Lung Master Protocol (Lung-MAP)—A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400

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Abstract

The Lung Master Protocol (Lung-MAP, S1400) is a groundbreaking clinical trial designed to advance the efficient development of targeted therapies for squamous cell carcinoma (SCC) of the lung. There are no approved targeted therapies specific to advanced lung SCC, although The Cancer Genome Atlas project and similar studies have detected a significant number of somatic gene mutations/amplifications in lung SCC, some of which are targetable by investigational agents. However, the frequency of these changes is low (5%–20%), making recruitment and study conduct challenging in the traditional clinical trial setting. Here, we describe our approach to development of a biomarker-driven phase II/II multisubstudy “Master Protocol,” using a common platform (next-generation DNA sequencing) to identify actionable molecular abnormalities, followed by randomization to the relevant targeted therapy versus standard of care. Clin Cancer Res; 21(7); 1514–24. ©2015 AACR.

Introduction

Despite dramatic advances over the past decade in understanding the molecular biology of cancer and innovations in drug development technology, translation of these findings into effective cancer treatments remains difficult. The application of modern technologies to study genomic alterations associated with cancer growth and progression has provided for targeted development of new treatment options for patients with specific molecular abnormalities (biomarkers). Particularly, non–small cell lung cancer (NSCLC) is a disease in which a number of molecular targets have been identified (1–3). Great strides have been made in efficient and successful development of molecularly targeted drugs [e.g., crizotinib, ceritinib, and alectinib for patients bearing anaplastic lymphoma kinase (ALK) fusions (refs. 4–7); and EGFR mutations (refs. 3, 8, 9)]. However, developing a potential therapeutic agent from the initial discovery stage through clinical testing and regulatory review still remains a complicated, expensive, and inefficient process. Even rationally developed targeted therapies fail late in development because relevant patient populations were not selected or preliminary data were inadequate (e.g., promising phase II results not recapitulated in phase III; ref. 10). The consequences of this often slow and complicated process are either delay or failure to offer new active drugs to the many desperate patients with lung cancer (or other cancers). However, identifying and accruing biomarker-selected patients to clinical trials is also challenging. This is particularly true for squamous cell carcinoma (SCC) of NSCLC. Because any putative oncogenic driver in SCC is rare, screening patients for solitary biomarker-driven studies requires substantial time and tissue with a low chance of enrollment—in fact, serial screening for individual biomarkers to determine eligibility for other trials is not feasible for SCC patients who have already progressed on standard therapy. Thus, new strategies are essential for matching

Note: R.S. Herbst, D.R. Gandara, F.R. Hirsch, M.W. Redman, and V.A. Papadimitrakopoulou contributed equally to this article.

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patients to therapies from which they are most likely to benefit. This process requires efficient clinical trial designs for evaluating these therapies, with rapid, multibiomarker patient evaluation and accelerated drug development timelines (11–13).

Recently, a new trial design has been used to address these issues (14). This design has two components, screening and treatment. In the screening component, patients are evaluated systematically for the presence of biomarkers of interest. Then, in the treatment component, patients are assigned to substudies with investigational therapies targeting the biomarkers present in their tumors. This design allows more efficient screening and facilitates the addition of new drugs and biomarkers into the protocol on a rolling basis.

Two categories of studies follow this design (Fig. 1 and Table 1): “umbrella” studies examine the effect of specific therapeutic agent(s) on a defined molecular target regardless of the underlying tumor type. This design facilitates a particular targeted therapeutic strategy (i.e., inhibition of an oncogenically mutated kinase) across multiple cancer types. Examples are the NCI Molecular Analysis for Therapy Choice (MATCH; ref. 15) and the Molecular Profiling-based Assignment of Cancer Therapeutics (MPACT) trials. The second type, “basket” studies, evaluate multiple targeted therapeutic strategies in a single type of cancer. Examples are Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY TRIAL 2, I-SPY 2; ref. 16), the FOCUS4 study in advanced colorectal cancer (17), and the phase II adaptive randomization design Biomarker-integrated Approaches of Targeted Therapy for lung cancer elimination (BATTLE; ref. 18) and BATTLE-2 (14, 19) in NSCLC.

The Lung Master Protocol (Lung-MAP) is a recently initiated umbrella trial specifically for patients with advanced lung SCC. It is built on the principles and approaches of the previously mentioned trials. Particularly, I-SPY 2 established infrastructure for conduct of a Master Protocol (including development of the master investigational new drug application with the FDA; ref. 16), and it has been successful in meeting its objectives of matching drugs with subtypes of breast cancer in which they are most likely to be effective, potentially leading to smaller phase III trials in the selected subpopulations (20, 21). BATTLE and BATTLE-2 are direct precursors of Lung-MAP that have been successful in developing strategies to screen patients for and to define biomarkers for optimal patient selection for evaluation of drugs and drug combinations that have shown promise in treatment of NSCLC (18, 19). Although based on concepts developed in I-SPY 2 and the BATTLE trials, Lung-MAP has a different overall strategy. It does not use adaptive randomization to evaluate drug/biomarker combinations, and it goes beyond phase II development. It is designed to provide a path for FDA approval of active agents identified in the initial phase II study. That is, a drug that is found to be effective in phase II will move directly into the phase III registration setting, incorporating the patients from phase II. This will reduce time, resources, and patient numbers needed to accomplish the ultimate goal of bringing novel agents to the clinic. Lung-MAP also addresses other unmet needs, including applications of broad-based genomic screening in clinical trial settings and shortened turnaround times to allow effective use of molecular testing in selection of therapy for patients who are progressing rapidly. This Master Protocol mechanism is expected to increase access to genomic screening for SCC patients, improve definition of genomically defined biomarkers for clinical trial entry for these patients, and decrease time lines for drug-biomarker testing, allowing for inclusion of the maximum numbers of otherwise eligible patients (13). The authors hope that this article will increase awareness of Lung-MAP in the research community, allow us to share our experience with other groups looking to launch similar projects, and motivate oncologists to offer Lung-MAP as a treatment option to their eligible patients.

The concept for Lung-MAP was developed jointly in 2012, by the NCI’s Thoracic Malignancy Steering Committee (TMSC; ref. 7).

Figure 1. The trials listed are currently ongoing or soon to be activated trials with “umbrella” or “basket” designs with partial funding from the U.S. or UK government. Details of these studies are presented in Table 1.
Table 1. Representative basket and umbrella trials

<table>
<thead>
<tr>
<th>Status</th>
<th>Lung-MAP</th>
<th>BATTLE</th>
<th>BATTLE 2</th>
<th>I-SPY 2</th>
<th>NCI MATCH</th>
<th>NCI MPACT</th>
<th>FOCUS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sites</td>
<td>700+</td>
<td>1</td>
<td>2</td>
<td>23</td>
<td>Est. 2,400</td>
<td>1 ND</td>
<td>ND</td>
</tr>
<tr>
<td>Design and enrollment to screening and to substudies of molecularly targeted therapeutics</td>
<td>Umbrella design Phase II/III</td>
<td>Umbrella design Phase II</td>
<td>Umbrella design Phase II</td>
<td>Umbrella design Phase II</td>
<td>Basket design Phase II</td>
<td>Basket design Phase II</td>
<td>Umbrella design Phase II/III</td>
</tr>
<tr>
<td>3,125–6,250 planned for screening enrollment</td>
<td>341 enrolled</td>
<td>253 randomized</td>
<td>400 planned for enrollment to substudies</td>
<td>800 planned for randomization to substudies</td>
<td>3,000 planned for screening; 1,000–1,500 anticipated for assignment to substudies</td>
<td>700 planned for screening; 180 anticipated to be evaluated; feasibility study to be conducted in first 60 evaluable patients.</td>
<td>2,000 estimated for randomization to substudies</td>
</tr>
<tr>
<td>Substudies compare molecularly targeted drug(s) with or without standard therapy to standard therapy; drugs meeting phase II efficacy criteria continue to phase III; regulatory approval may be sought for drugs meeting phase III efficacy criteria</td>
<td>Open-label, equal randomization for 97 patients across biomarkers and drugs followed by adaptive randomization on the basis of DCR at 8 weeks and KRAS status; predictive biomarkers for biomarker status for 106 patients based on DCR results for patients previously evaluated</td>
<td>Open-label; Stage I: 200 patients adaptively randomized on the basis of DCR at 8 weeks and KRAS status; predictive biomarkers for biomarker status for 198 patients based on DCR results for patients previously evaluated</td>
<td>Open-label; adaptive randomization based on pCR results (and MRV) and combination of MammaPrint, BR/PR, and HER2 status</td>
<td>Moleculary targeted drugs are tested with standard neoadjuvant chemotherapy (including anti-HER2 therapy, as appropriate); concurrent control arms are included</td>
<td>Substudies compare molecularly targeted drugs with placebo; drugs meeting phase II efficacy criteria continue to phase III</td>
<td>Substudies compare molecularly targeted drugs with placebo; drugs meeting phase II efficacy criteria continue to phase III</td>
<td></td>
</tr>
<tr>
<td>Overall duration</td>
<td>8+ years</td>
<td>9 years</td>
<td>6 years</td>
<td>5+ years</td>
<td>ND</td>
<td>4 years</td>
<td>ND</td>
</tr>
<tr>
<td>Estimated number of substudies</td>
<td>4-7 concurrent throughout study duration</td>
<td>4</td>
<td>4</td>
<td>8+</td>
<td>20–25</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Disease</td>
<td>Advanced squamous NSCLC</td>
<td>Advanced NSCLC</td>
<td>Advanced NSCLC</td>
<td>Advanced locally invasive breast cancer (neoadjuvant setting)</td>
<td>Advanced solid tumors or lymphomas</td>
<td>Advanced solid tumors</td>
<td>Advanced or metastatic colorectal cancer</td>
</tr>
<tr>
<td>Endpoints</td>
<td>1’ PFS at 8 weeks; RR, toxicity</td>
<td>1’ PFS at 8 weeks; RR, OS, TTP, safety, biomarker, drug PK</td>
<td>1’ DCR at 8 weeks</td>
<td>1’ pCR at 26 weeks; 2’ prognostic biomarkers for PFS and fs (RBC and MRV), RFS and OS at 3 and 5 years, safety</td>
<td>1’ RR</td>
<td>1’ RR (CR+PR) and/or PFS at 16 weeks</td>
<td>1’ PFS in phase II PFS and/or OS in phase III</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 1. Representative basket and umbrella trials (Cont’d)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Lung-MAP</th>
<th>BATTLE</th>
<th>BATTLE 2</th>
<th>I-SPY 2</th>
<th>NCI MATCH</th>
<th>NCI MPACT</th>
<th>FOCUS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to analysis</td>
<td>Phase II: at progression; phase III: at progression and death (specified number of events)</td>
<td>8 weeks</td>
<td>8 weeks</td>
<td>26 weeks</td>
<td>26 weeks</td>
<td>16 weeks</td>
<td>At progression (specified number of events)</td>
</tr>
<tr>
<td>NCI ClinicalTrials.gov and literature citations</td>
<td>NCT02154490</td>
<td>NCT00409968, NCT0041671, NCT0041632, NCT00410059, NCT00410189</td>
<td>NCT004248247 (19)</td>
<td>NCT01042379 (16)</td>
<td>NCT01827384 (17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagnostic:**
- Archival or fresh tumor biopsy: NGS supplemented as needed with IHC and other assay methodologies. See Table 2 for initial biomarkers assayed.

**Tumor biopsy:**
- Analysis for BRAF, PIK3CA, KRAS, and NRAS mutations, epiregulin mRNA, and IHC for MMR and PTEN.

**Fresh tumor biopsy:**
- EGFR mutation and CN, KRAS/BRAF mutation, VEGF/VEGFR-2 expression, RXR/cyclin D1 and CCND1 CN.
- KRAS mutations and assays of predictive biomarkers for EGFR, PI3K/AKT, and MEK inhibitors.
- MammaPrint, IHC for ER and PR, IHC or FISH or TargetPrint for ERBB2.
- NGS supplemented as needed with IHC and FISH assays; approximately 200 genes evaluated; drugs chosen will target major cancer pathways.
- Gene mutations and amplifications relevant to DNA repair, PI3K, or RAS/RAF pathways.
- Analyses for BRAP, PIK3CA, KRAS, and NRAS mutations, epiregulin mRNA, and IHC for MMR and PTEN.

**Abbreviations:**
- CCND: cyclin D gene; CN: copy number; DCR: disease control rate; ER: estrogen receptor; MEK: mitogen-activated kinase kinase; MMR: mismatch repair; MRV: magnetic resonance imaging volume; ND: no data; NGS: next-generation DNA sequencing; pCR: pathologic complete response; PK: pharmacokinetics; PR: progesterone receptor; RCB: residual cancer burden; RFS: relapse-free survival; RR: response rate; RXR: retinoid x receptor; TTP: time to progression.

Lung-MAP: www.clinicaltrials.gov/ct2/show/NCT02154490
BATTLE: www.clinicaltrials.gov/ct2/show/NCT00409968
BATTLE 2: www.clinicaltrials.gov/ct2/show/NCT01042379
I-SPY 2: www.clinicaltrials.gov/ct2/show/NCT01827384
NCI MATCH: www.cancer.gov/clinicaltrials/note-worthy-trials/match#match
NCI MPACT: www.clinicaltrials.gov/ct2/show/NCT01827384
FOCUS4: (ref. 17)
Figure 2.
Lung-MAP study schema. Fresh tumor biopsy or archival FFPE tumor from eligible patients with stage IIB or IV lung SCC whose disease has progressed on first-line therapy is evaluated using NGS (FoundationOne) and, in some cases molecular assays (e.g., IHC-based), carried out in a CLIA-certified laboratory for the presence of drug-specific biomarkers relevant to lung SCC that may serve as targets for drugs currently under study in Lung-MAP. Results are returned within 10–14 days of tissue submission. Patients are then assigned to substudies based on their biomarkers or to a nonmatch therapy substudy; within the substudies the patients are randomized to biomarker-driven targeted or standard-of care (SOC) therapy. Patients with more than one relevant biomarker are assigned to substudies based on an algorithm designed to best balance accrual among the substudies. Accrual and treatment in phase II continues within each substudy until a sufficient number of progression events have occurred to estimate whether or not a drug will likely be successful in the phase III component. Drugs meeting PFS criteria will continue on in phase III until a sufficient number of progression events has occurred to determine whether or not the targeted drug regimen shows statistically and clinically significant improvement in PFS over SOC. Patients will be followed for up to three years to determine effects on OS.
complete remission, or other cancers from which they have been disease free for at least 5 years, are evaluated using next-generation DNA sequencing (NGS) along with additional agent-specific molecular assays for the presence of relevant biomarkers. A key factor in the efficiency of the Master Protocol design is rapid turnaround of screening results to establish substudy eligibility (within 10–14 days). Eligible patients are then assigned to substudies based on their biomarkers or to a ‘nonmatch’ therapy substudy if the patient does not qualify for the biomarker-specific substudies. For enrollment to a substudy, patients must have measurable disease as measured by CT or MRI; if treated for brain metastases, they must have had sufficient time for recovery. They will not have had within the past 28 days and are not planning to have other cancer therapy while on study; have no EGFR mutations or ALK translocations detected during screening; have recovered fully from drug treatment or surgery for their lung cancer; have other cancer therapy while on study; have no EGFR mutations or ALK translocations detected during screening; and are assigned. Within the substudies, patients are randomized to biomarker-driven targeted or standard-of-care (SOC) therapy. In some substudies, targeted therapy plus SOC is compared with SOC. Figure 3 shows the overall schema with the five initial substudies (four targeted therapies and one nonmatch therapy), and Table 2 provides details of the initial substudies.

SCC accounts for approximately 20% to 35% of lung cancer incidence annually (8, 22–26). On the basis of this statistic and the widespread availability of the protocol throughout the NCTN, accrual of 500 to 1,000 patients per year is expected in four to seven concurrent substudies. New substudies will enter the trial on a rolling basis as substudies close, or relevant drug–biomarker pairs with sufficient proof-of-concept become available. Each substudy functions autonomously, opens and closes independently, and is analyzed independently of the other substudies. The duration estimates for each substudy are based on historical data regarding the prevalence of the associated biomarker among lung SCC patients. These estimates may be modified as needed on the basis of the actual prevalence among patients accrued to the study using the Lung-MAP–specific assays (See Table 3). The duration for each substudy is approximately inversely proportional to prevalence, and the accrual is expected to range from 2 to 7 years through phase III. Each substudy will require approximately 300 to 400 patients to complete phase III.

Patients with tumors bearing more than one relevant biomarker are assigned to a substudy based on a predefined algorithm that helps facilitate even enrollment across all substudies. Initially the algorithm will be based on observations in previous studies of lung SCC relevant to the drugs on study, for example, the evaluation of 108 tumors by NGS carried out on the Foundation Medicine (FMI) FoundationOne platform (Fig. 3). In this analysis, overlaps of 2.8%, 2.9%, and 2.0% were estimated for the FGFR biomarker with the CDK, PIK3CA, and c-MET biomarkers, respectively; overlaps of 1.9% and 2.8% were estimated for the CDK biomarker with the PIK3CA and c-MET biomarkers, respectively; and overlap of 1.9% was estimated for the PIK3CA and c-MET biomarkers. The algorithm will be modified as needed during the course of Lung-MAP to accommodate the actual prevalence of overlaps observed for the biomarkers on study. A nonmatch substudy will be open to accrual throughout the trial, ensuring that all enrolling patients receive treatment on protocol.

Each substudy specifies investigator-assessed progression-free survival (IA-PFS) and overall survival (OS) as the coprimary endpoints for the phase III primary objectives. The primary objectives for phase III are to determine whether there is a statistically significant difference in OS and to determine whether there is both a clinically meaningful and statistically significant difference in IA-PFS. The phase II interim analysis in each trial is a “go-no go” decision based on IA-PFS to either continue accruing patients or to close the study for lack of evidence of efficacy at a phase II sample size (8). Along with the paired biomarker, drugs that satisfy the primary objectives have the potential for registration. The choice of PFS as a coprimary endpoint for phase III was made in collaboration with NCI and FDA, based on the well-known difficulties in obtaining unconfounded OS in trials in advanced lung cancer (27). The bar for PFS is high. In phase II,
Table 2. Initial substudies in Lung-MAP

<table>
<thead>
<tr>
<th>Drug (TT, NMT) manufacturer</th>
<th>Substudy regimens</th>
<th>Mechanism of action</th>
<th>Target/biomarkers</th>
<th>Initial estimated prevalence</th>
<th>Estimated duration in months (phase II/III)</th>
<th>Initial estimated patients (phase II/III)</th>
<th>Scientific rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taselisib (GDC-0032) Genentech</td>
<td>TT vs. CT</td>
<td>PI3K Inhibitor (β-isof orm Sparing)</td>
<td>PI3K</td>
<td>6%-8%</td>
<td>152/400</td>
<td>19/72</td>
<td></td>
</tr>
</tbody>
</table>
|                             |                   |                     | PIK3CA mutation  |                           |                                          |                                       | • More potent against PIK3CA mutant than wild-type in vitro (30)
|                             |                   |                     |                  |                           |                                          |                                       | • Promising preliminary clinical activity in PIK3CA mutant cancers, including SCC (30, 31); early data suggest that taselisib is less toxic than other PI3K inhibitors |
| Palbociclib Pfizer          | TT vs. CT        | CDK4/6 inhibitor (highly selective) | CDK4/6 CCND1,2,3 mutation | 12% | 124/312 | 11/45 | 
|                             |                   |                     | CDK4 amplification |                           |                                          |                                       | • Activity in RB+ cell lines and xenografts (32-34)
|                             |                   |                     |                  |                           |                                          |                                       | • Showed clinical activity (SD prolongation) as monotherapy (32-34)
|                             |                   |                     |                  |                           |                                          |                                       | • Very active in combination with letrozole in ER+, HER2+ breast cancer (32-34)
| AZD4547 AstraZeneca         | TT vs. CT        | FGFR kinase inhibitor | FGFR | 9% | 112/302 | 11/53 | 
|                             |                   |                     | FGFR amplification, mutation, fusion |                           |                                          |                                       | • In vitro activity in FGFR amplified, mutated, gene translocated cell lines (35, 36)
|                             |                   |                     |                  |                           |                                          |                                       | • Amplification of FGFR in Chinese NSCLC patient tumors, particularly in SCC patients (36)
|                             |                   |                     |                  |                           |                                          |                                       | • Potent tumor stasis or regression in xenograft models of SCC NSCLC (35, 36)
| Rilotumumab [AMG102] Amgen  | TT + E vs. E     | Anti-HGF            | c-MET            | 16% | 144/326 | 9/37 | 
|                             | [In process of being replaced, Amgen has decided not to continue development for cancer indications] | | c-MET expression |                           |                                          |                                       | • EGFR and MET may cooperate in driving tumorigenesis; well-tolerated in phase I study in patients with advanced solid tumors; evidence of prolongation of stable disease in these patients (37)
|                             |                   |                     |                  |                           |                                          |                                       | • Positive results in phase II trial in gastric cancer; has been in registration trial in gastric cancer (with CT; ref. 38)
| MEDI4736 AstraZeneca/ MedImmune | NMT vs. CT | Anti-PD-L1 | Nonmatch study | 56% | 170/380 | 8/21 | 
|                             |                   |                     | Activity in a PD-L1+ xenograft model |                           |                                          |                                       | • Anti-PD-1 and anti-PD-L1 monoclonal antibodies are active in NSCLC; work is ongoing to define selected populations that will derive most benefit from treatment with these agents (39, 40)

NOTE: Column 1 lists the four targeted therapies (TTs) and one nonmatch therapy (NMT) that comprise the initial set of drugs being evaluated in Lung-MAP. Column 2 shows the arms of the substudies. Three of the TTs are being evaluated as monotherapy against chemotherapy (docetaxel; CT); the fourth is being evaluated in combination with erlotinib (E) against E. Column 3 lists the putative mechanisms of action of the drugs, which form the basis for using these drugs against the targets with corresponding biomarkers listed in Column 4. Column 5 shows the prevalence of the target/biomarkers in lung SCC as estimated using FMI’s FoundationOne NGS platform in 108 lung SCC samples for PIK3CA, CDK4/6, and FGFR (see Fig. 3). c-MET overexpression prevalence is estimated from previous studies of c-MET inhibitors. The estimated prevalence for the nonmatch substudy is 100% less the prevalence for the other targets. Column 6 shows the initial expected size and duration of the phase II and III studies for each drug. Column 7 is a brief description of the evidence supporting testing the drugs in Lung-MAP. Additional information on the biologic activity, clinical efficacy, and toxicity of these drugs can be found in the references cited in this table.

Abbreviations: CCND, cyclin D gene; CDK4/6, cyclin-dependent kinases 4 and 6; ER, estrogen receptor; HGF, hepatocyte growth factor; PD-1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; PIK3CA, gene for PI3K catalytic subunit α; RB, retinoblastoma gene; SD, stable disease.

Target HR is 0.5 (at least a 2-fold increase over controls; based on 55 progression events, yielding 90% power, 10% type I error); the approximate threshold for continuing to phase III is the observation of at least a 41% improvement in median PFS (HR, 0.71). In phase III, the sample size for each substudy is based on a target of 50% improvement in median OS (HR, 0.67), with 90% power and a 2.5% one-sided type I error rate, requiring 256 deaths. The approximate threshold for clinically and statistically significant PFS is 75% improvement in median PFS (HR, 0.57), based on 290 events, power 90%, and type I error rate = 0.014. Drug companies may also choose more stringent criteria for phase II.

Negative trials will be interpreted only as failure of the specific therapeutic agent, and other drugs inhibiting the same target will
be considered for future arms as appropriate (e.g., drugs or drug combinations with different specificity for the target and/or different toxicity profiles).

**Biomarkers and Drugs**

Detailed genomic analysis has identified potential therapeutic targets in more than 60% of lung SCC patients; each of these targets exists in a relatively rare subset of patients (2). Biomarkers for these targets of interest within Lung-MAP are defined by specific genomic alterations (mutations, amplifications, and rearrangements) detected by NGS using the FoundationOne platform (28), supplemented with IHC assays (to detect overexpression of the actionable target) or other methodologies as appropriate, performed in a Clinical Laboratory Improvement Amendment (CLIA)–approved setting. It is anticipated that the NGS-defined biomarker will often be a suitable companion diagnostic for registration purposes. The rationale for an NGS-based screening approach stems from the identification in SCC of multiple genetic alterations that are putative oncogenic "drivers," the comprehensive coverage of markers ensuring a high hit rate, and the short turnaround time for obtaining results (Fig. 4).

Candidate drugs are evaluated by a multidisciplinary drug selection committee using specific criteria such as demonstrated biologic activity against the target associated with a proposed predictive biomarker(s), well-understood mechanism of activity against the target, evidence of clinical activity in cancer, particularly in squamous cell cancers (e.g., phase I responders),manageable toxicity, and practical dosage regimens that are acceptable to the patient and clinician. To date, the study team has focused on monotherapy, but understands, as described below, that more effective therapy may be achieved by targeting multiple components of signaling pathways simultaneously and will begin to explore combinations of targeted drugs. Drug and biomarker selection will be a continuous process during Lung-MAP to replace drugs or drug combinations that leave the study; to ensure that the nonmatch drug arm is always open to accrual; and to add substudies with new drugs or drug combinations/targets. Drug selection for Lung-MAP is a fluid process, intended to be responsive to research advances. The drug selection committee meets frequently, up to monthly, as needed. As described above, when current drugs leave Lung-MAP, other drugs or drug combinations for their targets also may be considered. Candidate drugs will be sought from multiple sources, including interested pharmaceutical companies, clinical investigators, and comprehensive literature surveys. Although the primary focus of Lung-MAP is on strategies with targeted drugs, the nonmatch substudy is also important. It both allows the exploration of new therapies with expected broad-ranging activity across cancers, such as immunotherapy [represented by the current nonmatch substudy with the anti–programmed death receptor ligand 1 (anti–PD-1) drug MEDI4736], and provides a way to offer screen-negative patients access to a promising agent in a clinical trial setting.

Finally, Lung-MAP will provide a rich resource of tissue, blood, and imaging associated with well-documented clinical outcomes from patients with refractory lung SCC for additional translational medicine studies. Considering that SCC is one of the most genetically complex of all tumor types, it is anticipated that many lung SCC tumors will require combination therapies to simultaneously inhibit multiple oncogenic drivers and overcome innate resistance mechanisms, likely necessitating custom-tailored regimens for each patient based on his or her unique tumor genetic profile. Tackling this complexity will require not only comprehensive marker assessment, but also a constant reevaluation and optimization of treatment outcomes that can only be conducted in a systematic clinical trial setting. The typical approach of clinical trials evaluating single biomarker–single treatment pairs in isolation will not be transformative. In addition, although the comprehensive analysis of genetic alterations provided by NGS technology, including DNA mutations, insertions, deletions,

![Table 3. Comparison of prevalence of gene alteration in the substudy eligibility criteria between FMI and TCGA](https://example.com/table3.png)

<table>
<thead>
<tr>
<th>Drug (TT, NMT) manufacturer</th>
<th>Alteration type</th>
<th>FMI prevalence (n = 108 lung squamous cell carcinoma samples)</th>
<th>TCGA prevalence* (n = 178 lung squamous cell carcinoma samples)</th>
<th>FMI vs. TCGA Difference P value (Fisher exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD4547 AstraZeneca Substudy D</td>
<td>FGFR1 Substitution</td>
<td>0.0%</td>
<td>0.6%</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>FGFR1 Fusion</td>
<td>0.0%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>FGFR1 Amplification</td>
<td>7.4%</td>
<td>16.9%</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>FGFR2 Substitution</td>
<td>0.0%</td>
<td>2.2%</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>FGFR2 Fusion</td>
<td>0.0%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>FGFR2 Amplification</td>
<td>0.0%</td>
<td>0.0%</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>FGFR3 Substitution</td>
<td>2.2%</td>
<td>0.0%</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>FGFR3 Fusion</td>
<td>0.0%</td>
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<td>NA</td>
</tr>
<tr>
<td></td>
<td>FGFR3 Amplification</td>
<td>0.0%</td>
<td>0.6%</td>
<td>1</td>
</tr>
<tr>
<td>Palbociclib Pfizer Substudy C</td>
<td>CDK4 Amplification</td>
<td>2.8%</td>
<td>33.3%</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>CCND1 Amplification</td>
<td>1.9%</td>
<td>21.0%</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>CCND2 Amplification</td>
<td>1.9%</td>
<td>21.0%</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>CCND3 Amplification</td>
<td>1.9%</td>
<td>21.0%</td>
<td>0.05</td>
</tr>
<tr>
<td>Rilotumumab (CLX-0032) Genentech Substudy B</td>
<td>PIK3CA Substitution</td>
<td>3.3%</td>
<td>11.8%</td>
<td>0.56</td>
</tr>
</tbody>
</table>

NOTE: This table compares prevalence of gene alterations in the substudy eligibility criteria between FMI and TCGA lung SCC datasets (P values from Fisher exact test shown). The observed prevalences are similar between the two datasets, with the exception of FGFR1 amplifications, observed at a lower prevalence in the FMI dataset.

*TCGA data of SCC (2) were retrieved using cBioPortal (41, 42). Because FMI detects copy-number alterations by fitting a statistical copy-number model to normalized coverage and allele frequencies, whereas the TCGA data used in this comparison were generated using the GISTIC algorithm (43) and application of a per-sample variable threshold, the absolute level at which amplifications are called could not be directly compared. Given that amplifications in the FMI approach are called at an estimated 6 copies or above and adjusted to 7 copies for triploid and 8 copies for tetraploid specimens, it is likely that the difference is explainable by the more stringent definition of amplification in the FMI approach.
There are challenges to Lung-MAP, and to cancer drug development generally, that can be tackled as the study progresses, and the strategies for handling the challenges can be incorporated into designs to facilitate future trials. One example is that the Lung-MAP approach requires large and rapid accrual from many sites. This is addressed in part by the NCTN mechanism, which coordinates activities between different cooperative group research sites and their affiliates, allowing Lung-MAP to be offered as a clinical trial option at hundreds of institutions and treatment centers around the country, and potentially internationally. To accelerate access to as many sites as possible, Lung-MAP uses the NCI Central IRB (CIRB). By doing so, individual research institutions that allow the CIRB to replace institutional IRBs have fewer administrative steps to activating the trial, while maintaining the safety of study participants. Use of the CIRB is currently optional for NCTN sites; however, its use will become mandatory in 2015. Although the general NCTN site qualification procedures are cost-effective and rigorous regarding requirements for study staff and facilities, they do not suffice for ensuring that adequate awareness, training, staff, and facilities are in place for individual studies across the NCTN. Additional qualification and planning activities through direct contact with sites, NCTN-wide webinars, and regional investigator meetings are warranted.

Another challenge is that Lung-MAP requires commitment by pharmaceutical partners and the FDA to ensure that the trial provides a regulatory approval pathway. To support this need, all partners—NCI, FDA, pharmaceutical companies, academic leaders, SWOG, Friends, and FNIH—have been involved in the design and development of the study as a whole, as well as of individual substudies. Furthermore, it is difficult to conduct randomized trials in settings in which patients have multiple options for obtaining treatment with targeted agents. To reduce confusion and help patients reach the best decisions for their care, a system has been put in place for Lung-MAP to provide guidance to physicians and patients on evaluation of screening results.

Finding the best drugs is another challenge. More than 100 candidate drugs were reviewed to identify the five in the first round that coordinates activities between different cooperative group research sites and their affiliates, allowing Lung-MAP to be offered as a clinical trial option at hundreds of institutions and treatment centers around the country, and potentially internationally. To accelerate access to as many sites as possible, Lung-MAP uses the NCI Central IRB (CIRB). By doing so, individual research institutions that allow the CIRB to replace institutional IRBs have fewer administrative steps to activating the trial, while maintaining the safety of study participants. Use of the CIRB is currently optional for NCTN sites; however, its use will become mandatory in 2015. Although the general NCTN site qualification procedures are cost-effective and rigorous regarding requirements for study staff and facilities, they do not suffice for ensuring that adequate awareness, training, staff, and facilities are in place for individual studies across the NCTN. Additional qualification and planning activities through direct contact with sites, NCTN-wide webinars, and regional investigator meetings are warranted.

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Lung-MAP: A Protocol for Accelerating Drug Development

**Disclosure of Potential Conflicts of Interest**

R.S. Herbst is a consultant/advisory board member for Biothera, Diaceutic, Eli Lilly, Genentech, Merck, N-of-One, and Pfizer. F.R. Hirsch is a consultant/advisory board member for AstraZeneca and Genentech. L.H. Schwartz is a consultant/advisory board member for Pfizer and is on the endpoint analysis committee for Celgene, ICON, and Novartis. S.S. Ramalingam is a consultant/advisory board member for Amgen, AstraZeneca, and Genentech. J.D. Bradley reports receiving a commercial research grant from Varian Medical Systems. V.A. Miller, R. Yelensky, and Y. Li are employees of and have ownership interest in Foundation Medicine. C.C. Signman is an employee of CCS Associates. V.A. Papadimitrakopoulou is a consultant/advisory board member for Amgen, AstraZeneca, Biothera, Clovis Oncology, Eli Lilly, Genentech, Genesignia Life Sciences, and Janssen. No potential conflicts of interest were disclosed by the other authors.

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Writing, review, and/or revision of the manuscript: R.S. Herbst, D.R. Gandara, F.R. Hirsch, M.W. Redman, M. LeBlanc, D. Sparks, Y. Zhou, R. Yelensky, G.M. Blumenthal, S. Malik, C.D. Blanke, V.A. Papadimitrakopoulou

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.S. Herbst, D.R. Gandara, F.R. Hirsch, M.W. Redman, D. Sparks, Y. Zhou, C. Ntiva, C.C. Signman, G.M. Blumenthal, C.D. Blanke, V.A. Papadimitrakopoulou


Other (managing and administering underlying partnership and governance; project management): D. Wholley

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**References**


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