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Squamous Cell Lung Cancer: From Tumor Genomics to Cancer Therapeutics

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Abstract

Squamous cell lung cancer (SCC) represents an area of unmet need in lung cancer research. For the last several years, therapeutic progress in SCC has lagged behind the now more common NSCLC histologic subtype of adenocarcinoma. However, recent efforts to define the complex biology underlying SCC have begun to bear fruit in a multitude of ways, including characterization of previously unknown genomic and signaling pathways, delineation of new potentially actionable molecular targets, and subsequent development of a large number of agents directed against unique SCC-associated molecular abnormalities. For the first time, SCC-specific prognostic gene signatures and predictive biomarkers of new therapeutic agents are emerging. In addition, recent and ongoing clinical trials, including the Lung-MAP master protocol, have been designed to facilitate approval of targeted therapy-biomarker combinations. In this comprehensive review we describe the current status of SCC therapeutics, recent advances in the understanding of SCC biology and prognostic gene signatures, and the development of innovative new clinical trials, all of which offer new hope for patients with advanced SCC.

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Introduction

Squamous cell carcinoma of the lung (SCC), formerly the most common histologic subtype of non-small cell lung cancer (NSCLC), has steadily fallen in incidence over the last few decades, largely attributed to decreased smoking rates and changes to cigarette composition and filtering, which favor adenocarcinoma histology (1). Nevertheless, lung SCC remains a common malignancy overall, accounting for approximately 85,000 new cases in the USA each year and over 400,000 worldwide. The great majority of patients with SCC are current or former heavy smokers, in contrast to adenocarcinoma, where a growing proportion are never-smokers or former light smokers. (2,3) SCC remains highly associated with cigarette smoking; it is therefore not surprising that recent efforts to genomically characterize lung cancer, such as those of The Cancer Genome Atlas (TCGA) and others, have demonstrated that in general, SCC reflects the genomic complexity and high overall mutational load expected from tobacco carcinogenesis. As described below, genomically-defined subsets of SCC have now been identified, some of which have therapeutic implications for a growing number of developing targeted agents. In a similar fashion, despite multiple studies, there are currently no universally accepted prognostic gene signatures upon which to gauge risk of recurrence and subsequent death, or need for adjuvant chemotherapy in post-surgical patients with SCC.

While therapy of early stage SCC mimics that of other histologic subtypes of NSCLC, therapeutic options for advanced stage SCC in comparison with lung adenocarcinoma, in part due to discovery of “druggable” oncogene targets in never-smoker subsets of adenocarcinoma, such as those with activating mutations in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) gene rearrangements (4). As of this writing, there is still no FDA-approved targeted therapy for advanced SCC, in which a biomarker is utilized to select patients most likely to benefit. Instead, the standard of care for frontline palliative systemic therapy remains platinum-based doublet chemotherapy, a clinical scenario that has not changed considerably for nearly two decades.

Here we describe recent advances in the molecular profiling of SCC, ongoing work to establish reliable prognostic gene signatures in early stage SCC, and new therapeutic approaches to advanced stage disease. Finally, unique perspectives are offered on how these developments will impact clinical care for the SCC patient and ultimately enhance patient outcomes.

Genomics of Lung SCC

Recent comprehensive genomic surveys have defined the genomic and epigenomic alterations driving lung SCC. Prior to these studies little was known about SCC genomics. However, several reports using single platform methods such as gene expression profiling, Single Nucleotide Polymorphism (SNP) arrays and focused DNA sequencing showed that the genetic alterations defining lung adenocarcinomas and SCC were distinct, likely explaining the lack of efficacy of targeted therapeutic agents in SCC which had been applied successfully in lung adenocarcinomas.

Lung SCC is defined by a strong genomic signature of tobacco use with most cohorts reporting a rate of tobacco exposure in excess of 90%(5). SCC displays a somatic mutation rate and spectrum comparable to that of patients with small cell lung cancer or other smoking-related cancers and is dissimilar to lung adenocarcinoma in which cancers from non-smokers harbor one-fifth to one-sixth the genomic alterations of a smoker's cancer(6–9). This homogeneity is evident on a worldwide basis, as most genomic studies of lung SCC performed by investigators from North America, Europe and Asia have identified similar spectra of genomic alterations in their patient populations and similar subclasses of SCC. Further, the genomic alterations in lung SCC are strikingly similar to those found in Human Papilloma Virus (HPV) negative head and neck cancers(10, 11). The high mutation rate in SCC is likely to result in expression of a large complement of tumor antigens, and many of these are in the process of being defined in the context of immunotherapy trials.

In lung adenocarcinoma much attention has been devoted to the concept of "driver oncogenes," genomic alterations in kinase genes or other key mitogenic pathways which are required for ongoing tumor proliferation and on which the tumor is dependent. This concept has led to the clinical use of a number of kinase inhibitors in lung adenocarcinomas in genomically-selected patients and has improved outcomes for these individuals. In lung SCC recurrent alterations in kinase genes do not appear to be core genomic events with the most common genomic alterations being loss of *TP53* and *CDKN2A* in the vast majority of cases(7–9). Other highly prevalent alterations that occur in a mutually exclusive manner are mutations of *NFE2L2/KEAP1/CUL3*, which activate a transcriptional program associated with response to oxidative stress, and truncating mutations of the *NOTCH1* gene, a critical regulator of squamous cell differentiation(7, 8, 12, 13). SCCs of the lung and other organs are further defined by common amplification of 3q, a region containing *SOX2, TP63* and *PIK3CA* and also by amplification of 7p11 and 8p12, regions harboring the *EGFR* and *FGFR1* genes(3, 9, 14, 15). Highly recurrent tyrosine kinase mutations have not been reported in lung SCC, though mutations in *FGFR2, FGFR3* and *DDR2* have been described as potential therapeutic targets along with *BAG4-FGFR1* and *FGFR3-TACC3* fusions(16–19). Moreover, many SCC lung tumors display somatic alterations in one or more genes involved in PI3K/AKT signaling, though the functional consequences of many of these alterations remain unclear(7). Finally, genomic alterations in genes governing cellular immunity and immune evasion have been described including *HLA-A, HLA-B, HLA-C, B2M, MICA, MICB, ULBP1* and *ULBP2*(7) (Table 1).

FGFR kinases as genomically altered targets

With frequent focal amplification of *FGFR1*, recurrent activating mutations of *FGFR2* and *FGFR3* as well as *FGFR1/3* fusion events the fibroblast growth factor receptor family represents the biggest and best studied class of "druggable" targets in lung SCC. Given the high recurrence of *FGFR1* amplifications (10–15%) in lung SCC several groups have focused on the study of FGFR1 as a drug target in these tumors. A number of preclinical studies have shown that within the group of FGFR1-amplified SCC cell lines, a subgroup of cell lines is exquisitely sensitive to inactivation of FGFR1 signaling (3, 15). Consequently, in selected FGFR1-driven mouse xenograft models deactivation of FGFR1 leads to tumor shrinkage(20). Similar striking sensitivity to FGFR inhibition has been reported for a subset

of tumors within the group of FGFR-mutant and FGFR-fusion positive samples in both pre-clinical and early clinical studies.

However, the modulators of FGFR1-dependency remain controversial and initial clinical data suggest that a minority of patients with *FGFR1* amplification will derive clinical benefit from FGFR kinase inhibitors(21, 22). A number of studies have shown that the genomic pattern of the 8p12 locus amplifications is heterogeneous and that only a minority of tumors shows focal, high level amplification of *FGFR1*(3, 15, 23). The genomic complexity of the 8p12 locus together with the low resolution of routine FISH-based diagnostics for the detection of *FGFR1* amplification might potentially lead to misclassification of tumors and subsequent underestimation of the activity of currently tested FGFR inhibitors. The difficulties with the precise determination of *FGFR1* amplification status might also contribute to the fact that high mRNA and protein FGFR1 levels are found only in a subset of cells that are classified as *FGFR1*-amplified(3, 15, 24). This may be of importance as gene expression and protein levels of FGFR1 might correlate with the response rate to FGFR targeted drugs(24). Another source for modulators of FGFR1-dependency are FGFR ligands. It has been shown that *FGFR1*-amplified cells may be able to express and secrete a variety of FGFR ligands such as FGF-2 and FGF-9 that may be required to fully activate intracellular FGFR signaling(24, 25). An additional layer of complexity for the determination of FGFR1-dependency is the co-occurrence of *FGFR1*-amplifications with other genomic lesions such as *MYC* (Fig. 1). Recent evidence suggests that in *FGFR1*-amplified tumors high protein expression of the transcription factor MYC may be associated with pronounced response to FGFR inhibitors(23). However, a mechanistic link between the lineage-specific role of *MYC* in SCC tumors and FGFR1-dependency is currently missing.

Analogous to other oncogenically driven lung tumors, feedback-loop mediated activation of resistance signaling may further complicate the ability to effectively treat patients with *FGFR1*-amplified tumors. Multiple studies have shown that EGFR and MET activation can facilitate adaptive resistance to FGFR inhibition in pre-clinical models (26–28). Overall, a major challenge for future initiatives will be the translation of the understanding of potential modulators of FGFR-dependency into routine clinical diagnostic for the enrichment of patients that might benefit from FGFR targeted drugs.

Prognostic Gene Signatures and the SPECS Project

Prognostic factors for SCC have been mostly derived from surgically resected tumors in patients with early stage disease. In patients with advanced disease, treatments such as chemotherapy, radiotherapy, or targeted therapies may alter prognostic associations, and/or be predictive or combined prognostic/predictive. Of interest, among the numerous reports on genomic classifiers, there is surprisingly little overlap (29) (Fig. 2), and very few validation studies. Therefore, none of the prognostic classifiers are commonly used today in clinical practice. Additionally, studies reporting on prognostic factors are very heterogeneous regarding study populations and histology, which makes comparisons and validation even more difficult. Here we describe ongoing efforts to develop a validated prognostic classifier, being undertaken by a dedicated group of investigators who have established a “Squamous Lung Cancer Consortium” with the overall goal of validating existing (published and non-

published) prognostic signatures within clinically well-defined SCC cohorts by using a standardized protocol for tissue processing, one centralized lab for RNA (and eventually DNA) extraction and with central histo-pathologic evaluation (Fig. 3). Once validated, the signatures can be used to develop clinically useful tests to differentiate patients with early stage SCC who have a poor prognosis versus a good prognosis.

The “Consortium”, which includes investigators from seven US/ Canadian institutions (University of Colorado, Mayo Clinic, University of Michigan, The Brigham and Women’s Hospital, University of California Davis, Washington University in St. Louis, Duke University and Princess Margaret Hospital in Toronto) was awarded the NCI SPECS (Strategic Partnering to Evaluate Cancer Signatures) grant. The SPECS project will determine if existing mRNA and miRNA prognostic signatures can distinguish between SCC patients with good prognosis versus poor prognosis first in a test set of 300 patients with early stage SCC (no adjuvant therapy and with a minimum of 3 years follow-up). Based on this evaluation and eventual development of “new signature (s)”, two validation sets have been identified and accepted for use: one a surgically treated SCC cohort (N=150) from the previous Cancer and Leukemia Group B (CALGB) and one from the American College of Surgeons Oncology Group (ACOSOG) (N=250), both cohorts today under the Alliance. The SPECS project includes also a validation of The Cancer Genome Atlas (TCGA) Project for SCC (7). Thus, it is the goal with the ongoing SPECS SCC Program to validate and eventually develop new prognostic classifier (s) based on standardized protocols and well-defined clinical cohorts and validate the prognostic association of the gene abnormalities found in the lung TCGA project and eventually identify new therapeutic targets.

Current Therapeutic Options for Lung SCC

Standard therapy

Patients diagnosed with metastatic or recurrent SCC of the lung are candidates for frontline systemic therapy given with a palliative (i.e., non-curative) intent. Unlike adenocarcinoma of the lung for which initial therapy is guided by the presence or absence of an increasing number of driver mutations, the standard of care for metastatic lung SCC is cytotoxic chemotherapy, most commonly a platinum-based doublet. Either cisplatin or carboplatin is used as the platinum backbone of these regimens, while agents like paclitaxel, nab-paclitaxel, docetaxel, or gemcitabine constitute the cytotoxic partner.

Phase III studies of cytotoxic therapy in NSCLC have shown differential outcomes for patients with SCC versus non-SCC cancers. In a phase III trial of cisplatin/pemetrexed versus cisplatin/gemcitabine in advanced NSCLC, patients with SCC histology were reported to have better survival with the gemcitabine-based doublet (median survival time 10.8 v 9.4 months, respectively) (30). Nab-paclitaxel, an albumin-bound nano-formulation of paclitaxel, was shown to have a higher rate of tumor response when combined with carboplatin versus standard paclitaxel/carboplatin (response rate ratio of 1.68, $p<0.001$) in the patient subset with SCC (31). Survival for the overall population was similar between the arms.

For patients with advanced NSCLC who complete four to six cycles of frontline platinum-doublet therapy and have documented stable or responding disease, maintenance therapy is an option, and is reported to improve progression-free survival in some patient subsets(32, 33). However, the role of maintenance therapy in those patients with SCC is less established. In the second line setting, agents such as docetaxel or erlotinib are considered reasonable therapeutic options, but these are not specifically approved for SCC. In the phase III BR-21 trial of erlotinib vs. placebo in the second/third line setting that included all histologic subtypes, the survival benefit for erlotinib was of equivalent magnitude in SCC and adenocarcinoma, and was even seen in a subset analysis of male, ever-smokers with SCC (34). Additionally, the US FDA recently approved ramicirumab, a VEGFR2-targeted monoclonal antibody, for use in combination with docetaxel in patients with advanced NSCLC progressing after primary platinum-based chemotherapy, regardless of tumor histology. This approval was based on the results of a phase III randomized trial (REVEL) that demonstrated a modest OS and Progression Free Survival (PFS) FS benefit for the addition of ramicirumab to docetaxel. (35)

It is notable that certain systemic therapies are specifically not recommended for use in patients with lung SCC. Specifically, the angiogenesis inhibitor bevacizumab and the multi-targeted antifolate pemetrexed are not approved for use in these patients due to either increased toxicity (in the case of bevacizumab) or decreased efficacy (in the case of pemetrexed) (36).

Investigational approaches

It is apparent that outcomes for patients with advanced lung SCC remain suboptimal, warranting diversification of targets and therapeutic options. Among these targets is the EGFR. It must be emphasized that in this SCC histologic subset, EGFR activating mutations are exceptionally uncommon, but that most cancers avidly express the wild type EGF receptor and a subset demonstrate *EGFR* amplification. A monoclonal antibody directed against EGFR - necitumumab – was evaluated specifically in lung SCC in a large phase III trial (SQUIRE) (37). In that study, 1093 patients with advanced SCC were randomized to gemcitabine-cisplatin with or without necitumumab. Treatment was given for up to six cycles. Subsequently, patients assigned to the necitumumab arm continued to receive maintenance necitumumab every three weeks until disease progression. Overall survival (OS) was significantly increased in necitumumab-treated patients (median survival time was 11.5 versus 9.9 months, HR 0.84, 95% CI 0.74–0.96). PFS was also significantly increased (HR 0.85, 95% CI 0.74–0.98). However, there were higher rates of grade 3 or greater toxicities seen in the necitumumab arm. Nevertheless, this was one of the first trials to show superior survival for a new agent when combined with chemotherapy versus chemotherapy alone in lung SCC.

In a Phase III trial focusing on patients with SCC, typically characterized by wild type EGFR, LUX-Lung 8, 795 patients with relapsed/refractory disease after first-line chemotherapy were randomized to either erlotinib or afatinib, an irreversible ErbB family blocker. The primary endpoint was PFS, while secondary endpoints included OS, objective response rate (ORR), and disease control rate (DCR). Median PFS was significantly higher

for afatinib than erlotinib (2.4 vs 1.9 months; p=0.0427). The ORR was similar between the arms (4.8% vs. 3.0%, p=0.233), but DCR was significantly higher with afatinib than erlotinib (45.7% vs 36.8%; p=0.020) If OS results, currently pending, are positive for afatinib, this approach may prove to be another option for the SCC population (38).

Most recently, immunotherapy – particularly checkpoint inhibitor therapy with PD1 antibodies – has shown encouraging activity in patients with SCC. A more detailed description of immune checkpoint modulation is provided in a companion article from Soria and colleagues in this *CCR Focus* (37). Nivolumab, a humanized IgG4 antibody against PD1, was shown in a phase I dose-finding trial to have an overall response rate of 18% in a NSCLC subset which included patients with SCC. Interestingly, some of these responses appear to be durable (i.e., > 1 year in duration). Responses may be related to higher PDL1 expression in pretreatment tumor specimens, although data are mixed (39). In an updated analysis of this trial, one and two year survival rates of 42% and 14% were reported (40). Subsequently, nivolumab was tested in a phase III trial versus docetaxel in patients with advanced SCC progressing during or after platinum based therapy, with a primary endpoint of OS. According to a recent press release, a statistically significant OS benefit for patients receiving nivolumab was achieved. Specifically, nivolumab showed significantly superior OS as compared to docetaxel, with a 41% reduction in the risk of death (HR 0.59, p=0.00025]). The median OS was 9.2 months in the nivolumab arm (95% CI: 7.3, 13.3) and 6 months in the docetaxel arm (95% CI: 5.1, 7.3). These data led to the recent FDA approval of nivolumab for the treatment of metastatic lung SCC.

Pembrolizumab is another humanized IgG4 PD1 antibody (approved for use in melanoma) which was prospectively tested in patients with advanced solid tumors, including SCC (41, 42, 43). In a phase I trial (KEYNOTE1), pembrolizumab was given at 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 10 mg/kg every two weeks until progression, death, or unacceptable toxicity. Tumor PDL1 was assessed by immunohistochemistry in archival specimens. A pooled analysis of 282 patients with treatment-naïve or previously treated advanced NSCLC was recently presented (41). The RECIST ORR was 21% in the overall study population; ORR was 18% in patients with SCC and 23% in patients with non-SCC. Response rates and PFS appeared to be higher for patients whose tumors more highly expressed PDL1; for instance, hazard ratio for PFS was 0.52 for patients with PD-L1 strong-positive versus PD-L1 weak-positive or negative tumors.

Lung Master Protocol in SCC (Lung-MAP, S1400)

The Lung-MAP project, a multi-substudy master protocol designed to facilitate approval of targeted therapy-predictive biomarker combinations, represents a unique public-private partnership engaging the National Cancer Institute (NCI) and its Thoracic Malignancies Steering Committee (TMSC), the Foundation of the NIH (FNIH), the pharmaceutical industry, advocacy groups such as Friends of Cancer Research (FOCR), and most importantly, the Federal Drug Administration (FDA). The design is multiple simultaneously running Phase II/III trials, each capable of independently opening and/or closing without affecting the other substudies, in which patients eligible for 2nd line therapy for lung SCC have their cancers genomically screened through a next generation sequencing (NGS)

platform (Foundation Medicine). Patients are then randomized into one of several sub-studies, each comparing an experimental targeted therapy with standard of care therapy, based on identification of candidate predictive biomarkers associated with each sub-study. Fig. 4 displays the overall schema for Lung-MAP (Fig. 4A) and the initial drug classes being tested, PI3K, FGFR, CDK 4/6, HGF and PD-L1 (Fig. 4B). Rapid turnaround time of NGS screening results, within 2 weeks, allows real time assignment into the appropriate sub-study. For those patients with cancers that do not “match” into a biomarker-driven sub-study, there is a ‘non-match” sub-study, in which a predictive biomarker is not yet of sufficient validation to utilize it in a drug-biomarker registration strategy. If successful, Lung-MAP will change the way new drugs are developed in lung cancer, and the approach will be extrapolated into other settings in lung cancer, and into other tumor types as well. Already, a master protocol design is being developed in ALK positive cancers based on the Lung-MAP design.

In summary, recent advances in understanding the underlying tumor biology of lung SCC, a subset of NSCLC for which progress has been modest at best over the last decade, have identified new “druggable” tumor targets and potential associated biomarkers. The ongoing SPECS project is seeking to validate prognostic gene signatures to better define subsets within lung SCC with differing natural histories and variable chances of relapse after surgical resection. Recent clinical trials dedicated to lung SCC are also showing promise. Finally, a SCC master protocol (Lung-MAP or S1400) is exploring a novel strategy designed to hasten approval of new targeted therapeutics and their companion diagnostics for this important subset of NSCLC.

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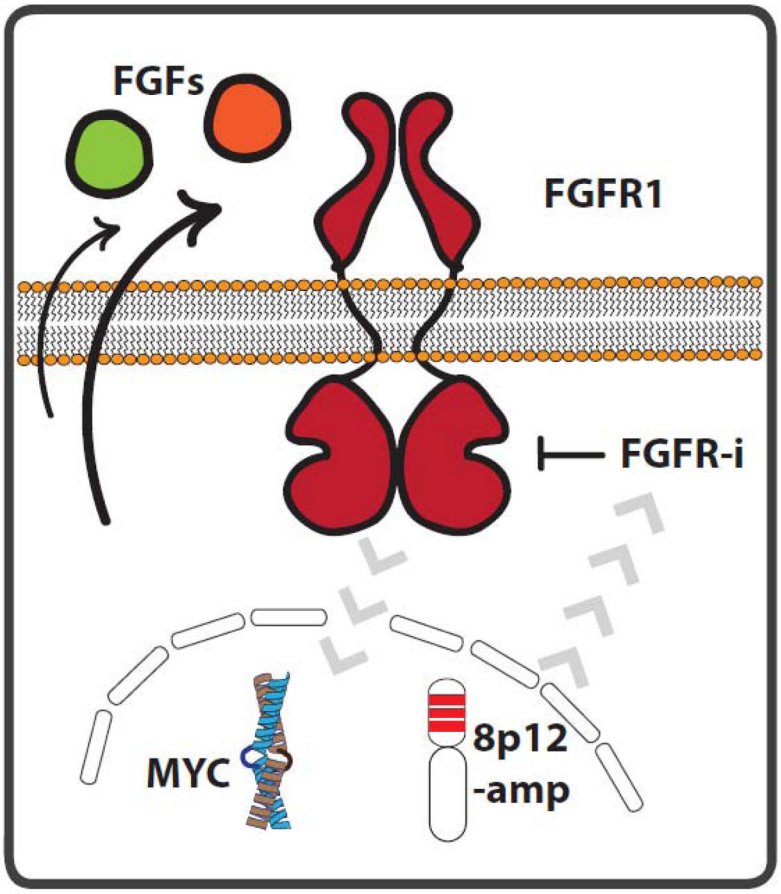

Figure 1.

Schematic overview of potential modulators of cellular response to FGFR targeted drugs in FGFR1-amplified lung SCC. It has been shown that the chromosomal architecture of the 8p12 locus as well as the expression of c-MYC can modify (gray arrows) the cellular dependency on FGFR1 and therefore the efficacy of FGFR inhibitors in these tumors. Similarly, the secretion (black arrows) of FGF ligands (e.g. FGF2, FGF9) can perturb the activity of FGFR1 and modify the response to targeted inhibition of its kinase activity.

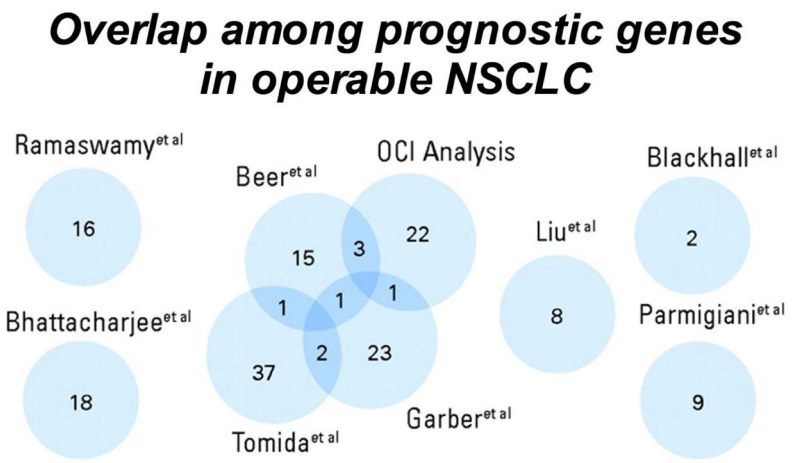

Figure 2.

Venn diagram for degree of overlap of 158 candidate prognostic genes. Reference sources are shown. Reprinted from Lau et al. (29).

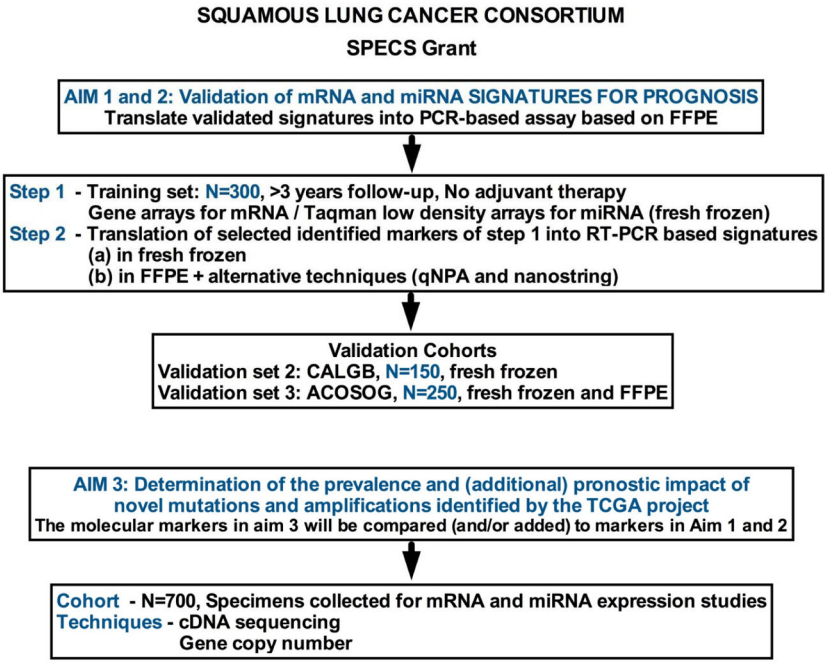

Figure 3.
Aims and research approach for the Squamous Lung Cancer SPECS Consortium.

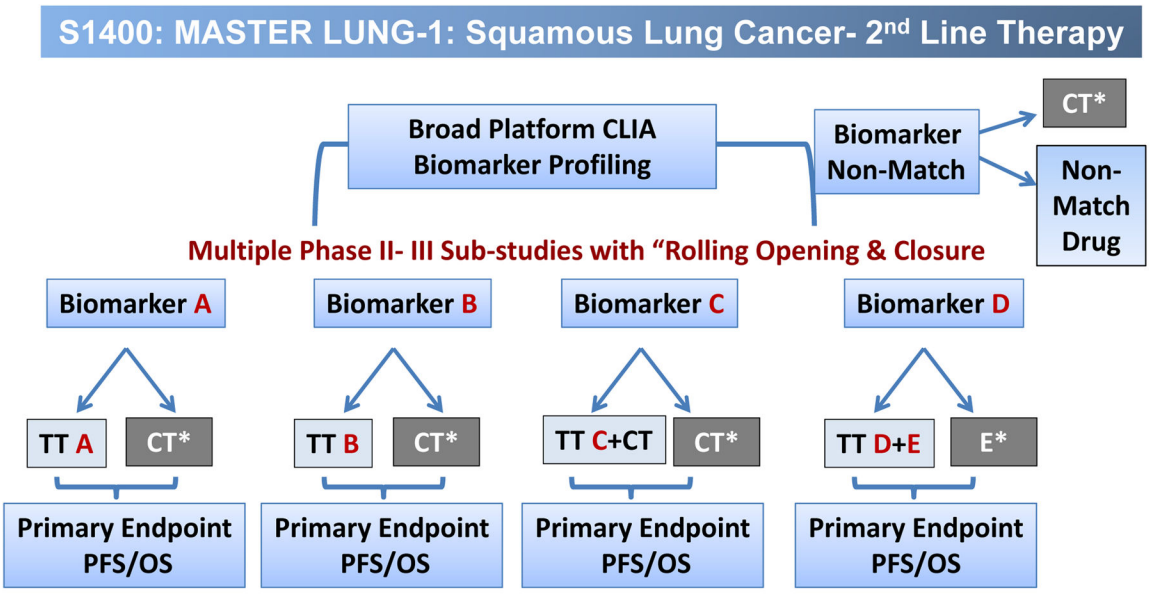

Figure 4A

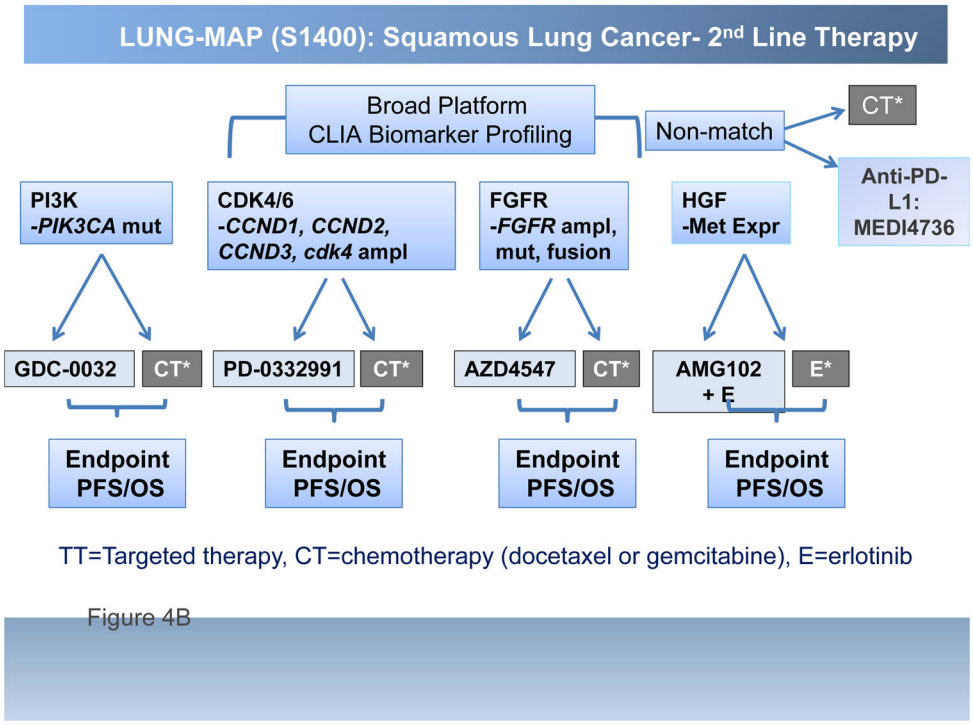

Figure 4B

Figure 4.

A, Overall schema for Lung-MAP and B, the initial drug classes being tested, PI3K, FGFR, CDK 4/6, HGF and PD-L1. TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

Table 1

Commonly identified alterations in genomic studies of lung SCC

Genetic Pathways and Alterations	Prevalence	Clinical Trials
RTK Amplification	>30% with *EGFR* and *FGFR1* most common	EGFR mAbs, FGFR TKIs, FGFR mAbs, FGFR ligand traps
RTK mutations/fusions	Rare (<10% of cases), most common in *FGFR2* and *FGFR3* (*FGFR3-TACC3*), rare *DDR2* mutations	FGFR TKIs, FGFR mAbs, FGFR ligand traps, dasatinib
RAS	10–20%, most commonly loss of *NF1* or *RASA1*, *RAS* mutations rare	MEK and ERK inhibitors, direct RAS inhibitors
PI3K	Common ~50% alterations in *PIK3A, PTEN, PIK3R1*	PI3K and mTOR inhibitors
TP53 and CDKN2A/RB1	Genomic loss in nearly all cases, amplification of *CDK4/CDK6/CCND1* in *CDKN2A* intact tumors	CDK inhibitors?
Oxidative Stress Regulation	Common mutation of *NFE2L2/KEAP1/CUL3* (25%)	PI3K inhibitors?
Differentiation	Common loss of *NOTCH1; TP63* and *SOX2* gain	?
Immune evasion	Rare *HLA* and *B2M* mutations, <10%	Immune checkpoint inhibitors, vaccines