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THE MASTER PROTOCOL CONCEPT

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Abstract

During the past decade, biomedical technologies have undergone an explosive evolution---from the publication of the first complete human genome in 2003, after more than a decade of effort and at a cost of hundreds of millions of dollars---to the present time, where a complete genomic sequence can be available in less than a day and at a small fraction of the cost of the original sequence. The widespread availability of next generation genomic sequencing has opened the door to the development of precision oncology. The need to test multiple new targeted agents both alone and in combination with other targeted therapies, as well as classic cytotoxic agents, demand the development of novel therapeutic platforms (particularly Master Protocols) capable of efficiently and effectively testing multiple targeted agents or targeted therapeutic strategies in relatively small patient subpopulations. Here, we describe the Master Protocol concept, with a focus on the expected gains and complexities of the use of this design. An overview of Master Protocols currently active or in development is provided along with a more extensive discussion of the Lung Master Protocol (Lung-MAP study).

BACKGROUND

The paradigm for developing new cancer therapeutics is undergoing an evolutionary shift of substantial magnitude not witnessed since the incorporation of the randomized clinical trial (RCT) as the gold standard benchmark for therapeutic progress. The advent of the RCT is rooted in the post-war antibiotic era of the late 1940s and saw its first application in oncology in the 1960s. Since that time, it has been used as the ultimate level of evidence

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supporting the clinical application of specific therapeutic interventions. Over the past half century, the RCT has been the platform upon which advances in cancer have been tested primarily through a multidisciplinary approach combining various systemic agents along with optimal radiation and surgical techniques delivered to populations of patients with similar stages of a particular cancer type defined by its organ of origin. There is no question that this approach has resulted in substantial improvements in outcomes for patients with various cancers. However, particularly in patients with common cancers of solid organs, advances have been tedious, incremental and often associated with significant toxicities related to the collateral cellular damage to normal tissues resulting from the non-specific nature of classic cytotoxic agents.

During the past decade, biomedical technologies have undergone an explosive evolution from the publication of the first complete human genome in 2003 after more than a decade of effort and at a cost of hundreds of millions of dollars to the present time where a complete genomic sequence can be available in less than a day and at a small fraction of the cost of the original sequences. The widespread ready availability of relatively inexpensive next generation genomic sequencing has opened the door to the development of precision oncology, wherein the cancer of each patient may be interrogated to reveal specific genomic or proteomic abnormalities that may be specifically targeted with agents highly selective for the identified abnormality. The recognition that cancers of a particular organ of origin may be driven to proliferate and metastasize by cellular alterations that differ among individual patients or patient subpopulations has led to the realization that new paradigms are needed to develop strategies to test targeted agents in populations of patients whose cancers harbor specific genetic abnormalities and therefore may represent only a small fraction of the total patient population with a cancer arising from any particular organ. For example, in patients with adenocarcinoma of the lung only about 15% will have a mutation in the epidermal growth factor receptor (EGFR). Thus, targeting this receptor will result in significant clinical benefit with modest toxicities in only a small fraction. Using classic clinical trials methods would require the screening of at least 6 patients to identify one patient who may be eligible for and ultimately consent to participation in a clinical trial investigating a new EGFR inhibitor thus resulting in a marked increase in time, resources and funding to accrue to even a modest size trial.

In parallel with the advances in “omic” technologies has been an ever-increasing understanding of the cellular pathways that underpin the dysregulated growth and spread of malignant cells. New appreciation of the specific proteins responsible for cancer growth has led to an intense effort on the part of academic investigators and industry to discover and develop a multitude of small molecules capable of interacting with and inhibiting the function of many intracellular proteins constitutively activated as a result of genetic alterations. It has become evident that the various intracellular pathways responsible for cellular proliferation are extremely complex with redundant pathways, feedback loops and multiple points along any given pathway that may be activated or suppressed by numerous cellular proteins. The realization of this complexity and early clinical evidence with the use of single targeted therapeutics has led to the widely accepted hypothesis that it is highly likely that more than a single targeted therapeutic will be needed to affect a long term clinical benefit.

The parallel availability of highly multiplex technologies along with the need to test multiple new targeted agents both alone and in combination with other targeted therapies as well as classic cytotoxic agents demands the development of novel therapeutic platforms (e.g., Master Protocols) capable of efficiently and effectively testing multiple targeted agents or targeted therapeutic strategies in relatively small patient subpopulations. To this end, a number of platform clinical trials have been spawned with the short-term goal of identifying active agents and strategies in molecularly defined patient subpopulations. The idea of creating a platform such as a Master Protocol to gain efficiencies is not a new one, but it has not been until this era of targeted therapies that the true potential of this concept has been appreciated.

THE MASTER PROTOCOL CONCEPT

The general goals of a Master Protocol are to improve genomic screening efficiency and to increase the speed of drug development and evaluation. Screening efficiency is improved by subjecting the tumors of a large number of patients to assays capable of identifying abnormalities in multiple potential targets, reducing the screen failure rate by both ensuring a sufficient amount of a patient's specimen is submitted for screening multiple biomarkers and by screening patient specimens using a common platform or set of assays to evaluate for the candidate biomarkers. Such a strategy is designed to provide a sufficient "hit rate" for biomarker-driven studies to allow enrollment of a substantial percentage of the screened patients into clinical trials; thus, promoting the engagement of patients, physicians and drug sponsors. The speed of drug development and evaluation is increased by providing an infrastructure to open and close studies of new agents and biomarkers more quickly. In general these types of studies also increase the speed of development and evaluation by looking for "large effects" and therefore requiring fewer enrolled patients per trial. Finally, with the use a common platform/design a Master Protocol can also facilitate US Federal Drug Administration (FDA) approval of new drugs and bring safe and effective drugs to patients faster.

The general design for a Master Protocol is presented in Figure 1. This Figure depicts the general idea of a Master Protocol, which is to provide a platform for simultaneously evaluating multiple agents in patients with specific genetic abnormalities that may be targeted by the agent under investigation. Patient specimens are evaluated for the set of biomarker/biomarker assays and then on the basis of this evaluation are assigned to a sub-study within the Master Protocol. The sub-studies may have a common design or the designs may vary across the biomarker/biomarker assay groupings and the platform may or may not include a sub-study for patients who are not eligible for any of the biomarker-driven studies.

The benefit to including a "non-match" study is to maximize the opportunity for clinical trial enrollment for all screened patients. However, depending on the disease setting under study, there might not be a reasonable choice for a "non-match" study. Moreover, while the biomarker-driven sub-studies may be set up for FDA approval of the drug, the undefined and potentially changing nature of the "non-match" population may not be as clear for FDA approval.

A benefit to use of a common design across sub-studies is operational efficiency, development and approval of the sub-study design occurs generally once and also allows for standardization across the studies. However, use of a common design requires some level of common criteria or evidence around the biomarker/biomarker assay and investigational therapy for use in the Master Protocol. Varying clinical experience and stage of development for different agents may mean that a common design is not appropriate.

One question to address in the design is how to deal with patients with multiple actionable biomarkers detected. In this setting it may not be clear as to which of the biomarkers is potentially an oncogenic driver for that patient. The questions arise as to whether there should be prioritization of biomarkers for sub-study assignment, should there be studies designed for patients with multiple biomarkers, or should patients be randomly assigned to a particular sub-study when they have overlapping biomarkers? Sub-study assignment depends on the expected overlap and prevalence of overlap of the study biomarkers. If there is expected overlap, then the algorithm for sub-study assignment needs to be pre-specified: sub-study assignment could be prioritized or randomization could be used to assign patients to a sub-study. A benefit of the use of a Master Protocol with multiple sub-studies is that the assignment mechanism and overlap of biomarkers/assays is known and may be accounted for in the analysis.

Within the Master Protocol framework, a sub-study design is broadly speaking either a discovery-based or confirmatory design. Discovery designs, such as single arm or randomized phase II designs are used to determine what biomarker/assay and investigational therapies should be pursued in a future study. Whereas a confirmatory design is typically a randomized phase III trial, which may or may not be used for regulatory approval of the biomarker and investigational therapy pair. It is possible that a single arm trial using response rate as the primary endpoint could be considered a confirmatory trial, but use of such a trial design would require discussions with the FDA to ensure these data would be considered “registration” worthy.

What do we hope to gain from a Master Protocol? As stated above, there are a number of expected efficiency gains with a Master Protocol: improved screening and screen success rate, reduced time for drug evaluation and development and potentially the ability to streamline FDA approval of investigational therapies. In addition to these gains there are also efficiency gains through the incorporation of a master budget. There is shared cost across sub-studies for the shared infrastructure and screening platform for multiple sub-studies and also the potential for efficiency gains in terms of the time for regulatory approval; the regulatory agencies review the study design and platform up front, but subsequent sub-studies will not necessarily require the same level of approval and evaluation as stand-alone clinical trials. Embrace of the Master Protocol concept by regulatory agencies will represent a change in the paradigm for cancer drug testing and regulatory approval. It also allows for a direct application of preclinical scientific discoveries in clinical trials

Many potential obstacles are involved with the conceptualization and conduct of a Master Protocol. Master Protocols are inherently more complex than the standard clinical trial,

whether or not they are biomarker-driven. Therefore a major challenge in implementation of a Master Protocol is negotiating these complexities. Even if the conduct of each sub-study is independent of each other, the success of individual sub-studies is dependent on the infrastructure of the entire Master Protocol. A number of challenges are related to study start up and activation while others are associated with continued success of the platform once the study has been initiated. One so-called start-up challenge is to convince industry partners of the value added of a Master Protocol. It is unlikely that one industry partner will have all possible drugs to be tested within a given Master Protocol; therefore, there must be involvement from multiple industry partners. Depending on the chosen design if there is a potential for cross-sub-study comparisons there could be perceived competition between agents or regimens from different industry partners.

Master Protocols are logistically challenging and because they are a newer type of design, there is much to be learned as to how best to design and implement these study platforms. This is a new way of doing business and therefore transparency and communications between all the partners is needed, including between drug and device partners. But, determining how much information transfer between partners is needed and how best to communicate can be challenging. There can be a period of education between partners not used to working with each other and each partner may not be fully aware of the investigative group's strengths and weaknesses. Therefore, such an effort requires more pre-planning than the standard clinical trial.

There are a number of questions to be answered in the developing the budget for a Master Protocol. For example: who will fund the profiling and if multiple entities are sharing the costs, how should the costs be distributed? If the costs are shared amongst the study sponsors then one approach could be to split the screening costs based on the number of patients per sub-study. Another approach could be to split the costs equally between the sponsors. The first approach favors sponsors with lower prevalence biomarkers and the second approach acknowledges that all sponsors are benefiting from the shared infrastructure and screening for the sub-studies. In addition, an important aspect of budgeting for screening is accounting for the rate of screen failures (i.e. patients without sufficient tissue or those with sufficient tissue but who are clinically not eligible for a sub-study, or decide to not register for a sub-study for any reason).

Contract negotiations between multiple industry partners can also be a challenge. The use of a Master Protocol design which requires some level of standardization across sub-studies necessitates release of some level of control or specificity that a partner may standardly employ in their sponsored trials. Moreover, as it is likely in most setting that combinations of targeted agents are the future, contracting for a given sub-study evaluating a combination of agents would require negotiations with more than a single industry partner for participation in a given sub-study arm. This clearly requires trust and a wiliness to collaborate among sponsors in the development of their agents

There may also be extra regulatory complexities; if multiple assays are to be used to assign patients to a sub-study, then each assay may need their own Investigational Device Exemption (IDE). Alternatively, if a single platform is to be used for all of the sub-studies,

then there needs to be support for use for the single platform among all the stakeholders involved with the master study. If a single platform is used, individual partners may also have their own assay that they would like to use for the drug or drug combination, which would require potentially bridging studies and sufficient residual specimens for this additional testing.

Additional considerations

Since patients are constantly being screened for abnormalities that would allow eligibility for specific trial sub-studies yet only a fraction of those screened will be found to meet eligibility requirements for any given sub-study, it is imperative that as many sub-studies are open for accrual as needed to allow entry into a biomarker-driven sub-study for the vast majority of screened patients. If only a small subset of all screened patients are eligible for trial entry, much resource will have been expended for little gain for the various stakeholders in the trial including, and most importantly, the patients. To maintain active eligibility for the majority of screened patients, multiple sub-studies may be needed to be open at any given time and as sub-studies close, new sub-studies would need to be rapidly opened. Thus, there is a constant need for new agents and combinations to be tested. How should these agents be selected and prioritized?

Master Protocol Efforts

There are a number of biomarker-driven Master Protocols currently in development or actively accruing patients, such as the FOCUS 4 trial being conducted in the United Kingdom (UK) in Colon cancer, the National Lung Matrix trial, also being conducted in the UK, the US National Cancer Institution's (NCI) Match trial which will evaluate multiple disease and histology types, the ALCHEMIST trial for adjuvant treatment in lung cancer, and the Lung-MAP trial for previously-treated squamous lung cancer.¹⁻⁴ Motivation and support for use of Master Protocols in NCI-supported trials in lung cancer was the result of a meeting held in February of 2012, which was jointly organized, by the NCI, FDA, and the Thoracic malignancy steering committee within the NCI.⁵ Also of note is the I-SPY 2 trial in breast cancer, while provides an example of a non-biomarker driven platform trial.⁶ We here provide an overview of the aforementioned master protocol efforts with specific attention to the Lung-MAP trial. We use the Lung-MAP trial as an example of how one study addressed the challenges related to design and implementation discussed in this paper.

ALCHEMIST—The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing (ALCHEMIST) trials, initiated in August of 2014, are a series of biomarker-driven phase III trials for patients receiving adjuvant biomarker-driven therapy.¹ The trial opened with two studies, one evaluating erlotinib, an EGFR inhibitor in EGFR mutation positive patients and the other evaluating crizotinib, a drug targeting the echinoderm microtubule-associated protein-like 4 - anaplastic lymphoma kinase (EML4-ALK) fusion gene. Only patients with one of the targeted biomarkers may enroll onto one of the biomarker driven studies in ALCHEMIST. As essentially no patients have been found to have both the EGFR mutation or the EML4-ALK fusion, there was no need to specify an algorithm for sub-study assignment for patients with multiple eligibility biomarkers. The screening component of this trial is being conducted by the NCI ALLIANCE clinical trials

network group and the treatment trials are being implemented by the NCI cooperative groups, ALLIANCE and ECOG-ACRIN. Investigators are currently working on adding an additional study to ALCHEMIST, which will evaluate an immune therapy agent. While this platform includes phase III trials the studies are not set up to be FDA registration trials so a positive result may not result in FDA approval of the investigational therapy. This trial is funded by the NCI.

I-SPY 2—The I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis 2) trial is a non-biomarker driven phase II discovery platform in neo-adjuvant breast cancer designed to evaluate candidate drugs to be tested in the phase III setting.to evaluate candidate drugs to be tested in the phase III setting.⁶ This trial, which was initiated in 2010, is designed to evaluate up to 12 different agents against a common control and has graduated two drugs to date: neratinib and veliparib, at a cost of \$27 million and has enrolled approximately 800 patients. This trial is funded outside of the National Cancer Institute, largely by the Safeway Foundation.

NCI-Match—The NCI Molecular Analysis for Therapy Choice Program (NCI MATCH), currently in development, is also a phase II discovery platform which plans to enroll 3000 patients with advanced solid tumors and lymphomas refractory cancer of any origin and assign patients to a series of biomarker driven single arm, single agent phase II trials.⁷ This trial is entirely funded by NCI. Only patients with one of the biomarkers of interest may enroll on one of the trial arms of NCI Match. However, because the trial is designed to include approximately 20 different targeted agents, it is expected that a relatively high percentage of screened patients will be found to have an actionable alteration and therefor, be eligible for one of the arms of investigation

The National Lung Matrix Trial—A trial similar to NCI Match, albeit restricted to non-small cell lung cancer, and also in development is the National Lung Matrix Trial, which will be conducted in the UK. This trial will test 8 drugs to be tested in 21 single arm studies of 30 patients each. The therapies to be tested will target specific mutations and the drugs will be tested in multiple cohorts with different abnormalities.

Lung-MAP—The final trial described here is the Lung Master Protocol (Lung-MAP), formally titled, SWOG S1400.^{2,4} This trial is being conducted by SWOG in partnership with the NCI, Foundation for the NIH, Friends of Cancer Research and the participating pharmaceutical companies. The FDA has also been actively involved and supportive. The trial also includes active participation and input by a variety of patient advocacy organizations. Funding for this study is shared between the NCI and the pharmaceutical companies at a total expected cost of \$160–170 million over 5 years. Lung-MAP is a multi-drug, multi-sub-study Master Protocol in previously treated patients with squamous advanced non-small cell lung cancer. Biomarker screening for this trial is done using the research version of the Foundation One panel of Foundation Medicine, Inc. (FMI). The design of the “trial” is comprised of multiple biomarker-driven sub-studies with biomarker eligibility defined by a specific set of genomic alternations within each sub-study and a “non-match” study for patients with none of the targeted biomarkers. Thus a sub-study is

available for all clinically eligible patients with results from the genomic screening, including patients with none of the targeted biomarkers. Following broad genomic profiling, patients are assigned to a sub-study on the basis of their genomic profile and randomized between an investigational therapy targeting the study-specific biomarker versus standard of care.

The original design of Lung-MAP included biomarker-driven studies of a 1) Phosphatidylinositol 3-kinase (PI3K kinase) inhibitor, 2) a cyclin-dependent kinase inhibitor (CDK), 3) a fibroblast growth factor receptor (FGFR) inhibitor, and 4) a monoclonal antibody directed against the human hepatocyte growth factor (HGF). Biomarker positivity for PI3K, CDK, and FGFR were based on the FMI panel and positivity for the HGF study was based on c-MET measured by immunohistochemistry. The non-match study investigational therapy is an immunotherapy targeting the PD-L1/PD-1 pathway. The expected proportion of patients with exactly one of these eligibility biomarkers was 35% and the expected proportion of patients with 2 or more of the eligibility biomarkers was approximately 10%. As there was no data to suggest prioritization of the individual biomarkers over another (biomarker equipoise) and to not prioritize one pharmaceutical collaborators drug over another, randomization is used to assign sub-studies for patients with multiple biomarkers. However, to ensure sufficient number of patients are assigned to studies with lower prevalence biomarker studies, sub-study assignment uses weighted randomization in favor of the lower prevalence biomarkers.

Each of the sub-studies within Lung-MAP is independently conducted and analyzed, and each has the potential to result in FDA approval of the investigational therapy if the trial proves successful. The trial is designed to be modular such that as new biomarker/drug pairs are discovered, new sub-studies can be added. Therefore the Lung-MAP study is designed to be a FDA registration platform. Lung-MAP was initiated in June of 2014 and opened with 4 biomarker-driven sub-studies and one non-match study.

The major patient-focused efficiency gain with the design of the Lung-MAP trial is that there is a study, be it biomarker-driven or the non-match study, for all screened patients, provided they satisfy the basic clinical and pathologic eligibility criteria. An additional efficiency gain focused specifically on the patient participants is the common platform for biomarker assessment. In many advanced cancers and lung cancer in particular, availability of tissue to perform multiple biomarker assays can be an issue. Use of the common platform addresses this concern. In addition, the time to assess patient tissue with multiple assays can result in an unacceptable duration of time for biomarker analysis results. Biomarker results for patients being screened for the Lung-MAP trial are returned to the patient's physician within 16 days from tissue submission. The study is also adding in a current amendment the allowance that patients can be "pre-screened" during first-line chemotherapy so that if and when they progress, they can immediately receive their sub-study assignment and initiate their next line of therapy, avoiding the 16-day turn-around delay for tissue analysis.

The Lung-MAP study is anticipated to achieve efficiency gains in the time to identification and implementation of new sub-studies. Selection of new sub-studies in Lung-MAP is governed by a Drug Selection committee. This committee meets on a regular basis to

evaluate new therapies and the evidence support their use in Lung-MAP. A major responsibility of this committee is to ensure that the pipeline for new sub-studies to maintain the study infrastructure and success. Therefore efficiency gains are achieved by assigning a specific group of individuals to constantly pursue new agents to be tested in this setting.

Efficiency gains in terms of the time to implement new sub-studies are achieved in a number of ways. Exemplifying the commitment of both SWOG and the NCI to support Lung-MAP as a new way of doing business, both SWOG and the NCI have allowed for a more expedited review process than is standardly employed. The FDA has also made review and discussion of this study a priority. The saving in start-up time is exemplified by the relatively short time from study planning launch to activation of only 16 months, which even for a single phase III registration trial is impressive. Finally, because Lung-MAP is structured as one study with multiple sub-studies and all implemented through SWOG, this trial has one IND for the investigational therapies and one IDE for the FMI panel that determines biomarker eligibility. Costs of screening and trial infrastructure are shared across all of the sub-studies. This design has resulted in a reduced per patient cost compared to that generally born by pharmaceutical companies or the NCI for biomarker-driven studies.

There have been many challenges in launching and implementing the Lung-MAP trial. Although it is described as a single trial, the study as activated in June 2014 is more accurately described as a screening trial and 5 FDA registration randomized trials. While the conduct and analysis of each of the sub-studies is independent, the infrastructure and implementation of the Lung-MAP sub-studies are not independent. The success of individual sub-studies is reliant upon the success of the entire infrastructure. Within the first year of study, the Lung-MAP trial had to close the sub-study in c-MET immunohistochemistry positive patients evaluating the addition of rilotumumab to erlotinib as a study with this drug and utilizing the same biomarker in gastric cancer was closed early due the risk of harm with the drug. Moreover, in March of 2014, the FDA approved Nivolumab, an immunotherapy directed against the PD-1 pathway, which is in the same class of agents as the non-match drug, in the same patient population as the Lung-MAP trial. The study team and sponsors are actively pursuing amendments to the trial to respond to these events.

A final challenge is that of studying a rare patient sub-population. Master Protocols are more complex to implement and they are more complex for institutions understand and negotiate the logistics to enroll patients. Squamous lung cancer accounts for about 25% of advanced lung cancer patients and is associated with worse prognosis than other histologies. As such, it is a challenging patient population to accrue.

SUMMARY

There is great promise that use of the Master Protocol design to discover, explore, and test multiple biomarkers and therapeutic regimens under one study mechanism will result in getting new and effective therapies to patients more quickly. Researchers most certainly will learn a great deal from these “first generation” Master Protocols in terms of the scientific objectives, as well as in terms of how best to perform such studies (specifically how to

overcome the unique challenges of using such a clinical trial design). A Master Protocol design may not be the best approach in all settings, but it is clear that well designed and well-conducted clinical trials with the flexibility to respond to the changing landscape of clinical knowledge, should result in swift evaluation of therapies and determination of what will be of the greatest benefit to patients, both in and outside of clinical trials.

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Figure 1.
Generic biomarker-driven Master Protocol Design

Table 1
Comparison and description of Master Protocols currently active or in development

Trial	Biomarker-driven	Disease setting	Design	Design type	Status/Activation date
ALCHEMIST	Yes	Adjuvant lung	Phase III	Confirmatory	08/2014
FOCUS 4	Yes	Advanced colon	Phase II followed by Phase III	Discovery and Confirmatory	01/2014
I-SPY2	No	Neo-adjuvant breast	Phase II	Discovery	2010
Lung-MAP	Yes	Previously-treated squamous lung	Phase II/III	Confirmatory	06/2014
National Lung MATRIX trial	Yes	Non-small cell lung cancer	Single arm Phase II	Discovery	Expected 2015
NCI-MATCH	Yes	Multiple	Single arm Phase II	Discovery	Expected 2015