

ISSUE BRIEF

Conference on Clinical
Cancer Research
November 2012

Design of a Disease-Specific Master Protocol

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center

Eric Rubin, Vice President, Clinical Research Oncology, Merck

Lisa LaVange, Director, Office of Biostatistics, CDER, FDA

Jeffrey Abrams, Associate Director, Cancer Therapy Evaluation Program, NCI

David Wholley, Director, The Biomarkers Consortium, FNIH

Karen Arscott, Patient Advocate, Lung Cancer Alliance

Shakuntala Malik, Medical Officer, FDA

Introduction

Despite several impressive therapeutic advances in recent years, cancer remains the second-leading cause of death in the United States, and effective new therapies are still desperately needed. Developing a potential therapy from the initial discovery stage through clinical testing and regulatory review is a complicated, expensive, and often inefficient process that can take up to 15 years. Included among the many challenges of drug development are the difficulties in recruiting cancer patients to clinical trials, the extensive bureaucratic processes required to initiate any clinical trial, and lengthy regulatory review. Modernizing this process with innovative approaches and new clinical trial designs is of high importance.

In standard drug development, each potential new therapy for a specific cancer is typically tested independently from other therapies seeking to treat the same condition. For every new trial, the protocol must be reviewed by a number of oversight entities that assess whether the proposed trial is feasible as well as ethically and scientifically sound. A recent analysis found that the process of activating a new phase III cooperative group clinical trial requires an average of 36 administrative or regulatory approvals and averages more than 2 years (1). Once a clinical trial is initiated, it must accrue enough patients for the results to be statistically valid. With only approximately 4% of adult cancer patients enrolled in cancer clinical trials, the inability to meet accrual goals is a frequent factor causing trials to close, wasting time, money, and limited patient resources (2). Compounding low accrual rates is the fact that many new therapies are molecularly targeted against specific oncogenic driver mutations that may be present in only a fraction of the patient population. Although the advent of targeted therapies holds great promise for improved efficacy, this also means that many patients may need to be screened before enough patients harboring the necessary mutation are available for the trial to be completed.

In order to address the expense and inefficiencies of the current drug development and in hopes to identify promising compounds in selected populations, stakeholders began to develop and test innovative approaches for clinical trials. Two adaptive Phase II screening trials, BATTLE (**B**iomarker-integrated **A**pproaches of **T**argeted **T**herapy for **L**ung **C**ancer **E**limination) and I-SPY 2 TRIAL (**I**nvestigation of **S**erial **S**tudies to **P**redict **Y**our **T**herapeutic **R**esponse with **I**maging **A**nd **m**o**L**ecular **A**nalysis **2**), used adaptive strategies combined with biomarker testing to increase trial efficiency and improve future phase III clinical trial designs for successful agents (3, 4). BATTLE was conducted in patients with heavily pretreated refractory non-small cell lung cancer (NSCLC). Based on testing of a mandated fresh core biopsy, BATTLE randomized patients to four different agents based on marker status of 11 biomarkers, and the results were used to design two new BATTLE trials. I-SPY 2, which investigates neoadjuvant treatment of new drugs added to traditional chemotherapy in women with locally advanced breast cancer

(3), is designed to test multiple novel drugs and biomarkers over a five-year timeframe. The trial may test up to five drugs simultaneously, and add new drugs as existing drugs complete testing. This design is enabled by a Master-IND held by the Foundation for the National Institutes of Health (FNIH), which eliminates the need for a new protocol each time an agent is added, allowing drugs and biomarkers to be added and removed over time, without needing to stop the study to write a new protocol and wait for approval. The successful implementation of these two randomized screening trials (and completion of BATTLE) provides examples of how multiple experimental agents can be tested within the same umbrella trial to make drug development more efficient.

Expanding on the success of these Phase II screening trials, we propose another alternative to traditional trial design. This development strategy is a master protocol for a Phase III registration trial in which multiple new therapies are tested simultaneously in a specific disease setting. However, this proposed trial would not be a Phase II adaptive screening trial like I-SPY 2 and BATTLE, but rather would be a multi-arm, multi-marker/drug Phase III trial designed to allow FDA approval of new therapeutics, along with matching companion diagnostics when applicable. Unlike the adaptive screening trials, where unknown associations between marker and drug are analyzed, screening in the Master Protocol Multi-drug Registration Trial is specifically for appropriate treatment-arm assignment and validation of clinical utility. Each biomarker included in the Master Protocol Multi-drug Registration Trial would have a corresponding treatment; assignment to that treatment would be based on results of a validated diagnostic assay. Here we lay out a conceptual approach to a nation-wide clinical registration trial with the ability to screen patients upon enrollment and randomize them to an arm of the trial based on the results of screening diagnostic tests.

Benefits to Master Protocol

There are multiple advantages to a multi-armed registration study, compared to the traditional alternative of multiple 2-arm registration studies. First, for drugs that have shown promise in a biomarker-selected patient population, grouping these studies under a single trial, with a common control (standard-of-care) arm reduces the overall screen failure rate. For example, assuming a prevalence of 20% for biomarkers A, B, C, D in a given histologic cancer type (with no overlap among each subpopulation), and a need for 200 biomarker positive patients each on an experimental arm and the treatment-control arm, 8000 patients would need to be screened in the case of 4 separate randomized studies, whereas only 2163 would need to be screened in the case of a single 5-arm study with 4 experimental arms and one control treatment arm. Second, there are process and operational efficiencies gained by having a single master protocol that could be amended as needed as drugs enter and exit the study. For example, following initial implementation, sponsors enrolling new drugs would benefit from the presence of a pre-existing infrastructure. A master protocol will also provide consistency, as every drug for the disease would be tested in the identical manner. Sponsors may be encouraged to include their drug in a master registration trial if there were assurances that if pre-specified efficacy and safety criteria were met, the drug and accompanying companion diagnostic would be approved. Finally, by improving the overall efficiency of drug development in a specific disease setting, this trial offers the advantage of bringing safe and effective drugs to patients sooner than they might otherwise be available.

Disease Model

We have chosen to use lung cancer as the prototype disease for this type of trial. Lung cancer is the most common cancer today, with an estimated 226,160 new cases expected in the United States in 2012 alone (5). Lung cancer is characterized by multiple and often independent mutations and potential therapeutic targets, and screening is rapidly becoming a part of treatment, making it an excellent case study for a multi-arm biomarker driven trial. The Cancer Genome Atlas recently performed the first attempt to comprehensively characterize the genomic alterations in lung squamous cell carcinomas, and identified numerous druggable targets (6, 7). As mentioned above, BATTLE and I-SPY 2 have demonstrated the

feasibility of biomarker-driven trials, and BATTLE showed the appropriateness of using biomarker expression and targeted therapies in treatment of NSCLC.

In the trial described here, we will expand on the designs used in BATTLE and I-SPY 2 to develop an approach to a biomarker-based trial that could provide the basis for FDA approval of new drugs with matching companion diagnostics. If this Master Protocol Multi-drug Registration Trial is successful, this type of biomarker-driven umbrella protocol could be used for registration trials in other settings.

Master Protocol Multi-drug Registration Trial Design Proposal

Sponsor

The Master Protocol Multi-drug Registration Trial will be run by a **neutral third party** (e.g., CRO or academic coordinating center).

Primary Objective

The primary objective of this trial is, for each experimental targeted therapy, to compare the overall survival of biomarker-selected patients with metastatic NSCLC treated with standard of care (SoC) versus the experimental targeted therapy. Secondary objectives include comparison of progression-free survival and response rates. The safety profile of each experimental agent will also be assessed.

Drugs and Biomarkers

The Master Protocol Multi-drug Registration Trial steering committee will evaluate each application to determine whether a drug/biomarker pair can enter the master protocol trial.

Drugs

For our purposes, we are assuming that there are at least 2 experimental drugs ready to enter a phase III confirmatory trial. **Each drug must have clinical data demonstrating activity in a responsive patient group** that can be identified by a biomarker assessed in patient tumor biopsies.

Biomarkers and Screening

The biomarker for each compound is based on a test or platform that has been analytically validated and is suitable for a pivotal trial. To date in oncology, drugs that have received FDA-approval with companion diagnostics have been limited to single drugs approved with the use of single tests, but technological advancements may alter that approach. Next generation sequencing has been used to characterize tumors; however, no such technology has been cleared by the FDA for the approval of a specific drug. The Lung Cancer Mutation Consortium has begun to use screening platforms to test specific markers in patients in order to help determine their best course of treatment. Similarly, this trial may benefit from the use of a common screening platform that assays multiple biomarkers. The presence of a particular predictive biomarker in the platform would enable the platform to be considered adequate for selecting patients for treatment with a new targeted compound. A CLIA-approved platform could obtain an Investigational Device Exemption (IDE) prior to the start of the trial to allow use of the platform to select patients for enrollment in the trial and for randomization between a specific experimental treatment and SoC. Assuming that a new drug meets predefined criteria for demonstrating clinical benefit in the patient population selected by the platform biomarker, the biomarker could be analyzed and given FDA clearance along with approval for the drug. The process of using this type of technology to select patients for treatment with multiple different drugs would require close communication with the FDA to determine its applicability.

The use of a multi-marker platform in this trial would provide several advantages over the current single test, single drug paradigm. It is likely that the Master Protocol Multi-drug Registration Trial will include multiple agents from different classes, one or more of which may have multiple targets or target pathways

with multiple components. Therefore, the use of as broad a test as possible with clinically acceptable turnaround time and which simultaneously detects all classes of DNA alterations (base substitutions, small indels, copy number changes-amplifications and homozygous deletions, and gene rearrangements) would allow the most judicious use of precious tumor samples and likely prove informative in explaining varied responses across patients with a given primary alteration. Testing protocols would also be easier to standardize. In addition, sponsors would not be responsible for designing their own diagnostic.

Study Design

This is a randomized, controlled Phase III trial in patients with advanced NSCLC refractory to prior chemotherapy. To simplify the discussion for this briefing document, we will assume 2 experimental treatments, A and B, with matching diagnostic tests tA and tB that determine the status of biomarkers A and B, respectively. At entry, patients will receive a fresh core needle biopsy, with the tissue analyzed by tA and tB. Patients whose tumors are positive for tA will be randomized to SoC vs drug A, while patients whose tumors are positive for tB will be randomized to standard-of-care vs drug B. In the simplest example, shown in Figure 1, there is no overlap between biomarkers A and B. Similar to the I-SPY2 study, additional drug/biomarker combinations can be added to the study over time, with similar randomization to SoC or the experimental drug, based on the test result (Figure 2). As discussed below, and again similar to I-SPY2, a drug/test combination may also be dropped from the study based on an interim futility analysis. The protocol design will use a group sequential methodology with overall survival (OS) as the primary endpoint. For simplicity in this hypothetical, only OS results are considered at the interim analysis, although a similar approach could be used for progression-free survival (PFS) results at the interim analysis. Although various effect sizes could be targeted, the starting sample size could be determined based on a postulated 25% reduction in survival hazard (hazard ratio of 0.75), which corresponds to a 4 month improvement for an experimental arm over an assumed median OS of 12 months for SoC in patients selected based on the assay that matches a specific experimental arm (bmx+). Of note, potential prognostic effects of the biomarker on clinical outcomes in the SoC arm would need to be considered when targeting effect sizes.

Although various approaches to interim analyses could be considered, one approach would be to perform an interim analysis of OS results when 30% of the OS events have occurred. Bounds are determined by Hwang-Shih-DeCani spending functions with $\gamma = -10$ (α spending) and $\gamma = 2$ (β spending) (8). With a Type I error rate of 2.5% (one-sided), 381 survival events for a combined SoC and experimental arm will yield 72% power to detect this targeted treatment-effect size on OS. Assuming enrollment to be piecewise constant at rates of 7.4 for months 0 - 1, 10.4 for months 1 - 3, 17.4 for months 3 - 6, 27.8 for months 6 - 24, and a dropout rate of 0.1% per month, this yields a sample size of 581 bmx+ patients for each biomarker. Planned recruitment duration is 24 months and the minimum follow-up planned is 12 months. In the case of 2 experimental treatments A and B, this results in an overall sample size of 1162 patients, 581 patients with cancers positive for test A, and 581 patients with cancers positive for test B. At the interim analysis, the HR boundary for futility is 0.90. At the final analysis, the HR boundary for an experimental arm to be considered successful is 0.82. Note that targeting a larger effect size, such as an OS HR of 0.5, yields a reduced sample size for each experimental treatment (111 bmx+ pts, in this example). In this case, an interim analysis might not be necessary.

The overall number of patients needed to be screened for entry into the study will depend on the prevalence of the bmx+ population for each assay used in the study.

Leveraging Control Patients

There may be additional advantages to this proposed trial design. Because the trial will be run by a neutral third party, it may be possible to leverage control patients across multiple trial arms. This will be dependent on the trial using a CRO/Coordinating Center that is able to establish appropriate firewall procedures to maintain masking of patients among the various trials. This firewall procedure will allow

multiple drugs against one biomarker to be included in the trial (Figure 3). No comparisons among active drugs are envisioned; the efficacy of each experimental agent would only be directly compared to SoC.

In this case, drugs still do not need to begin enrollment at the same time. However, leverage of shared controls will be limited to those patients enrolled concurrently with each drug. For example, if drug A1 is initially the only drug targeted against marker A, marker A/drug A1 is actively recruiting with 1:1 randomization allocation to drug A or standard of care. Once the protocol for marker A and drug A2 are approved to begin recruitment, randomization of the marker A positive patients changes, at this point, to 1:1:1 corresponding to drug A1: drug A2: SoC. During this time, use of the common protocol with standard procedures, visit schedules, and case report forms, will allow control patients' data to contribute to both trials.

If the drug A1 arm completes enrollment while the drug A2 arm is still ongoing, patient randomization allocation reverts to 1:1 for drug A2: SoC. The control patients recruited during the drug A1 arm that have completed follow-up in both arms have their data unmasked for analysis of the drug A1 protocol, while remaining masked to drug A2 arm personnel. Control patients recruited for the drug A1 arm that have not yet completed follow-up in the drug A2 arm also have their data unmasked for drug A1 analysis only; they remain masked to drug A2 personnel, and data collection on these patients continues under the drug A2 protocol. Potentially, the information about which control patients are unique to a given trial and which are shared may not need to be disclosed for analysis purposes. The benefit to sharing control patients could be substantial in terms of both recruitment time and trial costs.

It is noted that there could be cases where based on study results obtained from drug A1, this drug could replace the SoC for the biomarker A-defined population. In this case, the data monitoring committee for the study would decide whether randomization to the original SoC arm should continue for drug A2.

Randomization of Double Positive Patients

Ideally, as in Figure 1, the assays would be selected so that there would be minimal expected overlap between the bmx+ populations identified by each diagnostic assay. However, there are two options when there is marker overlap and patients test positive for one or more biomarkers. If the infrastructure described above can be established, the same approach of leveraging controls and randomizing patients 1:1:1 could be applied to patients who are positive for two biomarkers (Figure 4). Another option would be to randomize based on an assay hierarchy in order to avoid randomization of double positive patients to two experimental treatments. In this case, prior to enrollment assays will be ranked and a pre-specified hierarchical rule will be established based on assay, biomarker, and other factors pre-determined by the steering committee. The double positive patients will be randomized to SoC or the experimental arm that is selected based on a pre-specified hierarchical rule. For example, as shown in figure 5, patients who test positive for both bmx A and B would be assigned to randomization between SoC and treatment A. For both options, implications for statistical evaluations as well as use of the companion diagnostic would need to be carefully considered.

Standard of Care

The SoC will be determined prior to trial initiation by the steering committee.

Figure 1. A simplified CONSORT diagram of the Master Protocol Multi-drug Registration Trial without marker overlap. In this simple hypothetical, there are presumed to be two biomarkers, A and B, and only one targeted therapeutic for each biomarker. The two biomarkers are mutually exclusive and there is no overlap of biomarker expression.

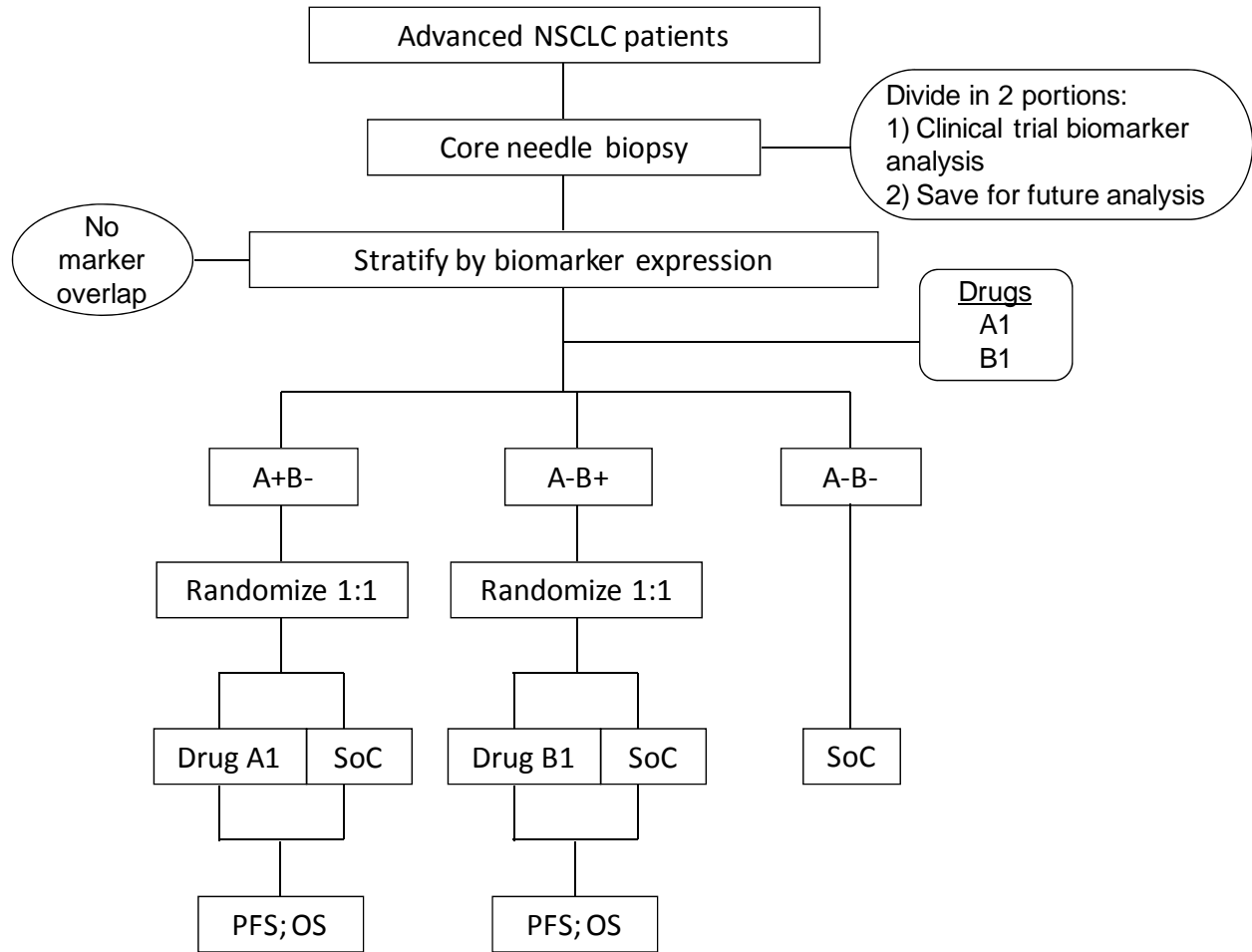


Figure 2. Master Protocol Multi-drug Registration Trial: Steps During Development. An example of a hypothetical trial using a Master Protocol, in which new drugs and markers are added throughout the process. Each drug undergoes interim analysis at 30% of OS events. At this stage, if the trial meets a pre-specified endpoint, the trial continues; if not, the treatment is dropped.

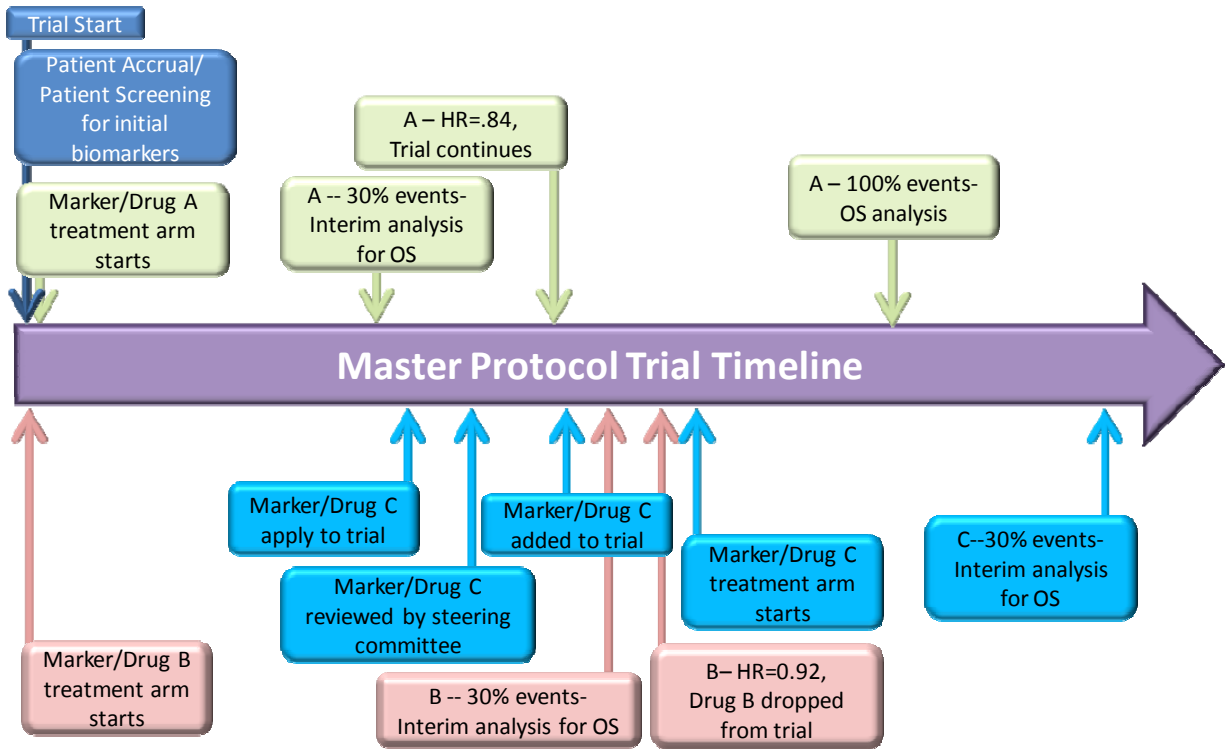


Figure 3. CONSORT diagram of a Master Protocol Multi-drug Registration Trial when there are two drugs targeting one biomarker. In this case, there are two biomarkers, A and B, with no expression overlap; Biomarker A is targeted by two drugs, A1 and A2, while biomarker B is targeted by B1. In this situation, SoC control patients can be shared with experimental drugs A1 and A2, but a firewall will prevent comparison between the two drugs.

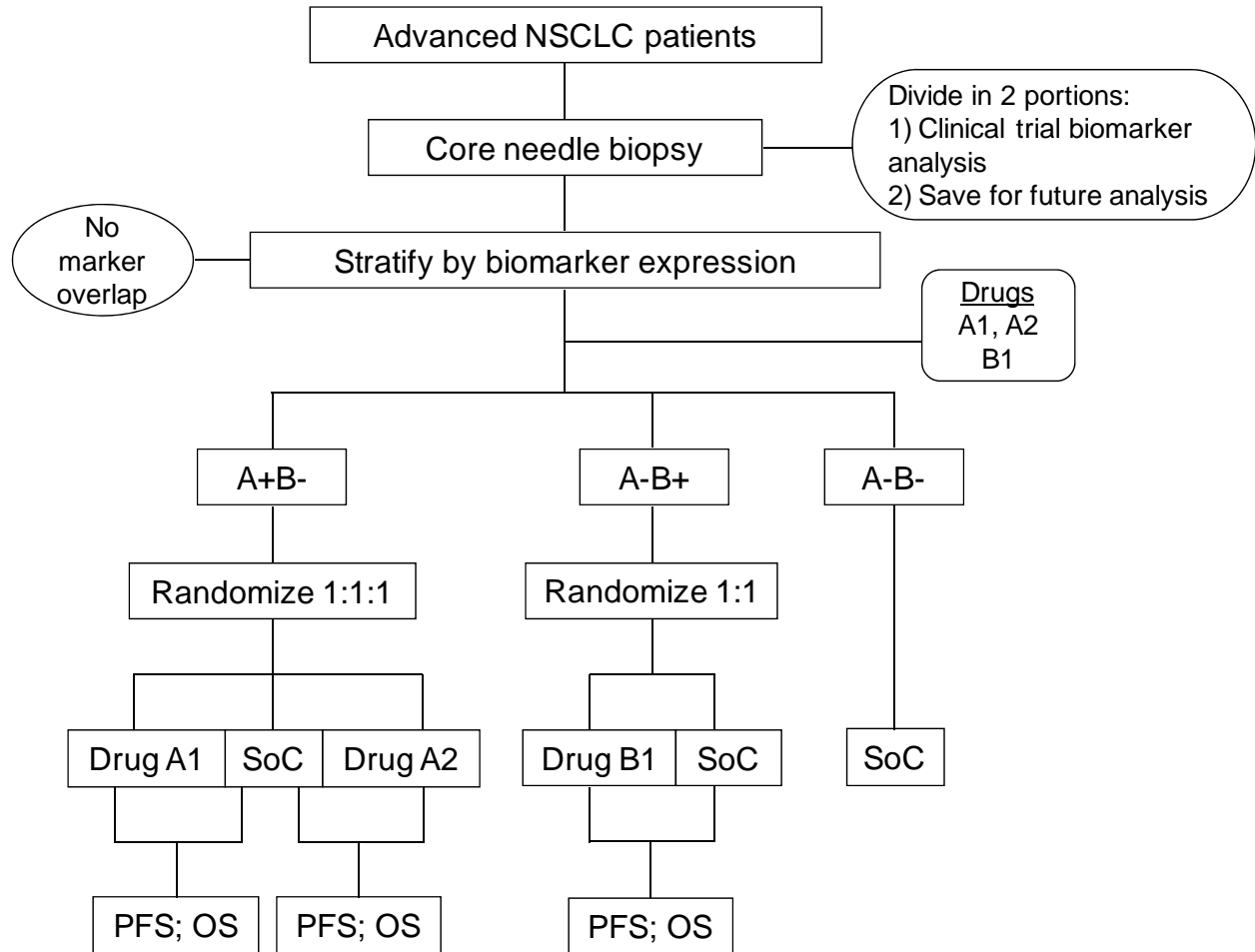


Figure 4. Simplified CONSORT diagram of a Master Protocol Multi-drug Registration Trial when there is overlapping expression of the biomarkers. In this schematic, there are only two biomarkers, A and B, and one targeted therapeutic for each biomarker. However, in this case there is overlap of biomarker expression, with some tumors being double positive for both A and B. Double positive patients will be randomized to one of the two experimental drugs or SoC in a 1:1:1 manner, with a firewall preventing comparison of the experimental arms to each other.

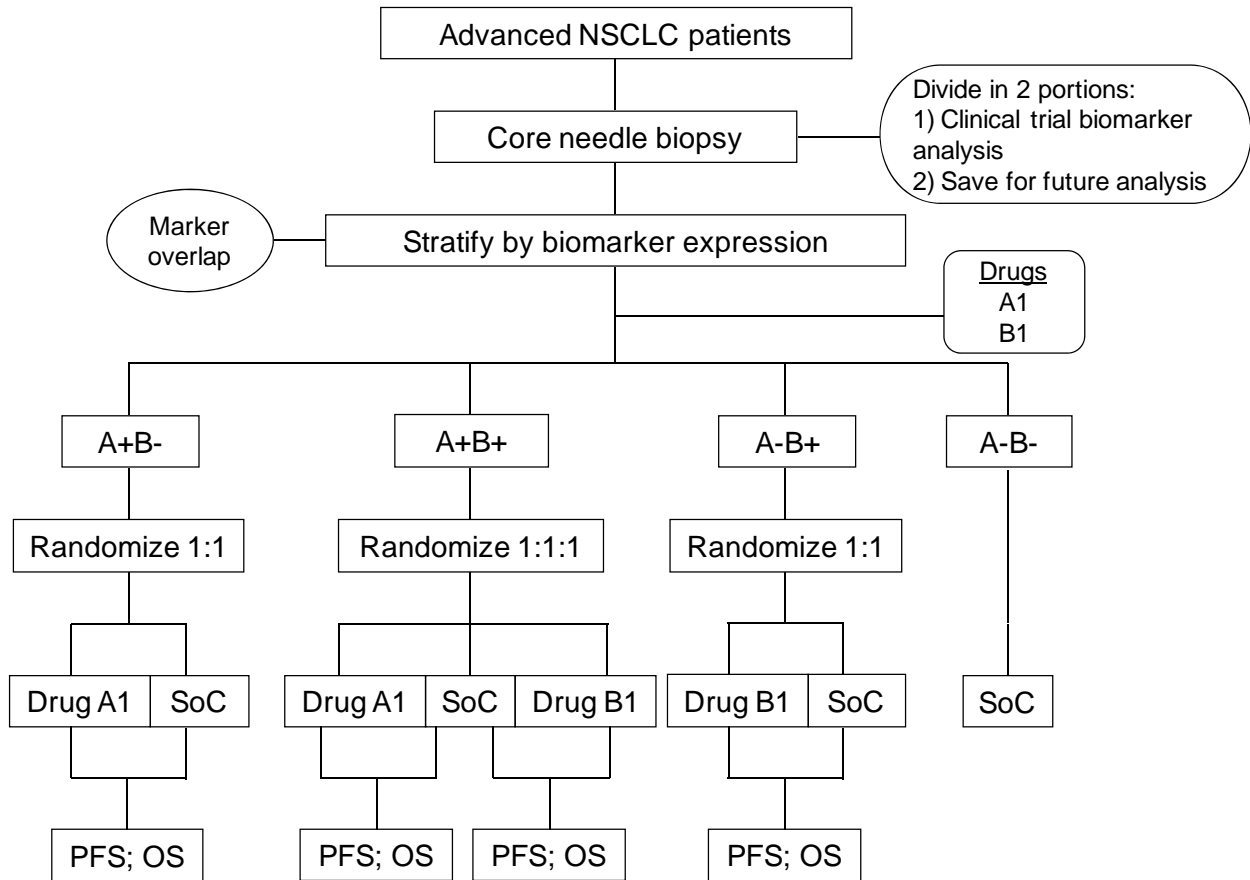
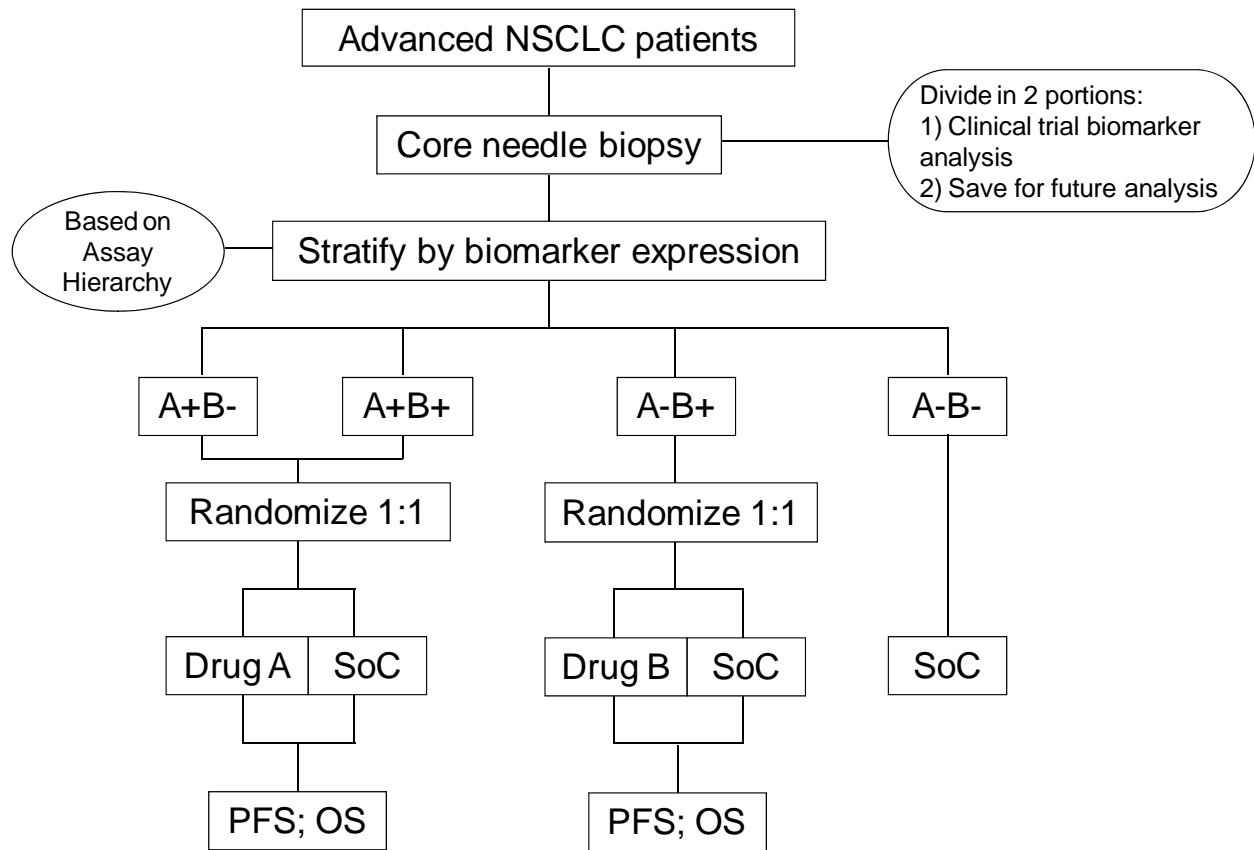


Figure 5: CONSORT diagram of the Master Protocol Multi-drug Registration Trial using a hierarchical assay approach to randomize patients. In this case there are two biomarkers, A and B, with one targeted therapeutic for each biomarker, and there is some overlap of biomarker expression. Randomization of patients to treatment is based on a pre-specified assay hierarchy, and the biomarker status of the lower ranked biomarker(s) does not affect stratification. (e.g. all patients positive for marker A will receive Drug A regardless of the status of other biomarkers; all patients negative for marker A and positive for marker B will receive Drug B regardless of status of other biomarkers, etc.)



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