

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

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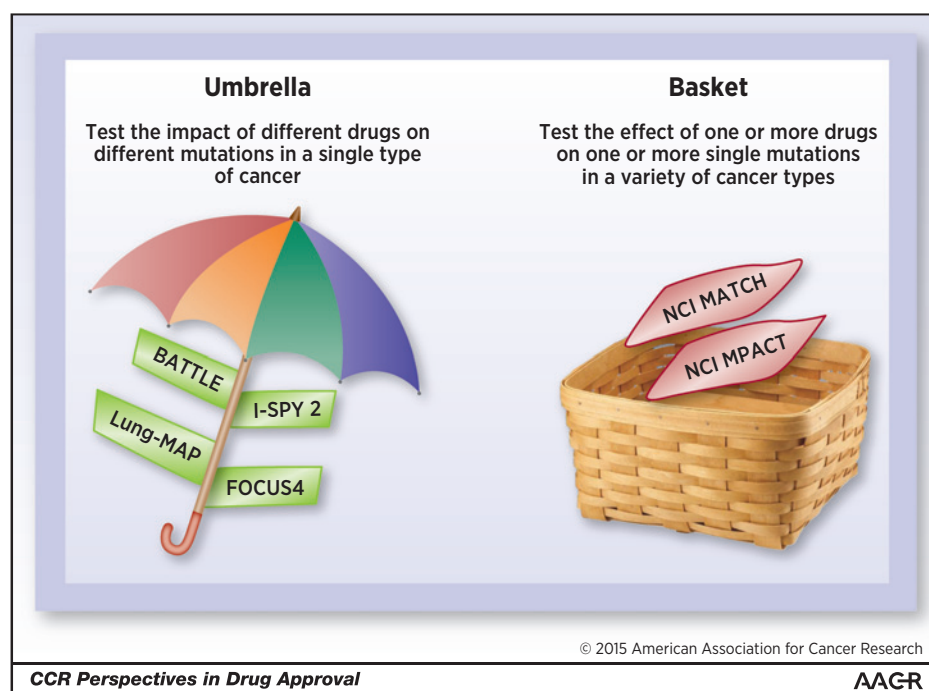
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Figure 1.
The trials listed are currently ongoing or soon to be activated trials with "umbrella" or "basket" designs with partial funding from the U.S. or UK government. Details of these studies are presented in Table 1.



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): "basket" 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, "umbrella" 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)

Table 1. Representative basket, and umbrella trials

	Lung-MAP	BATTLE 2	I-SPY 2	NCI MATCH	NCI IMPACT	FOCUS4
Status	Recruiting	BATTLE 2 Recruiting	I-SPY 2 Recruiting	NCI MATCH Not yet open	NCI IMPACT Recruiting	FOCUS4 Not yet open
Design and enrollment to screening and to substudies of therapeutics	Umbrella design Phase II/III	Umbrella design Phase II	Umbrella design Phase II	Basket design Phase II	Basket design Phase II	Umbrella design Phase II/III
Number of sites	700+	2	23	Est. 2,400	1	ND
Design and enrollment to screening and to substudies of therapeutics	3,125-6,250 planned for screening enrollment; 2,500-5,000 planned for randomization to substudies over 5 years	400 planned for enrollment to substudies	800 planned for randomization to substudies	3,000 planned for screening; 1,000-1,500 anticipated for assignment to substudies	700 planned for screening; 180 anticipated to be evaluable; feasibility study to be conducted in first 60 evaluable patients.	2,000 estimated for randomization to substudies
Design and enrollment to screening and to substudies of therapeutics	Open-label, equal randomization for 97 patients across biomarkers and drugs followed by adaptive randomization on biomarker status for 158 patients based on DCR results for patients previously evaluated	Open-label; Stage 1: 200 patients adaptively randomized on the basis of DCR at 8 weeks and KRAS status; predictive biomarkers/ biomarker signatures to be developed	Open label, adaptive randomization based on pCR results (and MRV) and combination of MammaPrint, ER/PR, and HER2 status		Substudies compare molecularly targeted drugs matching patients' molecular profiles with drugs not specific for the patients' molecular profiles	Multiarmed, multistage randomized trial design; patients are evaluated for the presence of relevant biomarkers during 16 weeks of standard first-line chemotherapy; patients who respond or have stable disease at the end of the 16 weeks are assigned to a substudy with drug(s) relevant to their biomarkers
Design and enrollment to screening and to substudies of therapeutics	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	Stage 2: 200 patients adaptively randomized on the basis of biomarkers/ signatures developed in stage 1	Molecularly targeted drugs are tested with standard neoadjuvant chemotherapy (including anti-HER2 therapy, as appropriate); concurrent control arms are included			Substudies compare molecularly targeted drugs with placebo; drugs meeting phase II efficacy criteria continue to phase III
Overall duration	8+ Years	9 years	5+ years	ND	4 years	ND (9 year est.)
Estimated number of substudies	4-7 concurrent throughout study duration	4	8+	20-25	4	5
Disease	Advanced squamous NSCLC	Advanced NSCLC	Advanced locally invasive breast cancer (neoadjuvant setting)	Advanced solid tumors or lymphomas	Advanced solid tumors	Advanced or metastatic colorectal cancer
Endpoints	1' PFS/phase II, PFS and/or OS/phase III 2' RR, toxicity	1' PFS at 8 weeks 2' RR, OS, TTP, safety, biomarker, drug PK	1' pCR up to 26 weeks 2' prognostic biomarkers for PFS and fs (RCB and MRV), RFS and OS at 3 and 5 years, safety	1' RR 2' PFS	1' RR (CR+PR) and/or PFS at 16 weeks	1' PFS in phase II PFS and/or OS in phase III

(Continued on the following page)

Table 1. Representative basket and umbrella trials (Cont'd)

	Lung-MAP	BATTLE	BATTLE 2	I-SPY 2	NCI MATCH	NCI MPACT	FOCUS4
Time to analysis	Phase II: at progression; phase III: at progression and at death (specified number of events)	8 weeks	8 weeks	26 weeks	26 weeks	16 weeks	At progression (specified number of events)
NCI ClinicalTrials.gov and literature citations	NCT02154490	NCT00403968, NCT00411671, NCT00411632, NCT00410059, NCT00410189 (18)	NCT01248247 (19)	NCT01042379 (16)	(15)	NCT01827384	(17)
Diagnostic	Archival or fresh tumor biopsy: NGS supplemented as needed with IHC and other assay methodologies. See Table 2 for initial biomarkers assayed.	Fresh tumor biopsy: EGFR mutation and CN, KRAS/BRAF mutation, VEGF/VEGFR-2 expression, RXR/cyclin D1 and CCND1 CN	Fresh tumor biopsy: KRAS mutations and assays of predictive biomarkers for EGFR, PI3K/AKT, and MEK inhibitors	Fresh tumor biopsy: MammaPrint, IHC for ER and PR, IHC or FISH or TargetPrint for ERBB2	Fresh tumor biopsy: NGS supplemented as needed with IHC and FISH assays; approximately 200 genes evaluated; drugs chosen will target major cancer pathways	Fresh tumor biopsy: gene mutations and amplifications relevant to DNA repair, PI3K, or RAS/RAF pathways	Tumor biopsy: analysis for BRAF, 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/NCT00403968
 BATTLE 2: www.clinicaltrials.gov/ct2/show/NCT01248247
 I-SPY 2: www.clinicaltrials.gov/ct2/show/NCT01042379
 MATCH: www.cancer.gov/clinicaltrials/noteworthy-trials/match#match
 MPACT: www.clinicaltrials.gov/ct2/show/NCT01827384
 FOCUS4: (ref. 17)

and Friends of Cancer Research (Friends)/Brookings Conference on Clinical Cancer Research (22), and was implemented in June 2014. A key design aspect is inclusion of a biologically driven approach to identify targets building on the NCI funded The Cancer Genome Atlas (TCGA; refs. 1, 2). In February 2012, the NCI, including investigators of the TMSC, FDA, European Medicines Agency, and pharmaceutical companies, met on the subject of "Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer." Following that meeting, a TMSC task force was established to develop a series of Lung Cancer Master Protocols. Simultaneously, Friends, in conjunction with FDA and NCI, initiated a similar effort presented as part of the November 2012 Conference on Clinical Cancer Research hosted by Friends and the Engelberg Center for Health Care Reform at the Brookings Institution, and published a white paper that formed the basis for Lung-MAP (22). In March 2013, at a follow-up Friends forum, the decision was made to go forward with the study as a public-private partnership. This partnership brings the different initiatives together, involving the NCI and its Cooperative Group/National Clinical Trials Network (NCTN) infrastructure, the FDA, multiple pharmaceutical companies, Friends, and lung cancer nonprofit organizations and patient advocates. The Lung-MAP public-private partnership is being conducted within the NCTN spearheaded by SWOG. The Foundation for the National Institutes of Health (FNIH) is the convener of the public-private partnership; Friends and FNIH are members of the project's oversight committees and, together with SWOG, are responsible for project management. The final design for Lung-MAP, including the first five drugs and biomarkers to be

evaluated, was announced at the 2013 Friends/Brookings Institution Conference on Clinical Cancer Research on November 7, 2013.

Here, we describe the study design, initial selection of drugs, and biomarkers, additional translational medicine studies that might be carried out under Lung-MAP, and a further discussion of the challenges and benefits of the Master Protocol design.

Study Design

The overarching goal for this trial is to establish an NCTN mechanism for genomically screening large, clinically well-defined cancer populations and assigning screened patients to substudies within a Master Protocol. These substudies are defined by genotypic alterations (biomarkers) in the tumor paired to drugs that target these alterations. Figure 2 shows the general schema for Lung-MAP. For screening, patients must have adequate tumor tissue for evaluation from either archival formalin-fixed paraffin-embedded (FFPE) or fresh tumor biopsies; archival tissue must be a tumor block or a minimum of 12 FFPE slides 4 to 5 μm thick (20 slides preferred). Patients ≥ 18 years of age, with adequate tissue and pathologically proven advanced-stage lung SCC (stage IIIB or IV), without known *EGFR* mutations or *ALK* fusions, whose disease has progressed on exactly one first-line platinum-based therapy (or therapy plus radiation treatment) for metastatic lung cancer, and with Zubrod performance scores ≤ 2.0 , who have had no prior malignancies except adequately treated basal and squamous cell skin cancers and cervical cancers *in situ*, treated stage I/II cancers from which they are in

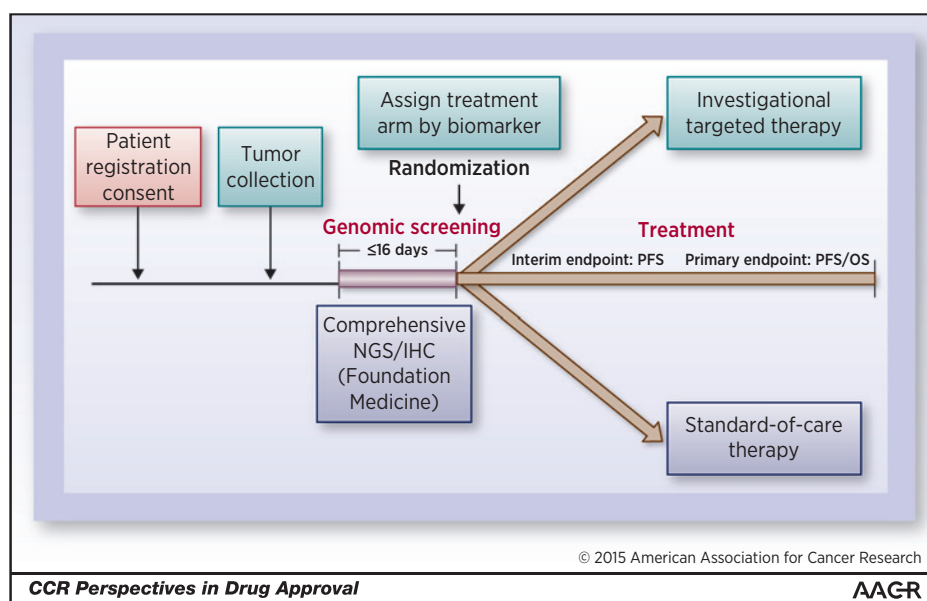
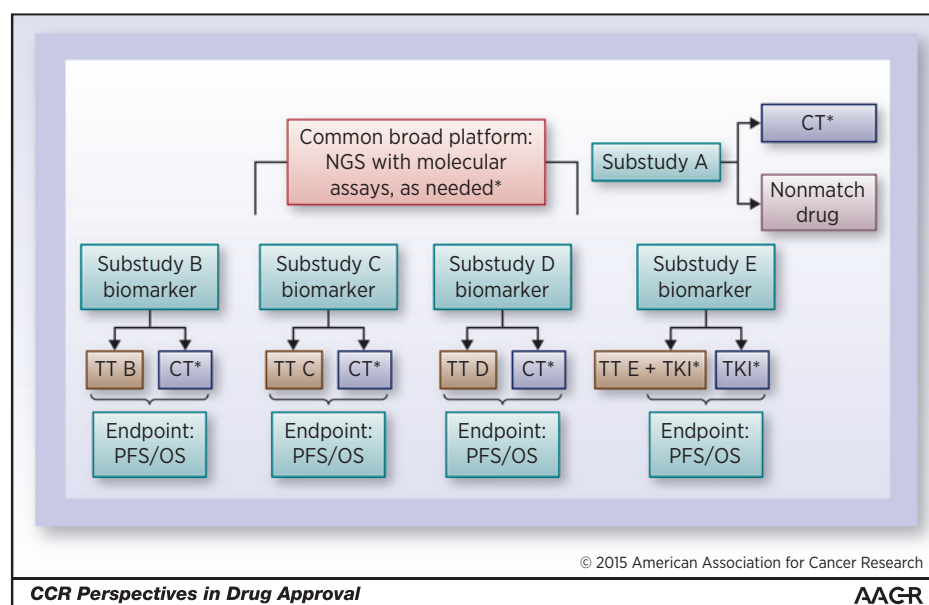


Figure 2.

Lung-MAP study schema. Fresh tumor biopsy or archival FFPE tumor from eligible patients with stage IIIB 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 been observed 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.

Figure 3.

Schema for Lung-MAP substudies, June 2014. *, Archival FFPE tumor, fresh core needle biopsy (CNB) if needed; TT, targeted therapy; CT, chemotherapy (docetaxel or gemcitabine); TKI, tyrosine kinase inhibitor (erlotinib). See Table 2 for description of initial substudies in Lung-MAP.



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 adequate organ function and Zubrod performance scores ≤ 2.0 , and meet other criteria specific to the substudy to which they 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%, 0.9%, 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

Drug (TT, NMT) manufacturer	Substudy regimens	Mechanism of action	Target/ biomarkers	Initial estimated prevalence	Initial estimated patients (phase II/III)		Scientific rationale
					Estimated duration in months (phase II/III)		
Taselisib (GDC-0032) Genentech	TT vs. CT	PI3K Inhibitor (β -isoform Sparing)	PI3K	6%–8%	152/400	19/72	<ul style="list-style-type: none"> • More potent against <i>PIK3CA</i> mutant than wild-type <i>in vitro</i> (30) • Promising preliminary clinical activity in <i>PIK3CA</i> mutant cancers, including SCC (30, 31); early data suggest that tselisib is less toxic than other PI3K inhibitors
			<i>PIK3CA</i> mutation				
Palbociclib Pfizer	TT vs. CT	CDK4/6 inhibitor (highly selective)	CDK4/6	12%	124/312	11/45	<ul style="list-style-type: none"> • Activity in <i>RB</i>⁺ 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)
			<i>CCND1,2,3</i> mutation				
AZD4547 AstraZeneca	TT vs. CT	FGFR kinase inhibitor	FGFR	9%	112/302	11/53	<ul style="list-style-type: none"> • <i>In vitro</i> activity in <i>FGFR</i> amplified, mutated, gene translocated cell lines (35, 36) • Amplification of <i>FGFR1</i> in Chinese NSCLC patient tumors, particularly in SCC patients (36) • Potent tumor stasis or regression in xenograft models of SCC NSCLC (35, 36)
			<i>FGFR</i> amplification, mutation, fusion				
Rilotumumab [AMG102] Amgen	TT + E vs. E	Anti-HGF	c-MET	16%	144/326	9/37	<ul style="list-style-type: none"> • 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)
[In process of being replaced, Amgen has decided not to continue development for cancer indications]			c-MET expression				
MEDI4736 AstraZeneca/ MedImmune	NMT vs. CT	Anti-PD-L1	Nonmatch study	56%	170/380	8/21	<ul style="list-style-type: none"> • 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)
			Activity in a PD-L1 ⁺				

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

Table 3. Comparison of prevalence of gene alteration in the substudy eligibility criteria between FMI and TCGA

Drug (TT, NMT) manufacturer substudy ID	Gene	Alteration type	FMI prevalence (n = 108 lung squamous cell carcinoma samples)	TCGA prevalence ^a (n = 178 lung squamous cell carcinoma samples)	FMI vs. TCGA Difference P value (Fisher exact test)
AZD4547 AstraZeneca Substudy D	FGFR1	Substitution	0.0%	0.6%	1
		Fusion	0.0%	NA	NA
		Amplification	7.4%	16.9%	0.03
	FGFR2	Substitution	0.0%	2.2%	0.30
		Fusion	0.0%	NA	NA
		Amplification	0.0%	0.0%	1
	FGFR3	Substitution	3.7%	2.2%	0.48
		Fusion	0.0%	NA	NA
		Amplification	0.0%	0.6%	1
Palbociclib Pfizer Substudy C	CDK4	Amplification	0.9%	0.0%	0.38
	CCND1	Amplification	8.3%	12.4%	0.33
	CCND2	Amplification	2.8%	2.2%	1
	CCND3	Amplification	1.9%	0.6%	0.55
Rilotumumab [GDC-0032] Genentech Substudy B	PIK3CA	Substitution	9.3%	11.8%	0.56

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.

^aTCGA 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.

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 FMI FoundationOne platform (28), supplemented with IHC assays (to detect over-expression 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-L1) 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,

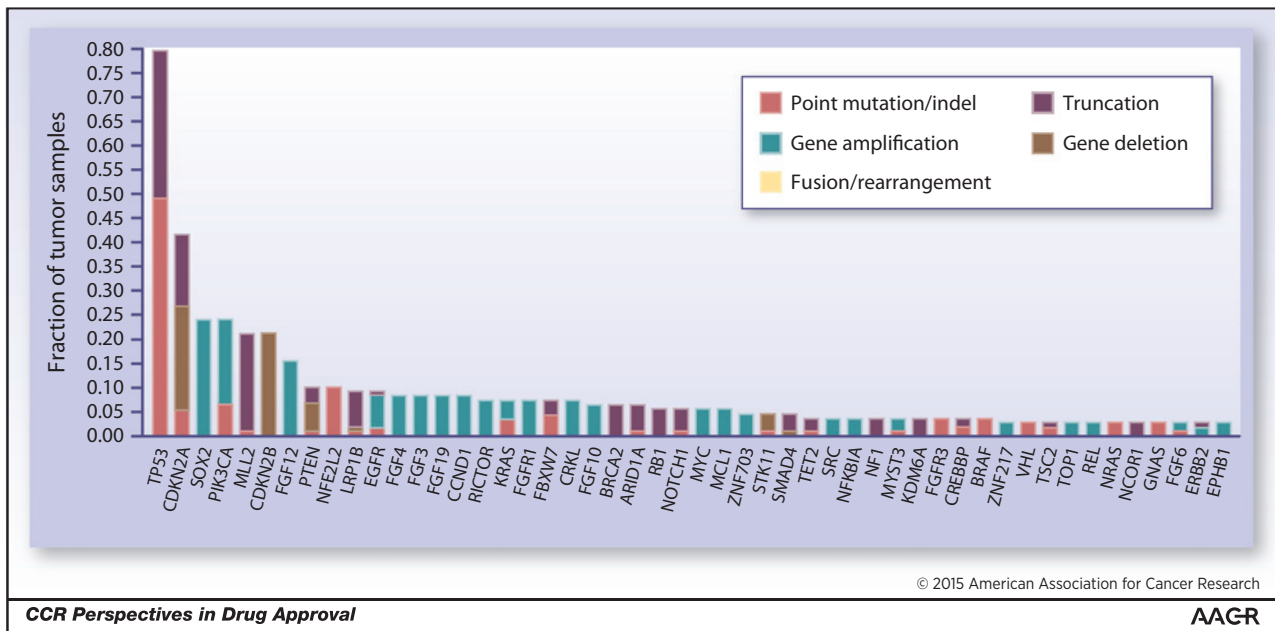


Figure 4.

Prevalence of genomic alterations in lung SCC. This chart shows the prevalence and pattern of mutations, amplifications, and rearrangements seen in 108 consecutive FFPE lung SCC tumor samples sequenced using the FMI FoundationOne platform to an average unique median depth (the number of times a given region has been sequenced by independent reads) of >500 \times . This plot highlights the diversity of alterations in lung SCC and the importance of a comprehensive genomic assessment with respect to both the number of genes assessed and alteration types.

copy-number abnormalities, and chromosomal aberrations, is by far the most promising screening approach currently available, analysis of protein disposition may prove equally informative in some instances, necessitating development of additional biomarker assays. Finally, analysis of blood-based biomarkers has seen a recent resurgence subsequent to the development of highly sensitive, highly accurate analytics. Many research groups are currently developing approaches to investigate cell-free tumor DNA in peripheral circulation or detailed multiplexed analysis of circulating tumor cells. In addition to obviating the need for arduous and expensive tumor biopsies, theoretical advantages to a blood-based biomarker approach include reduced sampling error from individual biopsies in heterogeneous tumors such as SCC, and the ability to detect emergence of acquired resistance mechanisms/alternative drivers over the course of therapy. The serial blood draws collected from each patient enrolled in Lung-MAP, added to the comprehensive tumor tissue analysis, will provide an invaluable resource for accelerated development of predictive blood-based biomarkers. The central collection of imaging data will allow for a better understanding of the radiomic signature of SCC, understanding of the image-based response and progression in these subsets and the potential to centrally verify IA-PFS.

Discussion—Challenges and Benefits

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

Text Box 1. Benefits of Lung-MAP approach for drug development

- Grouping biomarker-driven targeted drug studies under a single trial will reduce the screen failure rate, making the screening efficient and worthwhile for both patients and physicians
- Operational and protocol development efficiencies are provided by the Master Protocol framework; for example, consistency is provided by applying the Master Protocol—every drug for the disease would be tested in the identical manner
- A regulatory approval pathway is provided for drugs and companion diagnostic biomarkers
- Shared infrastructure for screening, database, enrollment, site management, etc., is less costly than in individual studies
- Improvement in overall efficiency of drug development is provided in a specific disease setting, bringing safe and more effective drugs to patients sooner than they might otherwise be available

of Lung-MAP. In many cases, exciting new drugs do not have the supporting clinical data needed for immediate selection for Lung-MAP. To address this problem, a pipeline could be established via phase I/IIa studies to identify candidates early in development and seamlessly develop needed data for the new candidate to become eligible for Lung-MAP. Another issue for access to drugs is company concerns regarding risks to primary development paths for their drugs. Although the costs to pharmaceutical companies for Lung-MAP are much less than for individual company-run studies, they are still significant. Particularly, the burden to smaller companies that may have exciting drugs, but limited development resources should be considered in funding strategies.

Finally, the importance of integrating measures of patient reported outcomes (PRO) into clinical trials is increasingly recognized. Lung-MAP will incorporate PROs so that this added dimension is accounted for in judging the overall impact of new therapies.

In summary, Lung-MAP is a public-private collaboration in which each partner is committed to rapidly identify new active drugs for SCC NSCLC and to shorten the approval pathway (29). Lung-MAP is a new model for high-quality drug development in less time, at less cost, and, most importantly to improve the lives of patients with lung cancer. The benefits of this approach are summarized in Text Box 1 (29). The shared goal of accelerating the pace in which new drugs are developed is the driving force behind the Lung-MAP partnership.

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Disclosure of Potential Conflicts of Interest

R.S. Herbst is a consultant/advisory board member for Biothera, Diatech, 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. Sigman is an employee of CCS Associates. V.A. Papadimitrakopoulou is a consultant/advisory board member for Amgen, AstraZeneca, Biothera, Clovis Oncology, Eli Lilly, Genentech, Gensignia Life Sciences, and Janssen. No potential conflicts of interest were disclosed by the other authors.

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