Targeting genomic alterations in squamous cell lung cancer

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INTRODUCTION

Lung cancer is the leading cause of cancer related deaths worldwide. Adenocarcinoma is the most common form of non-small cell lung cancer (NSCLC); the second most common is squamous cell (1,2). Targeted kinase inhibitors have successfully changed the treatment paradigm for adenocarcinoma. The discovery of epidermal growth factor receptor kinase (EGFR) activating mutations and echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase fusions have led to significant therapeutic gains in patients with adenocarcinoma. However, meaningful therapeutic gains based on the molecular pathobiology of squamous cell lung cancer have not yet been realized. A comprehensive genomic characterization of 178 cases of squamous cell lung cancer has recently been reported. Squamous cell lung cancer appears to be characterized by a broader and more complex group of genomic alterations than adenocarcinoma. In this review, potentially targetable genes or pathways in squamous cell lung cancer are emphasized in relation to available therapeutic agents in development or active clinical trials. This organization of data will provide a framework for development for clinical investigation. Squamous cell lung cancer appears to be characterized by not only driver mutations in candidate genes but also gene copy number alterations resulting in tumor proliferation and survival. Better understanding of these genetic alterations and their use as therapeutic targets will require broad collaboration between industry, government, the cooperative groups, and academic institutions with the ultimate goal of rapid translation of scientific advancement to patient benefit.

Keywords: EML4-ALK, DDR2, PIK3CA, AKT1, EphA2, LKB1, FGFR1, SOX2

Squamous cell lung cancer causes approximately 400,000 deaths worldwide per year. Identification of specific molecular alterations, such as activating mutations in the epidermal growth factor receptor kinase and echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase fusions have led to significant therapeutic gains in patients with adenocarcinoma. However, meaningful therapeutic gains based on the molecular pathobiology of squamous cell lung cancer have not yet been realized. A comprehensive genomic characterization of 178 cases of squamous cell lung cancer has recently been reported. Squamous cell lung cancer appears to be characterized by a broader and more complex group of genomic alterations than adenocarcinoma. In this review, potentially targetable genes or pathways in squamous cell lung cancer are emphasized in relation to available therapeutic agents in development or active clinical trials. This organization of data will provide a framework for development for clinical investigation. Squamous cell lung cancer appears to be characterized by not only driver mutations in candidate genes but also gene copy number alterations resulting in tumor proliferation and survival. Better understanding of these genetic alterations and their use as therapeutic targets will require broad collaboration between industry, government, the cooperative groups, and academic institutions with the ultimate goal of rapid translation of scientific advancement to patient benefit.

Keywords: EML4-ALK, DDR2, PIK3CA, AKT1, EphA2, LKB1, FGFR1, SOX2

MATERIALS AND METHODS

A literature search was conducted for articles on PubMed published in English language from 1980 to 2012. We used the search term “squamous cell cancer of the lung” with “gene copy number alterations,” “somatic mutations,” “gene amplifications,” and “clinical trials.” We also performed specific searches for the candidate genes reported in genomic studies of squamous cell cancer of the lung with emphasis on drugs currently in clinical trials. For the purpose of this review, targetable genomic alterations are being separated as “mutations” and “amplifications/overexpression” depending on the predominant targetable alteration known with the individual genes.
TARGETABLE GENOMIC ALTERATIONS

MUTATIONS

**DDR2**

Discoid death receptor 2 (DDR2) is a receptor tyrosine kinase activated by binding of its discoid domain to fibrillar collagen (Figure 1) (15). Apart from its important role in postnatal development and tissue repair, DDR2 also regulates primary and metastatic cancer progression. Though unclear, several downstream signaling pathways have been implicated in DDR2 signaling, including Shp-2, Src, STAT, and MAPK pathways (16). The S768R mutation results in substitution of serine with arginine at position 768 in DDR2. In addition to lung squamous cell cancers, DDR2 mutations are found in cancers of the kidney, breast, endometrium, colon, and brain (17). Hammerman et al. identified oncogenic mutations in the DDR2 kinase gene in 3.8% of the 222 Sanger sequenced lung squamous cell samples (18).

Dasatinib (Sprycel, Bristol-Myers Squibb, NY, USA) is a marketed multitargeted kinase inhibitor that blocks DDR2 (18, 19). Hammerman et al. reported selective in vitro killing of squamous cancer cell lines harboring DDR2 mutations by either knockdown of DDR2 with RNA interference or by treatment with dasatinib (18). In vivo sensitivity of DDR2 to dasatinib was demonstrated by inhibition of tumors induced into athymic nude mice. As demonstrated in other studies (19) potent inhibitory effect of imatinib on DDR2 induced oncogenic transformation was also reported in this study. However, such inhibition was most shown to be most potent with dasatinib, given concurrent Src inhibition. Hammerman et al. also independently verified the presence of S768R mutation in the pre-treatment tumor sample of a female patient with squamous cell cancer with no EGFR mutation who responded to a combination of dasatinib and erlotinib in a different study (20). Currently this combination is being studied in phase I trials recruiting patients with advanced cancer. Dasatinib monotherapy is being studied in advanced squamous cell lung cancers especially in individuals whose tumors harbor mutations in the DDR2 gene (Table 1). Dasatinib can cause pleural effusions. The Brown University Oncology Group evaluated dasatinib in a phase I study with chemomodulation in an unslected cohort of patients with stage III NSCLC. This trial needed to be terminated due to pulmonary toxicity. Therefore caution is needed when dasatinib is utilized for patients with lung cancer and prior thoracic radiation (21).

**PI3KCA**

Phosphatidylinositol-3-kinases (PI3K) belong to a family of heterodimeric lipid kinases. Normally, PI3K converts phosphatidyl inositol-3,4-bisphosphate [PI(3,4)P2] to phosphatidylinositol-3,4,5-trisphosphate [PI(3,4,5)P3], which in turn activates downstream AKT/mTOR pathway to regulate growth, survival, and motility. Three classes of PI3K exist; class IA is the only protein containing catalytic and regulatory subunits encoded by separate genes. Mutations mostly occur in the helical and kinase domains of PIK3CA, the gene that encodes the p110α catalytic subunit of PI3K. These mutations are reported in up to 9% of squamous cell lung cancers and are more common in squamous cell than in adenocarcinomas (22–24). Evidence for the oncogenic potential of PIK3CA mutations stems from the association of PI3K with various oncogenes like phosphatase and TENsin homolog (PTEN) and AKT (Figure 2) (25, 26). Amplification of PIK3CA in the 3q locus (3q26) is also a mechanism of oncogene activation in squamous cell lung cancer. Copy number gains of up to 43% in lung squamous cell cancer were demonstrated suggesting that amplifications of PIK3CA are more frequent than mutations (27, 28).

PIK3CA mutations were found to coexist with EGFR mutation in studies by Sun et al. (four of four tumors) and Kawano et al. (three of eight tumors) (24, 29). Activation of PI3K/AKT pathway promotes resistance to EGFR TKIs in EGFR-mutant NSCLC (30). PIK3CA mutations have been detected in about 5% of EGFR-mutant lung cancers with acquired resistance to EGFR-TKI therapy (31).

In a phase I dose-escalation study in advanced solid tumors using BMK120 (Novartis, Basel, Switzerland), an oral pan-Class I PI3K inhibitor, two lung cancer patients were included, and one responded with stable disease (32). PI-103, a dual PI3Kα and mTOR inhibitor showed clear antitumor activity in two gefitinib-resistant NSCLC cell lines, A549 and H460 (33). BYL719 (Novartis, Basel, Switzerland), BMK120 (Novartis, Basel, Switzerland), AZD5863 (AstraZeneca, London, UK), SAR256212 and SAR245409 (Sanofi, Paris, France) are other targeted PIK3CA inhibitors being studied in phase I trials for advanced solid tumors with an alteration of the PIK3CA gene (Table 1). Caution is needed when biologic agents that effect overlapping pathways are utilized together. For example in a Brown University Oncology Group phase I study combining the mTOR inhibitor ridaforolimus with anti-EGFR antibody, severe mucositis developed at ridaforolimus doses typically not associated with this toxicity (NCT01212627).

**PTEN**

Phosphatase and TENsin homolog encodes a lipid-protein phosphatase. By dephosphorylation of PI3P, PTEN negatively regulates PI3K/AKT leading to tumor suppression (34). The R233 mutation in exon 7 results in introduction of a premature stop codon into the PTEN gene resulting in inactivation of PTEN (35). PTEN inactivation therefore increases activity of the PI3K-AKT-mTOR pathway which promotes survival. Incidence of PTEN mutation is about 4–8% in NSCLC (35, 36). Jin et al. analyzed 176 surgically resected NSCLCs. PTEN mutations were only found in

![FIGURE 1 | Proposed DDR2 signaling in lung cancer.](image-url)
| Gene | Cytogenetic location | Mechanism of carcinogenesis | Frequency in squamous cell cancer | Frequency in adenocarcinoma | Novel agents | Clinical trial number | Study phase |
|------|---------------------|-----------------------------|----------------------------------|-----------------------------|--------------|----------------------|-------------|
| FGFR1 | 8p11–12             | Amplification               | 21% (57)                         | 3.4% (57)                   | NVP-BGJ398, AZD4547, E-3810, ASA404 + carboplatin/ paclitaxel/ cetuximab | NCT01004224 | I                        |
| DDR2  | 1q23.3              | Mutation                    | 3.8% (18)                        | Not reported                | Dasatinib + erlotinib, Dasatinib | NCT00895128 | I                        |
| PIK3CA | 3q26.3             | Mutation                    | 9% (23)                          | 1.5% (24)                   | BKM120, BKM120 + docetaxel, BKM120 + gefitinib, BKM120 + carboplatin + paclitaxel, BKM120 + MEK162, BKM120 + everolimus, BYL719, AZD5383, SAR256212 + SAR245409, SAR256212 + erlotinib, SAR256212 + cabazitaxel/capcitabine/pemetrexed | NCT0168483 | I                        |
| PTEN  | 10q23.3             | Mutation                    | 10.2% (35)                       | 1.7% (35)                   | GSK2636771 | NCT01458067 | I/IIa                  |
| AKT1  | 14q32.32            | Mutation                    | 7.1% (45)                        | 0% (45, 46)                 | GDC-0068 + paclitaxel/docetaxel, MK-2206 + gefitinib | NCT01362374 | I                        |
| MET   | 7p11.4–7qter        | Increased expression        | 52.6% (81)                       | 81.3% (81)                  | MetMAb + erlotinib | NCT00854308 | I                        |
|      |                     | Mutation                    | Infrequent                       | 1.5% (86)                   | METMAb + paclitaxel + platinum, PF-02341066 + PF-00299804, PF-02341066, EMD1214063, ARQ197 + pazopanib, INC280, SAR125844, GSK1363089 + erlotinib, X-396 | NCT01456325 | III                     |
| SOX2  | 3q26.33             | Amplification               | 20% (67)                         | 90% (68)                    | None | NCT01441128 | I                        |
|       |                     | Increased expression        | 90% (68)                         | 21% (68)                    | None | NCT00585195 | I                        |
| EphA2 | 1p36                | Mutation                    | 7% (50)                          | 0% (50)                     | None | NCT01014936 | I                        |
| LKB1  | 19p13.3             | Mutation                    | 19% (65)                         | 34% (65)                    | None | NCT01324479 | I                        |
smokers and were significantly more frequent in squamous cell lung cancers than in adenocarcinomas (10.2 vs. 1.7%) (35). Similar pattern was observed in the analysis of 173 NSCLC tumors by Lee et al. (36) PTEN inactivation decreases sensitivity of EGFR-mutant lung tumors to EGFR through partial uncoupling of mutant EGFR from downstream signaling leading to EGFR activation and through activation of AKT (37). PTEN loss on the contrary increases sensitivity to PI3K-AKT and FKB12-rapamycin associated protein (mTOR) inhibitors via increased S6 kinase activity and phosphorylation of ribosomal S6 protein (38) In addition to several studies involving unselected patient population treated with PI3K/AKT inhibitors and mTOR inhibitors, a selected population with PTEN deficiency is being studied with the experimental drug GSK2636771 (GlaxoSmithKline, London, UK; Table 1).

**AKT1**

v-AKT murine thymoma viral oncogene homolog 1 (AKT1 oncogene) encodes a class of serine-threonine protein kinases that are involved in growth, proliferation, angiogenesis, and survival. AKT1 is a downstream regulator of PI3K pathway and is activated by either loss of function of PTEN gene or mutations/amplifications of PIK3CA gene. AKT1 activation requires both plasma membrane translocation and phosphorylation at Thr308 and Ser473 (atleast at Thr308) (39–41) and involves binding of its pleckstrin homology domain (PHD) to P(3,4,5)P3 followed by Thr308/ Ser473 phosphorylation or phosphorylation of ribosomal S6 protein (38). In addition, AKT1 activation is oncogenic as evidenced by transformation of cells in culture and induction of leukemia in mice (44). E17K mutations occur in NSCLC at a rate of 1–2% and were identified in 1 of 14 lung squamous cell samples analyzed by Do et al. (45) and 2 of 36 lung squamous cell samples analyzed by Malanga et al. (46).

An open-label, multicenter, Phase I dose-escalation combination study using a 3 + 3 design of GDC-0068 (Genentech Inc., South San Francisco, CA, USA), a novel oral selective ATP-competitive AKT inhibitor targeting PI3k-Akt-mTOR pathway in metastatic cancer refractory to standard therapy enrolled 23 patients in the GDC-0068 + docetaxel (Taxotere, Sanofi-Aventis, Paris, France) arm and is ongoing. One patient with NSCLC in this arm experienced partial response as evidenced by 32% tumor reduction by modified Response Evaluation Criteria in Solid Tumors criteria (47). Another ongoing phase I study combining the AKT inhibitor MK-2206 (Merck, NJ, USA) with gefitinib in NSCLC patient population enriched for EGFR mutations is recruiting participants (Table 1). The PHD of PDK1 also provides another potential target for drug development.

**EphA2**

The erythropoietin-producing hepatocellular (Eph) family of receptor tyrosine kinases regulates a multitude of physiological and pathological processes. Eph receptors are tyrosine kinases involved in embryonic development (48). Eph A2 is over expressed in NSCLC (49). Mutations in EphA2 although over all rare, are more common in lung squamous cell cancer histology. Both over expression and mutation increase the risk of invasive disease. The mutation G391R in EphA2 confers susceptibility to treatment with rapamycin (Rapamune, Pfizer, NY, USA), an mTOR inhibitor and was seen in 7% of squamous cell lung cancers vs. 0% of other histologies in one report (50). Overexpression of EphA2 also leads to increased phosphorylation of Src.

Dasatinib a multitargeted TKI has activity against EphA2 receptors (51, 52). Therefore EphA2 is a potential target for specific drug development and clinical trials are indicated.

**LKB1**

Liver Kinase B1 (LKB1, also called STK11) is frequently mutated in NSCLC and is thought to act as a tumor-suppressor gene. LKB1 acts as a tumor suppressor by activating AMPK (5′ AMP-activated protein kinase). Loss of LKB1 by point mutation or deletion suppresses AMPK, leading to increased mTOR signaling. LKB1 is thought to function in early tumorigenesis, subsequent differentiation, and the development of metastases (53). Low levels of LKB1 protein were associated with high grades of dysplasia in atypical adenomatous hyperplasia lesions, suggesting that LKB1 has an early role in the development of premalignant lesions of the lung (54). LKB1 mutations (including point mutations and deletions) were found in 34% of adenocarcinomas and 19% of squamous cell lung cancers from 144 human specimens of NSCLC (55). Mutations are more common in Whites as compared to Asians. LKB1 inactivation and KRAS mutation enhanced tumor growth and metastatic potential in mouse models.

Recently researchers at The University of Texas MD Anderson Cancer Center, investigated the effects of LKB1 mutation and mTOR inhibition on cell signaling pathways, measuring protein expression in NSCLC cell lines by reverse phase protein array. LKB1 mutant cell lines have increased insulin-like growth factor receptor (IGFR) activity with higher baseline IGFR1, insulin-like growth factor-binding protein 2 (IGFBP2), and nuclear receptor coactivator 3 (AIB1), suggesting that IGFR may be a potential therapeutic target in LKB1 mutant tumors. In addition, inhibition of the mTOR pathway was shown to upregulate the IGFR...
pathway, possibly as a feedback mechanism. These results support the investigation of IGFR inhibitors in combination with drugs targeting the mTOR pathway, particularly for tumors bearing LKB1 mutations (56). Currently there are no trials looking at this combination.

AMPLIFICATIONS/OVEREXPRESSION

FGFR1

The fibroblast growth factor receptor type 1 gene (FGFR1) encodes a cell surface tyrosine kinase receptor of the FGFR tyrosine kinase family, which includes four kinases, FGFR1–4. They play a critical role in cell proliferation and survival (Figure 3). Based on single nucleotide polymorphism (SNP) array copy number analysis of 732 samples, Dutt et al. report that the region of chromosome segment 8p11–12 containing FGFR1 is somatically amplified in 21% of lung squamous cell cancers as compared to 3.4% of lung adenocarcinomas (57). This high frequency of FGFR1 amplification in squamous cell lung cancer was confirmed by Weiss et al. (22% in their analysis) using fluorescent in situ hybridization (FISH) (58). Lymph node metastases derived from FGFR1-amplified squamous cell cancer also are known to exhibit FGFR1 amplification (59).

Dutt et al. studied the effects of pan-FGFR inhibitor PD173074 (Pfizer, Groton, CT, USA) on NSCLC cell lines. FGFR1-amplified NCI-H1581 cells were sensitive to treatment with PD173074 as assayed by colony formation in soft agar with half maximal inhibitory concentration (IC50) in the range of 10–20 nM. In contrast, NCI-H2170 cells with wild type FGFR1 copy number were insensitive to PD173074 (57). Growth dependence of these cell lines on FGFR1 amplification identifies this genetic variation as a high-frequency therapeutic target in squamous cell lung cancer (57, 58, 60).

Genomic and cell line sensitivity studies on cancer cell lines also demonstrated sensitivity of FGFR gene alterations for the pan-FGFR small molecule inhibitor NVP-BGJ398 (Novartis, Basel, Switzerland) (61). In a phase I dose-escalation study in genetically preselected advanced solid tumors, patients received NVP-BGJ398 daily in a 28-day cycle in escalating dose cohorts starting from 5 mg once daily. After cohort 3, patients had to have FGFR1 or FGFR2 amplification or FGFR3 mutation. 26 patients, including three patients with FGFR1-amplified squamous cell cancer were treated. One lung cancer patient with an FGFR1/CEP8 ratio of 2.6 by FISH responded substantially to 100 mg of NVP-BGJ398 as assessed by computed tomography and positron emission tomography (62). NVP-BGJ398 is being studied in another multicenter phase I study. The safety and tolerability of AZD4547 (AstraZeneca, London, UK) in FGFR1 and/or FGFR2 gene amplified solid tumors and FGFR1 gene amplified squamous cell cancer is being studied in an ongoing study. E-3810 (EOS SpA, Milano, Italy), a novel dual-targeted small molecule inhibitor of VEGFR1, 2, 3 and FGFR1 showing strong anti-angiogenic and antitumor activity in preclinical models is currently being studied in a phase I trial in advanced solid tumors (Table 1).

SOX2 AMPLIFICATION AND OVER EXPRESSION

SRY (sex determining region)-box 2 (SOX2) protein is an evolutionarily conserved 317 aminoacid transcription factor containing a high mobility group (HMG) box. It is a critical transcription regulator of normal embryonic and neural stem cell function. SOX2 is required for foregut morphogenesis, playing an important role in the normal development of lung and esophagus (63, 64). When somatic DNA alterations develop in these cell lineages, SOX2 is activated, justifying its classification as a lineage survival oncogene (65, 66). SOX2 is expressed in peak genomic amplifications of chromosome segment 3q26.33 that occur in about 20% of squamous cell lung cancers and such expression is independent of the degree of histological differentiation (67). Sholl et al. examined 121 lung tumor specimens for Sox2 protein expression by IHC and demonstrated that SOX2 is strongly and diffusely expressed (extensive SOX2 staining described as immunoreactivity in >50% of tumor cells) in approximately 90% of squamous cell cancers, 21% of adenocarcinomas, and 72% of high grade neuroendocrine tumors (68). Oncogenic mechanisms induced through SOX2 overexpression include promotion of cell migration, anchorage-independent growth, and squamous cell viability by protection from apoptosis (67). Lu et al. have demonstrated that SOX2 overexpression is oncogenic in vivo. About 50% mice with upregulated SOX2 developed lung cancer (69). Targeting of SOX2 has not yet entered clinical investigations.

MET

MNNG-HOS transforming gene (MET-oncogene) was initially cloned from chemically transformed human osteosarcoma-derived cell line and was mapped to chromosome 7 (7p11.4–qter) (70). The MET-oncogene encodes the tyrosine kinase MET, which is the receptor for hepatocyte growth factor (HGF) or scatter factor (SF). Ligand binding or mutations/gene amplifications in the MET-oncogene, activate MET. Activated MET phosphorylates its substrates, activating multiple downstream pathways involving P13K, RAS-MAPK, and STAT3 (71, 72).

Hepatocyte growth factor-MET signaling mediates biological processes like proliferation, motility angiogenesis, and invasiveness (72–74). MET tyrosine kinases are crucially involved in the invasive growth program and aberrant activation contributes to tumor growth, progression, and metastasis (72, 75, 76). Cells which over-express either HGF or MET are tumorigenic and highly metastatic when implanted into nude mice (77). When MET is switched off, tumors were shown to become less aggressive (78). Germline and somatic mutations in MET-oncogene leading to MET activation were identified in papillary renal cell carcinomas (79). Somatic mutations in NSCLC were first identified by Kong-Beltran.
et al. (80) who also noted that tumors harboring these mutations were wild type for KRAS, B-raf, EGFR, and HER2. Strong MET expression was observed by immunohistochemistry in 52.6% of squamous cell lung cancer specimens (81). MET amplification is rare in lung cancer but is seen in up to 20% of tumors treated with EGFR TKIs and contributes to EGFR-TKI resistance (82, 83). Due to this reason, several researches have urged that the development of anti-MET therapeutic strategies should be focused on patients with acquired EGFR-TKI resistance (82). High MET expression indicates poor prognosis and may portend development of brain metastases in lung cancer (83).

Inhibitors of ALK and ROS also inhibit MET. A case report of an NSCLC patient with de novo MET amplification but no ALK rearrangement who achieved a rapid and durable response to crizotinib indicates that the drug is a potent MET inhibitor (84). A randomized phase II study evaluating anti-MET monoclonal antibody (MetMAb) or placebo in combination with erlotinib in 128 patients with advanced NSCLC has been reported. In the metastatic NSCLC group, the combination of MetMAb and erlotinib resulted in a statistically and clinically significant improvement in both the progression free and overall survivals resulting in a near threefold reduction in the risk of death (85). Several studies are underway evaluating role of ALK inhibitors like X-396 (Xcovery Holding Company, West Palm Beach, FL, USA), MET/HGF TKIs like PF-02341066 (Pfizer, Groton, CT, USA), and onartuzumab/MetMAb (Genentech Inc., South San Francisco, CA, USA) in NSCLC (Table 1).

#### PERSPECTIVE AND FUTURE DIRECTIONS

Lung carcinogenesis is due to the accumulation of mutations in oncogenes, tumor-suppressor genes, and genetic instability genes as well as alteration in gene copy number. Carcinogens such as cigarette smoke are an important cause of mutations in lung cancer especially squamous cell cancer. Squamous cell cancer of the lung is known for its genomic complexity and is characterized by an overall high mutation rate of 8.1 mutations per megabase as evident by the recent comprehensive genomic characterization of squamous cell cancers of the lung by “TCGA Research Network.”

Both driver mutations and pathways affected by gene copy number alterations can be potentially targeted for therapeutic benefit. A driver mutation results in survival advantage and tumor proliferation. It has been estimated that approximately 60% of lung adenocarcinomas will have driver mutations. True driver mutations that are currently targetable appear to be present in a minority of cases of squamous cell lung cancer and include DDR2 (3.8%), BRAF (4%), and EGFR (2%). Thus a single targeted therapy is unlikely to be effective in a large proportion of squamous cell lung cancer patients. However we know that mutations in PIK3CA, AKT, PTEN, EphA2, and LKB1 occur in squamous cell cancer of the lung and although we may not have a specific inhibitor at this point for all, combination of targeted agents or strategies to target downstream intracellular pathways such as the PI3K/PTEN/AKT/mTOR pathway may end up being more effective. Patients with squamous cell cancer of the lung harboring genetic defects that are targetable should be enrolled in clinical trials specific for the target.

The Lung Cancer Mutation Consortium (LCMC) represents the largest national initiative to prospectively examine lung adenocarcinomas with the potential to match patients to the best possible therapies. Targeting uncommon mutations in squamous cell lung cancer, with monotherapy and innovative combinations, will require similar broad collaborations between industry, academia, and government institutions. It is hoped that the dramatic gain in knowledge and understanding of genomic alterations in squamous cell lung cancer will steadily translate into meaningful patient benefit.

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