# National Cancer Institute's Precision Medicine Initiatives for the New National Clinical Trials Network

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## OVERVIEW

**The promise of precision medicine will only be fully realized if the research community can adapt its clinical trials methodology to study molecularly characterized tumors instead of the traditional histologic classification. Such trials will depend on adequate tissue collection, availability of quality controlled, high throughput molecular assays, and the ability to screen large numbers of tumors to find those with the desired molecular alterations. The National Cancer Institute's (NCI) new National Clinical Trials Network (NCTN) is well positioned to conduct such trials. The NCTN has the ability to seamlessly perform ethics review, register patients, manage data, and deliver investigational drugs across its many sites including both in cities and rural communities, academic centers, and private practices. The initial set of trials will focus on different questions: (1) Exceptional Responders Initiative—why do a minority of patients with solid tumors or lymphoma respond very well to some drugs even if the majority do not?; (2) NCI MATCH trial—can molecular markers predict response to targeted therapies in patients with advanced cancer resistant to standard treatment?; (3) ALCHEMIST trial—will targeted *epidermal growth factor receptor* (*EGFR*) and *anaplastic lymphoma kinase* (*ALK*) inhibitors improve survival for adenocarcinoma of the lung in the adjuvant setting?; and (4) Lung Cancer Master Protocol trial for advanced squamous cell lung cancer—is there an advantage to developing drugs for small subsets of molecularly characterized tumors in a single, multiarm trial design? These studies will hopefully spawn a new era of treatment trials that will carefully select the tumors that may respond best to investigational therapy.**



In 2014, the National Cancer Institute will launch a series of clinical studies with the overall aim being to use more precise diagnostics to allow selection of patients for therapies that target particular molecular abnormalities.[1,2,3] These initiatives will take advantage of next-generation sequencing (NGS) technologies to look for changes in tumor DNA, and some will go further using the high throughput technologies to search for changes in tumor RNA, methylation, and other "omics." Although similar efforts are currently ongoing at several NCI-supported cancer centers, this set of studies intends to introduce these new technologies on a broader, national scale. By making these studies accessible via NCI's new NCTN, patients seen at centers large and small, in cities and in rural communities, will have access to these new approaches to cancer diagnosis and therapy. The general goals, eligibility criteria, study designs, and planned outcomes analyses for each study are described below. Physicians wishing to get further information regarding these trials can visit the NCI website (cancer.gov), and those wishing to enroll patients, when the studies open, visit the Cancer Trials Support Unit website at ctsu.org.

## EXCEPTIONAL RESPONDERS INITIATIVE

The origin of this study derives from the observation of finding the occasional "exceptional response" (objective response; i.e., durable) in otherwise negative phase II clinical trials of new agents, or with agents used in the clinic.[4,5] It is not uncommon to find in such studies, or sometimes in clinical practice, a few patients whose tumors seem to respond to an agent that does not exhibit any sign of benefit in the majority of patients treated for a specific cancer diagnosis. This study (Fig. 1) will collect tumor (and normal tissue, if available) from patients who participated in previously performed phase II studies across the country, irrespective of study sponsorship, who had either a complete response or a long-lasting partial response to an agent(s) whose overall response

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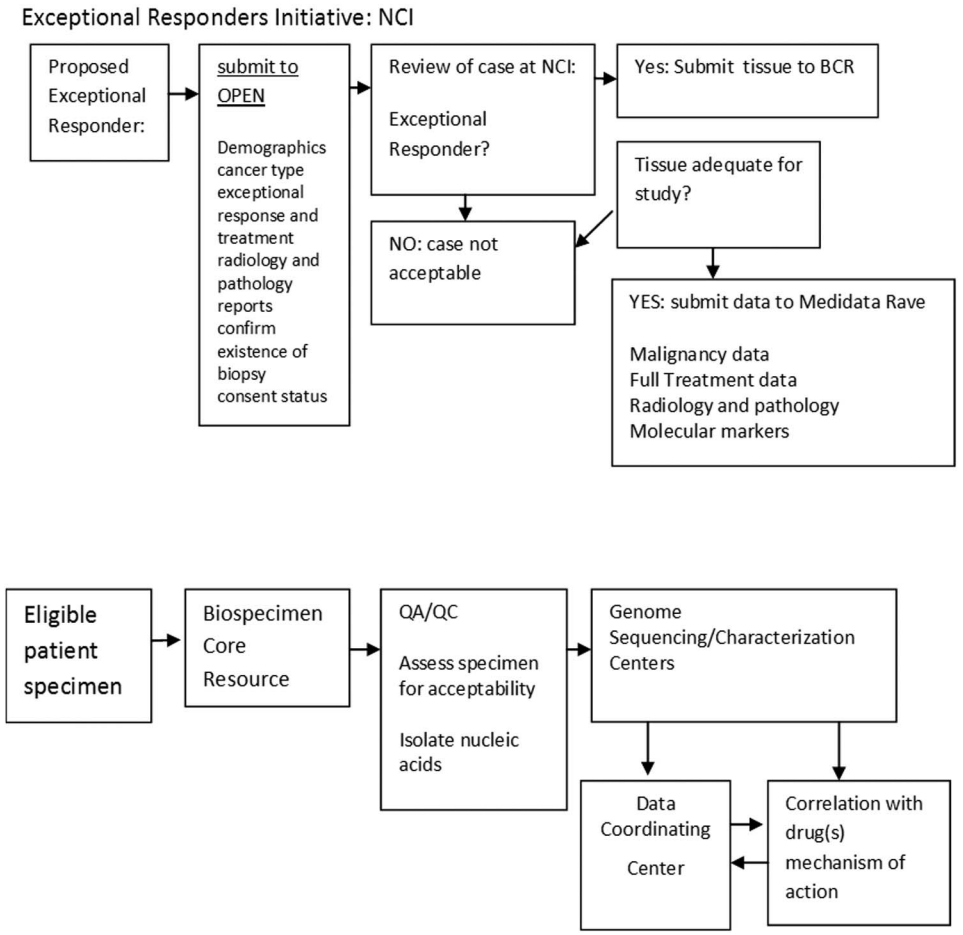


**FIG 1. Patients who are felt to have durable partial response or complete response to an agent in a study or disease setting in which such responses are unexpected are eligible for this trial. Physicians will have to submit the clinical data and scans to verify their response, and if confirmed, will be asked to submit a tissue specimen for genomic analysis.**



rate was less than 10%. Exceptional responders from U.S. Food and Drug Administration (FDA) approved agents will also be sought, if the regimen was not expected to lead to complete response or durable partial response in more than 10% of patients so treated. The response will be confirmed by a central review of tumor measurements and scans. Once the response is confirmed, adequate tumor tissue must be available for DNA whole-exome sequencing. If sufficient nucleic acids are available, RNAseq and whole-genome sequencing will be performed. It is desirable that tumor tissue be accessed as close to the time of the treatment with the new agent as possible, but it is recognized, and is acceptable, that in many cases there will only be tissue available from initial diagnosis or another procedure which may predate the patient's exposure to the agent associated with the exceptional response. It is assumed that many of these samples will be small as they will likely be obtained by core or needle biopsies, and thus may not be amenable to more than whole-exome sequencing. The overall aim is to find a molecular explanation for the exceptional responder phenotype by demonstrating via genetic sequencing a susceptible target for the therapeutic agent that caused the tumor response. This phenotype to genotype approach will hopefully lay the groundwork for discovery of small subsets of patients with a given tumor who can have major responses to carefully selected, targeted therapies.

## KEY POINTS

- NCI will launch a series of novel, molecularly guided trials in 2014.
- The Exceptional Responders Initiative will study patients who have had a response to a targeted agent(s) in a situation in which most patients do not usually have complete or durable responses.
- NCI MATCH will genotype patients' tumors to find a molecular alteration that can be paired with a targeted agent.
- ALCHEMIST will determine if *EGFR* or *ALK* inhibitors can improve survival for patients with resectable lung adenocarcinoma.
- Master Protocol will treat advanced lung squamous cell tumors with novel agents in a single trial directed by molecular biomarkers.

## NCI MATCH

NCI MATCH is a prospective clinical trial that will require a tumor biopsy before enrollment for targeted NGS supplemented by immunohistochemical or fluorescence in situ assays to assign treatment hypothesized to target selected molecular abnormalities. Eligible patients must be older than age 18, have good performance status and adequate organ function, and must have a solid tumor or lymphoma that has progressed on at least one standard therapy for metastatic or advanced disease. Patients must be willing and able to undergo a rebiopsy of their tumor before enrolling on the study. The biopsy tissue will be subjected to NGS sequencing assay that includes approximately 200 genes, supplemented by necessary immunohistochemical and/or fluorescence in situ hybridization assays, performed in one of four Clinical Laboratory Improvement Amendments-certified laboratories. These genes have been carefully selected for their alignment with a targeted agent that has demonstrated activity in a human tumor carrying this genetic abnormality. This trial will evaluate FDA approved agents outside of their approved indication as well as agents not yet approved but which have demonstrated evidence of activity against a known target in a specific human tumor. If an agent is known to be inactive in a certain histology, that is, *BRAF* inhibitors targeting V600e in colon cancer, that histology will not be evaluated for that agent. This trial will also not compete with current open trials sponsored by NCI or their pharmaceutical partners. However, if a patient with a sarcoma has a *BRAF* V600E mutation, they could receive a *BRAF* inhibitor in this study. Likewise, if a patient with melanoma has HER2 amplification, they could be treated with a HER2-targeted agent. There will be about 20 to 25 targeted agents available to treat patients in this study according to the molecular findings on their biopsy. The decision about which agent to use based on the molecular findings of the biopsy will be rule driven in the protocol, and will not be based on decisions by a tumor board. In the event of more than one mutation or abnormality in a patient's tumor, decision rules will be developed to select which genetic abnormality will predominate.

The study design is an umbrella protocol with multiple molecularly-based phase II studies (arms) and is depicted in Fig 2. Eligible patients will be assigned to a specific study drug based on the molecular abnormality and followed for response and progression-free survival (PFS). Each arm will have approximately 30 evaluable patients, all meeting the molecular eligibility criteria but having a mixture of malignancies. Once the tumor progresses, patients will be removed from the study. They and their doctor will receive the report of the molecular analyses performed in the Clinical Laboratory Improvement Amendments laboratory containing a list of the genes that have been tested as well as the findings, in the hope that the information may be useful for future treatment choices. Additionally, any patient with a progressive tumor is eligible for re-biopsy and may receive a second

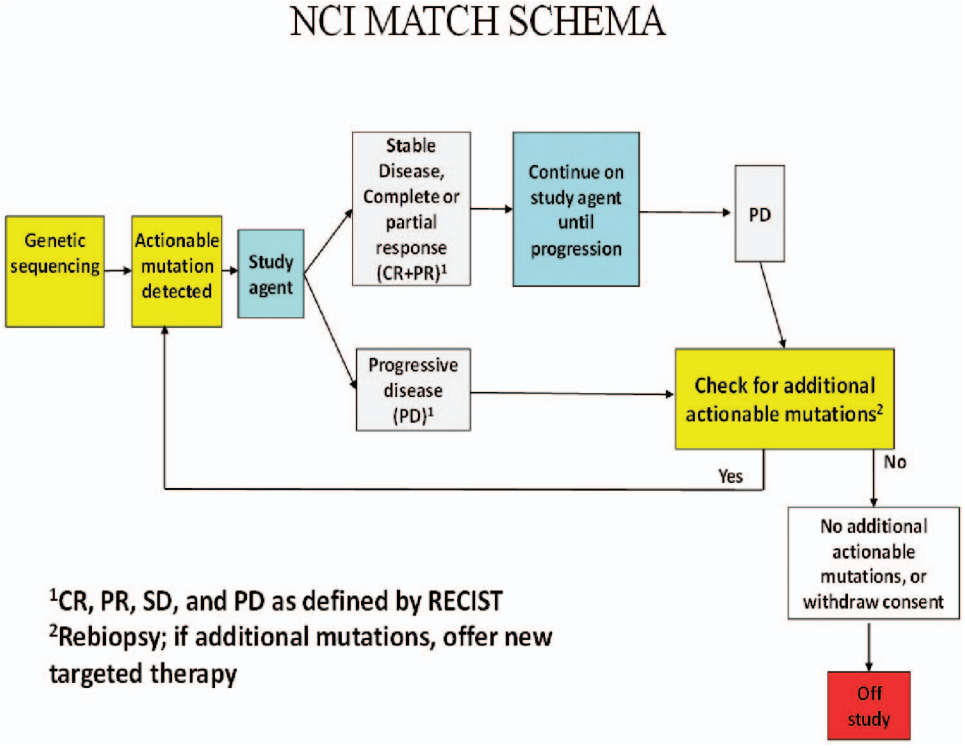


**FIG 2. NCI MATCH study design will target molecule abnormalities directed by NGS and will "match" patients with appropriate targeted agents. Patients with responsive disease remain in the study until progression, provided that toxicity is acceptable. Once progression occurs, the study drug is stopped, but the patient can opt for a repeat biopsy to detect additional changes that might allow another study drug to be offered.**

targeted agent should their tumor demonstrate an abnormality aligned with an available study drug. The NCI MATCH trial has the goal of finding signals of activity with targeted agents in a wide variety of histologies. If activity is found for targeted agents in this study, then additional follow-up phase II studies are likely to be needed to evaluate the agent(s) in a larger number of patients with the both the precise molecular abnormality and the same histology to determine the ultimate value of the targeted agent.

The NCI MATCH study will be open to all members of the four NCTN Adult Groups. ECOG-ACRIN Cancer Research Group will conduct the study with NCI, and it will be available via the Cancer Trials Support Unit. It is anticipated that approximately 3,000 molecular profiles will be conducted in the hopes to find about 1,000 patients with tumors with molecular abnormalities for which a study drug would be indicated. NCI will support the costs of the tumor biopsy as well as the costs of the genetic sequencing. It is estimated that the study duration will be 3 to 4 years.

## ALCHEMIST TRIAL

This clinical trial is focused on the adjuvant treatment of early-stage adenocarcinoma of the lung. Agents targeted against the *EGFR* and the *ALK-echinoderm microtubule-associated protein-like 4* fusion gene result in durable responses and an improvement in PFS in patients with advanced lung adenocarcinoma and the appropriate mutation. This study (Fig. 3) will examine if adding erlotinib or crizotinib to standard adjuvant therapy (if any) in patients with resectable, early-stage lung cancer (stage 1B to 3A) whose tumors have the pathognomonic molecular changes will result in improved survival. Because *EGFR* mutation and the *ALK* fusion occur in only 15% and 5% of early-stage lung cancer, respectively, it is estimated that it will be necessary to screen about 8,000 patients to have adequate patients in whom to test the role of erlotinib and crizotinib. (Fig. 3). Of all the patients screened, nearly 90%, or about 7,000 patients, will not have the required abnormalities to enter into the randomized clinical trials. Unfortunately, in a large percentage of these patients, perhaps half, the disease is destined to relapse. This study will enter these patients into a registry for long-term follow-up. All patients will be evaluated with an epidemiologic questionnaire and will have tumor samples from their surgical resection sent for whole-exome sequencing and other "omic" research tests. These patients will be followed until relapse, and every effort will be made to obtain another tumor sample at relapse to evaluate the natural genomic history of these tumors.

Figure 3 explains how eligible patients will initially be screened in a common umbrella study. *EGFR* mutations will be assessed using a polymerase chain reaction-based assay and *ALK* fusion will be assessed using the FDA approved break-apart fluorescence in situ assays assay. Patients whose tumors exhibit activating *EGFR* mutations will be randomly assigned to receive erlotinib or to not follow standard chemotherapy and, similarly, patients whose tumors exhibit *ALK* fusion will be randomly assigned to crizotinib or to not follow standard chemotherapy. Although there is reason to be hopeful that these targeted therapies will improve outcomes, it is unclear exactly how much they will add to chemotherapy in these early-stage disease or whether they will result in improvements in patients with the smallest tumors who already have the best outcomes. Only an appropriately sized, randomized trial of this type can answer this question definitively.

## NCI MASTER PROTOCOL FOR SECOND-LINE TREATMENT OF SQUAMOUS LUNG CANCER

This clinical trial is attempting a novel approach to drug development and regulatory approval in the setting of advanced squamous cell carcinoma of the lung. Patients whose tumor has progressed after front-line therapy for advanced disease will have their treatment selected based on molecular profiling results of their tumor from an NGS panel of approximately 250 selected genes. Tumor specimens for profiling can come from a sample derived at diagnosis or at any other point during care. The molecular profiling will be performed at no charge to patients, and patients will be able to obtain their test results if there is progression of their tumor after having received study treatment.

Patients with abnormalities in either the phosphoinositide 3-kinase, fibroblast growth factor receptor, *EGFR* or Ras pathways will each be randomly assigned to either an agent targeting the abnormal pathway or to standard second-line chemotherapy (docetaxel or gemcitabine) as shown in Fig. 4. If the patient's tumor profile does not show an abnormality in one of these pathways, they will be randomly assigned to either an immunotherapeutic approach using anti-programmed cell death 1 ligand 1 or standard chemotherapy (docetaxel or gemcitabine).

The study design will initially have five study strata involving 10 treatment arms. Each stratum consists of a phase II/3 trial design, which consists of a phase II endpoint of PFS that will be evaluated after 55 PFS events have occurred in that stratum. If the experimental agent is not superior to the standard chemotherapy by at least 40%, then the agent will be stopped. If it is superior, the study will continue to enroll a maximum of 300 to 400 patients. The primary endpoint of the phase III study is also PFS but with some important caveats. In order for the experimental agent to be deemed an improvement over standard therapy, a hazard ratio of approximately 1.75 for PFS must be observed with no decrement in overall survival for the experimental arm. Additionally, an absolute benefit of at least 2.25 months in median PFS must be observed for head-to-head comparisons of experimental agents versus standard chemotherapy. In arms where experimental agents are added to standard chemotherapy and compared with chemotherapy alone, the absolute benefit in median PFS should not be less than 2.5 months.

In view of the relative rarity of these genetic changes, this approach represents an efficient way to develop new agents from different companies in the advanced cancer setting by

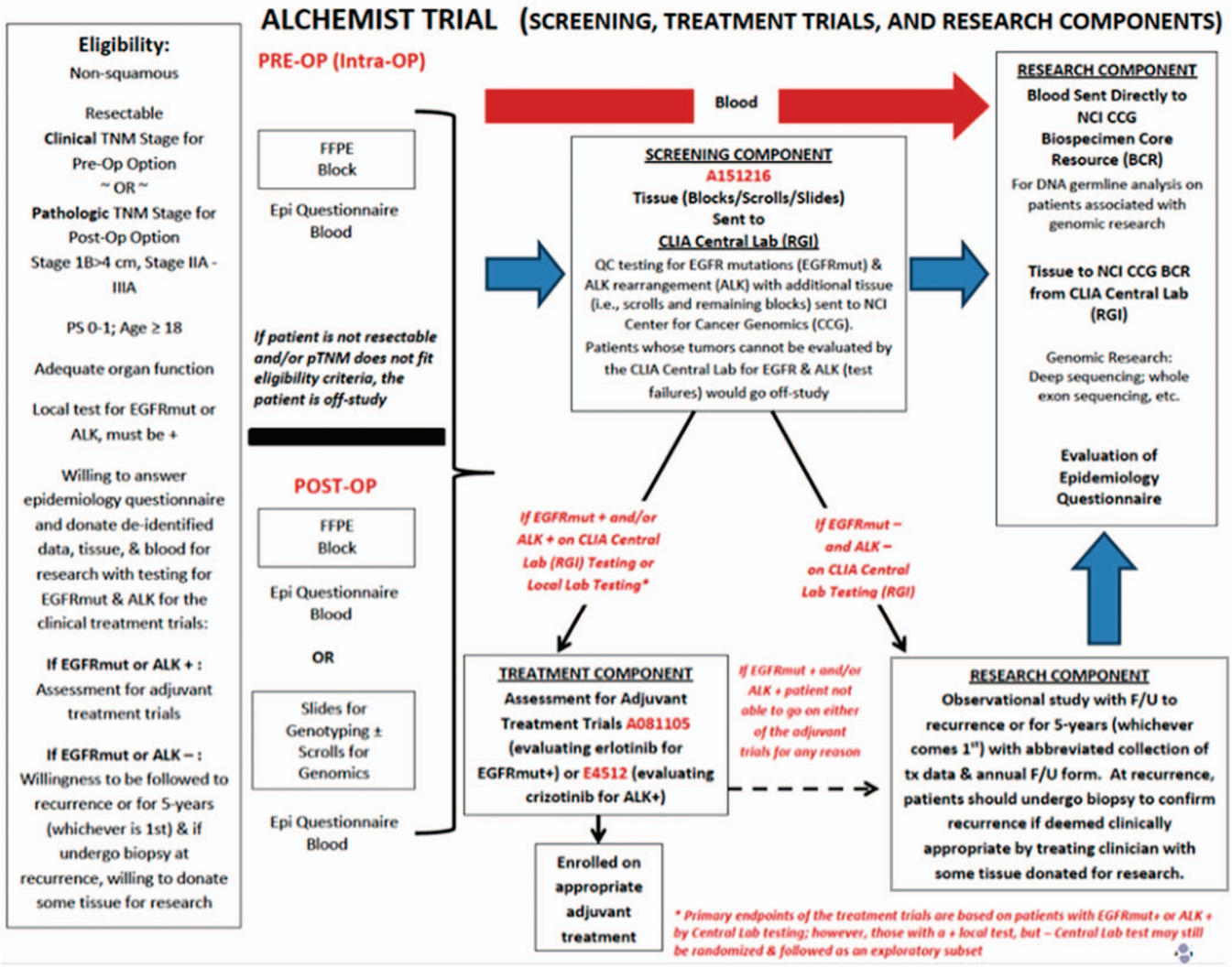


**FIG 3. The ALCHEMIST trial will study patients with resectable adenocarcinoma of the lung and screen their tumors for *EGRF* mutations and *ALK* fusion alterations. If detected, these patients will be eligible for separate adjuvant studies comparing the addition of erlotinib (for *EGFR* mutation) or crizotinib (for *ALK* fusions) in combination with standard treatment versus standard treatment alone without these targeted agents. For patients without these mutations, they will be enrolled in a registry study and have their tumors undergo whole-exome sequencing. If they should relapse, every attempt will be made to re-sequence their tumor DNA at that time to determine the natural genomic history of these cancers.**

sharing the expense of the initial screening. The common screening platform effectively allows patients an opportunity to receive a treatment appropriate for their specific tumor and leverages NCI's NCTN to provide accessibility across the United States. SWOG is conducting this study for the NCTN and it will be available via the Cancer Trials Support Unit. Collaboration between the NCI, SWOG, the Foundation for the National Institutes of Health, the Friends of Cancer Research, and multiple company partners has enabled the unique framework of this trial design. In addition, the FDA has contributed regulatory advice about how best to design and conduct this unique trial.

These four studies exemplify how the new NCTN is well positioned to conduct large-scale studies that require genetic screening to detect molecular abnormalities that may be infrequent even in common tumors. Effective utilization of new targeted agents will require that patients' tumors be screened to find those that manifest the molecular change that renders it susceptible to the agent being tested. The NCTN's single registration pathway, uniform informatics system for managing data and its centralized ethics review board have prepared the network groups to tackle the challenges of finding therapies for carefully diagnosed subsets of patients.

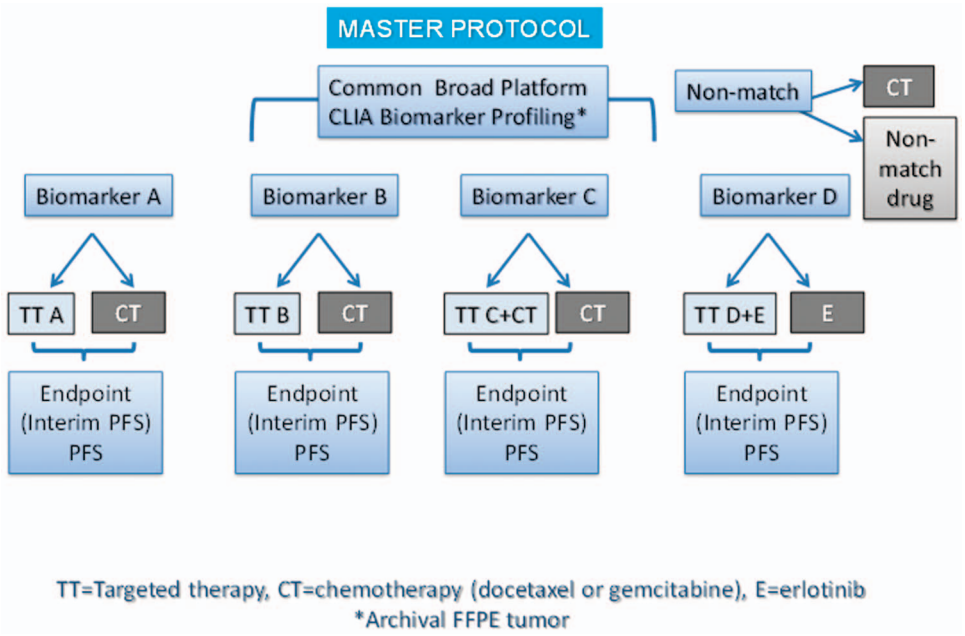


**FIG 4. The Lung Cancer Master Protocol trial will treat patients with advanced squamous cell lung carcinoma according to the molecular abnormality found via a tailored next-generation sequencing panel. Patients who have a study drug paired with their tumor's molecular alteration (biomarker) will be randomly assigned to the study drug or standard chemotherapy. In some cases (examples A and B), the study drug will be compared directly with the chemotherapy while, in other cases (examples C and D), the study drug will be added to the chemotherapy versus chemotherapy alone. Should the patient's tumor not possess a molecular alteration that pairs with a study drug, the patients will be assigned to a "nonmatch" arm and will be randomly assigned to an immunotherapy agent versus standard chemotherapy.**

## Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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