, more recent data in the area of ALK inhibitor support alectinib with superior efficacy and safety profile than crizotinib.[58] Similarly, more recent data have shown superior efficacy of osimertinib compared to standard EGFR-TKIs (gefitinib or erlotinib) as first-line treatment of EGFR-mutated advanced NSCLC.[59] Another important decision for the screening component of these trials is whether centralized screening is needed. If it is needed, the logistics of sample collection, shipping, and communications of results must be clearly specified and communicated with sites. If centralized screening is not needed, the quality and the consistency of assay across sites need to be reasonably ascertained. Inclusion of a well thought-out plan in the master protocol or the screening protocol will ensure a smooth screening process. Harmonization of data collection is a must to successfully carry out these large scale trials.

A major challenge to keep pace with the rapid advancement in science is to ensure rapid accrual to these trials so that the trial can remain relevant. A potential solution to accrual challenges is to encourage international partnership. For example, there is the higher frequency of EGFR mutations in NSCLC patients in most Asian countries compared to NSCLC patients in the United States. Willingness to share knowledge and infrastructure along with an open line of communications among stake holders across countries is essential to the success of such large-scale global trials. However, international trials require careful design and logistical planning to account for outcome heterogeneities across countries. Heterogeneities can come from biological and patient-related factors, differences in standard of care, reimbursement models, or drug distributions (for example, use of generics).

Conclusions and Future Directions

The current era of targeted therapy has brought a shift to the design and conduct of clinical trials in oncology. Tremendous progress has been made in the last decade in the identification of genetic mutations associated with various histologic subtypes of NSCLC. Lung cancer has evolved from being treated as a single disease to a disease with various histologic subtypes to the modern classification by histology and molecular mutation. This new knowledge has led to treatment options that target specific genetic aberrations. With patients classified into ever smaller subgroups and treatments customized to their specific mutation, traditional drug development paradigm using the standard phase I, phase II, and phase III is no longer feasible.

Bayesian adaptive designs provide the flexibility needed to continually incorporate new knowledge into an ongoing trial to keep the trials relevant to current treatment landscape which can shorten the drug development process. However, as with any design, there are disadvantages to adaptive design, especially with outcome-adaptive randomization trials.[60] The results of outcome-adaptive trials can be biased due to the imbalance in prognostic factors across arms early in the trial. The unequal sample size across arm can lead to inefficiency with trial design and there is a potential to have more patients on a worse treatment arm on occasions.[60] Transparency in the design and randomization process must be prioritized to minimize these drawbacks when designing outcome-adaptive trials.

Umbrella and basket trial designs allow simultaneous accrual of multiple cohorts and the use of a master protocol streamlines the protocol development process by cutting the time that would otherwise be required to develop separate protocols for the different substudies. The seamless addition of new substudies to the Lung-MAP and the ALCHEMIST trials illustrates the benefit of the master protocol design. Of course, such efficiency comes with operational challenges. The size of umbrella and basket trials can be large and the trial duration can be long. The control arm can become obsolete with changes in current standard of care during the life of the master protocol. International partnerships are critical.

Modern clinical trials need to be efficient and flexible to keep up with the fast pace of biomarker discovery and therapy development. For example, as the field moves forward, combination therapy has become increasingly common. The choice of primary endpoint for a

combination should consider the targeted biomarkers and the mechanism of action of the therapeutic agents. Considerations regarding the efficacy and the toxicity profile of the combination partners as monotherapy are also important.[61] Other considerations for future trials include therapies that target biomarkers which continuously adapt to treatment and strategies to address resistance to therapy (primary, adaptive, or acquired). For biomarkers that continuously adapt depending on response, sequential screening of biomarkers can be built into the trial design to allow for different treatments in response to changes in the biomarkers. One example of such trial design is the SWOG S0500 trial in metastatic breast cancer.[62] Regarding therapy resistance, multiple tumor-intrinsic and -extrinsic factors may contribute to therapy resistance.[63] As more knowledge about the mechanism of resistance becomes available, statistical designs should take these factors into consideration. All of these new discoveries continually impact trial design and conduct from the discovery phase to the confirmatory phase.

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