

## Squamous Cell Carcinoma of the Lung: Molecular Subtypes and Therapeutic Opportunities

Pablo Perez-Moreno<sup>1,2</sup>, Elisabeth Brambilla<sup>3,4</sup>, Roman Thomas<sup>5-9</sup>, and Jean-Charles Soria<sup>1,2</sup>

### Abstract

Lung cancer is the leading cause of cancer-related deaths worldwide. Next to adenocarcinoma, squamous cell carcinoma (SCC) of the lung is the most frequent histologic subtype in non-small cell lung cancer. Encouraging new treatments (i.e., bevacizumab, EGFR tyrosine kinase inhibitors, and ALK inhibitors) have afforded benefits to patients with adenocarcinoma, but unfortunately the same is not true for SCC. However, many genomic abnormalities are present in SCC, and there is growing evidence of their biologic significance. Thus, in the short term, the molecular characterization of patients with SCC in modern profiling platforms will probably be as important as deciphering the molecular genetics of adenocarcinoma. Patients with SCC of the lung harboring specific molecular defects that are actionable (e.g., fibroblast growth factor receptor 1 amplification, discoidin domain receptor 2 mutation, and phosphoinositide 3-kinase amplification) should be enrolled in prospective clinical trials targeting such molecular defects. *Clin Cancer Res*; 18(9); 2443–51. ©2012 AACR.

### Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide (1, 2). Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Adenocarcinoma and squamous cell carcinoma (SCC) are the most frequent histologic subtypes, accounting for 50% and 30% of NSCLC cases, respectively. Although the incidence of lung SCC is decreasing as a consequence of changes in tobacco consumption habits, SCC is still a major health issue (3, 4). Despite the recognition of histologic subtypes, the concept of "one size fits all" governed decisions for many years (5). Encouraging new treatments [i.e., bevacizumab, EGFR tyrosine kinase inhibitors (TKI), and ALK inhibitors] have afforded benefits to patients with adenocarcinoma, but unfortunately the same is not true for SCC. A correct histologic diagnosis is becoming increasingly important because it may predict response and toxicity to different therapies (6, 7).

Trials evaluating targeted therapies have failed to identify any benefits in patients with SCC, and the standard first-line treatment administered to such patients is chemotherapy

doublets. Moreover, figitumumab, an antibody targeting insulin-like growth factor I receptor, combined with chemotherapy, showed nonsignificantly worse survival when compared with chemotherapy alone in a phase III trial (8). Remarkably, patients with SCC are at higher risk of bleeding complications if they are exposed to bevacizumab. It is important to note that the development plans for all VEGF receptor (VEGFR) TKIs combined with chemotherapy in the SCC subtype have been halted due to higher mortality rates. Bleeding and cavitation are also induced by VEGFR TKIs, but this is probably not the only explanation for the increased toxicity in the SCC subtype. Thus, SCC represents an important field in which new therapeutic options are awaited.

The purpose of this article is to review the genetic alterations that seem actionable (from a therapeutic perspective) and could potentially define different molecular subtypes of SCC, rendering them eligible for personalized treatment strategies.

### Histologic Subtypes of SCC

SCCs are tumors that arise from bronchial epithelial cells through squamous metaplasia/dysplasia and are therefore characterized by keratinization and/or intercellular bridges, their most common features. However, the mere presence of at least 10% of the tumor bulk exhibiting these differentiation features is required for a diagnosis of SCC on resected specimens. The diagnosis of poorly differentiated SCC is made when the differentiated squamous component is minimal. This implies that many small biopsy specimens may appear as NSCLC, because large-cell carcinoma is not accepted as a diagnosis in small specimens. An immunohistochemistry (IHC) panel together with a mucin stain can help identify NSCLC subtypes (9). The expression of p63

**Authors' Affiliations:** <sup>1</sup>Département de Médecine, Unité INSERM U 981, Université Paris Sud, and <sup>2</sup>Institut Gustave Roussy, Villejuif; <sup>3</sup>Département d'Anatomie et Cytologie Pathologiques, INSERM Unit 823, Centre Hospitalier Universitaire Albert Michallon, and <sup>4</sup>Institut Albert Bonniot, University Joseph Fourier, Grenoble, France; <sup>5</sup>Max Planck Institute for Neurological Research, <sup>6</sup>Klaus Joachim Zülch Laboratories of the Max Planck Society, <sup>7</sup>Medical Faculty, University of Cologne; <sup>8</sup>Laboratory of Translational Cancer Genomics, and <sup>9</sup>Department I of Internal Medicine, Center of Integrated Oncology Köln-Bonn, University of Cologne, Cologne, Germany

**Corresponding Author:** Jean-Charles Soria, Institut Gustave Roussy, 114 rue Edouard Vaillant, Villejuif 94805, France. Phone: 33 1 42 11 42 96; Fax: 33 1 42 11 52 17; E-mail: soria@igr.fr

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### Translational Relevance

Squamous cell carcinoma (SCC) of the lung is the second most frequent histology in non-small cell lung cancer (NSCLC). Over the past decade, new approaches targeting specific pathways in NSCLC have emerged, but very few advances have been made in the treatment of SCC. Advances in translational research have revealed significant differences in molecular pathways among subtypes of NSCLC, and these genomic alterations have significant effects on tumor growth. Thus, a molecular characterization of SCC is essential to understand the biologic relevance and the true frequency of each alteration. Patients with SCC of the lung harboring specific molecular defects that are actionable (e.g., fibroblast growth factor receptor 1 amplification, discoidin domain receptor 2 mutation, and phosphoinositide 3-kinase amplification) should be enrolled in prospective clinical trials targeting such molecular defects.

and its N-terminal truncated P40 lacking TTF1 expression is a quite constant phenotypical trait that allows NSCLC subtypes to be distinguished from adenocarcinoma (10–12). SCC shows strong and diffuse expression of p63, which is a particular transcriptional factor of this histologic type (13).

The 2004 World Health Organization classification recognizes 4 variants of SCC: clear cell, small cell, papillary, and basaloid. The latter 2 have a specific clinicopathologic significance and deserve to remain in the forthcoming classifications. The papillary variant shows endobronchial obstructive growth, sometimes with limited intraepithelial spread, and invasion may be difficult to assess. The basaloid variant is characterized by a basal bronchial stem cell proliferation and shows a predominantly basaloid pattern and minimal areas of squamous differentiation (14). Basaloid SCC is difficult to recognize as SCC on small biopsy specimens. p63, cytokeratin (CK) 5/6, and CK1, CK5, CK10, and CK14 (15) recognized by the antibody CK34 $\beta$  E12 are the hallmarks of this very aggressive variant with a high mitotic index. Patient populations with this variant have significantly shorter survival than those with other stage I to III SCC (14, 16). The other 2 variants have no clinical relevance. Clear cell is considered to be more of a cellular change than a pattern, and can occur in all histological categories. The small cell variant is not recognized as being different from the basaloid variant.

### Molecular Subtypes in SCC

The acquisition of somatic genetic alterations is a main process in cancer. It is widely accepted that in most cases, this is a multistage process driven by progressive accumulation of mutations and epigenetic abnormalities (17, 18). Virtually all genomic aberrations can be summarized under the following headings: chromosomal copy-number altera-

tions (gains or losses), single base substitutions, translocations/rearrangement, and viral genome integration (19, 20). Overexpression of proteins can be due to gene amplification, transcriptional activation, or changes in chromatin conformation by epigenetic modifications.

As a consequence of genetic aberrations, tumors can become highly dependent on the function of even a single oncogene (driver oncogene) for proliferation and survival, despite the presence of many other genomic and epigenetic alterations (passenger mutations). Oncogene addiction refers to the apparent dependency of some tumors on one or a few genes for maintenance of the malignant phenotype (21). The demonstration of cells with genetic abnormalities that become addicted to oncogenes is a rational basis for the development of molecular targeted therapies, because normal cells in their vicinity do not bear the respective alteration.

We classify these molecular alterations according to their therapeutic targets: membrane receptor alterations, signaling pathway alterations, and transcription factor alterations. The following criteria can be used to define a genetic abnormality: (i) a molecular event with a frequency of >10%; and (ii) a molecular alteration for which there is clinical evidence of an objective response upon modulation by a molecular targeted agent that has been registered or is under clinical development. Table 1 and Fig. 1 summarize the genetic abnormalities observed in SCC.

### Membrane receptor alterations

Fibroblast growth factor receptor 1 (FGFR1) is a transmembrane tyrosine kinase receptor that plays a role in normal physiologic functions, and evidence exists for deregulated signals in the pathogenesis of many different cancer types. It signals downstream through 4 different pathways: RAS–RAF–mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)–AKT, STAT, and phospholipase C $\gamma$  (22). In a study using lung cancer cell lines with FGFR1 amplification and mice engrafted with FGFR1-amplified cells, Weiss and colleagues (23) showed that tumor growth is dependent on FGFR1 activation. Treatment with specific blockers resulted in tumor growth inhibition or shrinkage. In lung SCC, the frequency of FGFR1 amplification by FISH (Fig. 2) is 22%, whereas in adenocarcinoma it is much lower, and this high frequency of amplification was also found by other groups (23–25).

The discoidin domain receptor 2 (DDR2) is a tyrosine kinase that binds collagen as its endogenous ligand, and when activated interacts with Src and Shc (26, 27). Mutations may alter kinase activity, ligand binding, or DDR2 localization (28, 29). In a study by Hammerman and colleagues (30), mutations were found in 11 of 290 SCC samples (3.8%). Lung SCC cell lines harboring DDR2 mutations were selectively killed by RNA interference or dasatinib. In addition, tumors established from a DDR2 mutant cell line were shown to be sensitive to dasatinib in xenograft models. By contrast, xenografts with nonmutant tumors were insensitive to treatment. This response was also seen in a pretreated patient with SCC who carried a DDR2

**Table 1.** Frequency of selected genetic abnormalities in NSCLC

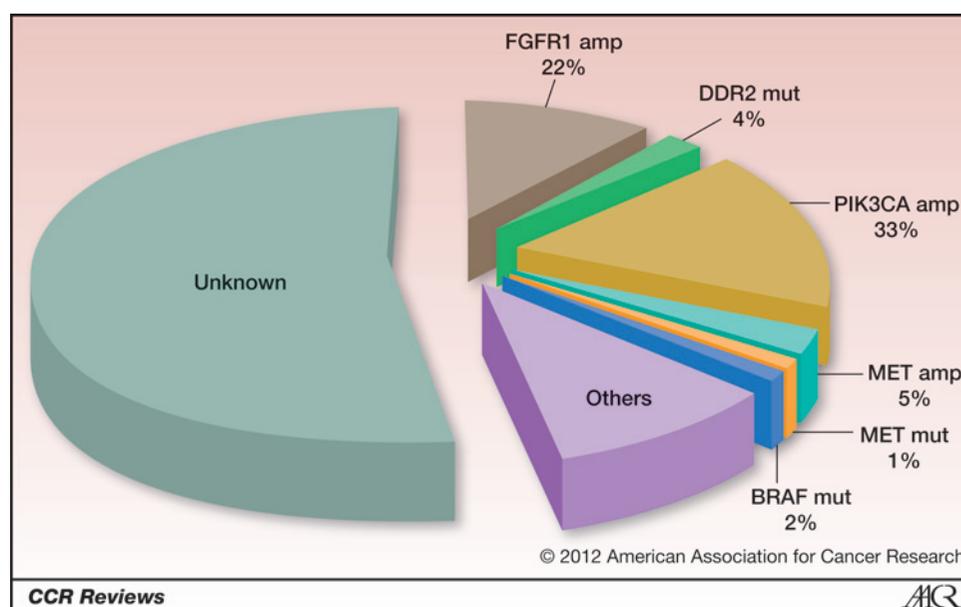
Genetic abnormality (references)	Gene location	SCC	Adenocarcinoma
TP53 (36, 71)	17p13.1	51%	36%
PI3KCA amplification (51, 52, 54)	3q26.3	33%	6%
SOX2 amplification (23, 24)	3q26.3-q27	23%	Very rare
FGFR1 amplification (24, 25)	8p12	22%	1%
PTEN mutation (36, 61)	10q23.3	10%	2%
MET amplification (34, 35)	7q31.1	3%–21%	3%–21%
PTEN loss (59, 62)	10q23.3	8%–20%	8%–20%
KRAS mutation (36)	12p12.1	6%	21%
Variant III mutation (36)	7p12	5%	Very rare
LKB1 mutation (70)	19p13.3	5%	23%
DDR2 mutation (30)	1q23.3	4%	1%
HER2 overexpression (39–42)	17q11.2-q12, 17q21	3%–5%	5%–9%
PI3KCA mutation (50–52)	3q26.3	3%	3%
BRAF mutation (36, 64)	7p34	2%	1%–3%
EGFR mutation (36)	7p12	<5%	10%–15%
AKT1 mutation (56)	14q32.32	1%	Very rare
MET mutation (36)	7q31.1	1%	2%
HER2 mutation (46, 48, 49)	17q11.2-q12, 17q21	1%	2%
EML4-ALK fusion (66, 67)	2p21, 2p23	1%	2%–7%

mutation and had a long-term response on erlotinib plus dasatinib, which suggests that DDR2 mutations may be clinically relevant.

MET is a proto-oncogene that encodes a transmembrane tyrosine kinase receptor for the hepatocyte growth factor. MET amplification serves as a mechanism of gefitinib resistance by activating ERBB3 signaling (31). In cells with MET gene amplification, MET is highly activated, and cell proliferation and survival are dependent on this activated MET kinase (32). Inhibition of MET in amplified cell lines leads to reduced cell growth and apoptosis (33). The frequency

of MET gene copy-number gains is between 3% and 21%, with no differences between adenocarcinoma and SCC, although it seems to be more prevalent in smokers (34, 35). Despite these results, it is estimated that true MET amplifications are rare in lung cancer, occurring at a frequency of ~2% for adenocarcinoma and somewhat less than that for SCC. This may be because there is a low-level copy-number gain of MET in a much higher percentage of the tumors, but the biologic implications are unclear. In lung cancer, the estimated frequency of mutations is low (1% for SCC

**Figure 1.** Frequencies of potentially actionable/targetable genetic abnormalities present in SCC of the lung. amp, amplified; mut, mutant.



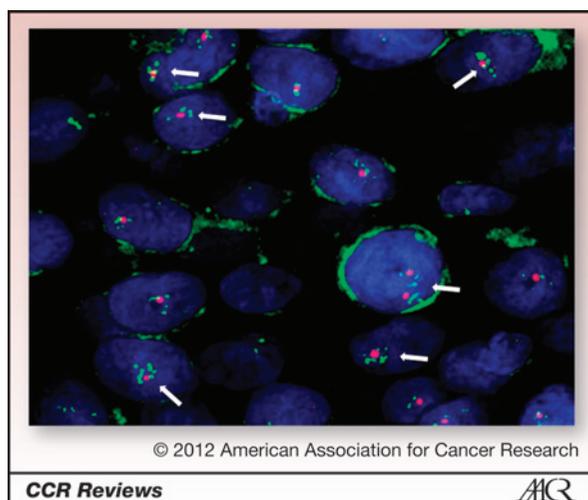


Figure 2. FGFR1 FISH-amplified SCC cells. White arrows show some of the amplified cells.

and 2% for adenocarcinoma), and MET-mutated cells reveal enhanced ligand-mediated proliferation and significant *in vivo* tumor growth (36, 37).

Human EGF2 (ERBB2/Her2) is a transmembrane tyrosine kinase receptor that has no ligand-binding domain of its own. In lung cancer, the frequency of Her2 amplification is not clear, due to the use of different techniques (e.g., FISH and IHC) and cutoff values. Studies have shown overexpression in 10% to 35% of NSCLC, and less than that when the cutoff is IHC 3+ (3%–9%). Amplification is higher in adenocarcinoma than in SCC, and it confers sensitivity to gefitinib (38–42). Mutations in the ERBB2 gene are rare (2% in adenocarcinoma and 1% in SCC) and are associated with resistance to EGFR inhibitors and sensitivity to Her2-targeted therapy (43–49).

### Signaling pathway alterations

Phosphoinositide 3-kinase catalytic  $\alpha$  (PI3KCA) encodes for the class IA PI3K $\alpha$  catalytic subunit p110 $\alpha$ . Mutations are seen in ~2% to 3% of SCCs; however, the precise frequency remains to be determined in sufficiently powered studies that are currently ongoing (36, 50–52). The mutational status of PI3KCA is not mutually exclusive to EGFR or KRAS (53). PI3KCA copy-number gains are more frequent in SCC (33.1%) than in adenocarcinoma (6.2%) or small-cell lung cancer lines [4.7% (51, 52, 54)]. Because the PI3KCA gene is located close to the SOX2 lineage transcription factor gene, which is frequently amplified in SCC, it is not clear whether these amplifications are functionally associated with PI3K dependency. In SCC cell lines, mutations or copy-number gains confer a growth advantage (52).

The v-akt murine thymoma viral oncogene homolog 1 (AKT1) gene encodes for protein kinase B  $\alpha$  (PKB $\alpha$ ), which is involved in the PI3K signal transduction pathway (55). The somatic mutation E17K in the AKT1 gene was found in 1% of lung SCCs but not in adenocarcinoma (56).

The phosphatase and tensin homolog (PTEN) is a phosphatase that plays a tumor-suppressive role. In the cytoplasm it plays the role of a phosphatase: It dephosphorylates PIP3 into phosphatidylinositol-3,4-bisphosphate (PIP2), thereby inhibiting PI3K–AKT signaling (57). Additionally, nuclear compartmentalization of PTEN is a key component of its tumor-suppressive activity, because it positively regulates APC/C-CDH1 in a phosphatase-independent manner to promote the down-regulation of its targets and tumor suppression (58). The loss of PTEN activity leads to hyperactivation of the PI3K–AKT pathway. Loss of PTEN can occur at the genomic level or by alternative mechanisms such as promoter hypermethylation, alternative splicing of pre-mRNA, and post-translational modifications. PTEN inactivation occurs more frequently at the protein level than at the genomic level, and promoter methylation is found in 35% of PTEN-negative NSCLC (59, 60). PTEN mutations have been described in 10% of lung SCC samples, compared with 2% of adenocarcinomas (36, 61). At the genomic level, PTEN loss is seen in 8% to 20% of both histologic subtypes (59, 62).

The BRAF protein is a cytoplasmatic serine/threonine kinase that plays an important role in the RAS–mitogen-activated protein kinase (MAPK) signaling pathway (63). BRAF mutations are associated with increased kinase activity that leads to constitutional activation of MAPK2 and MAPK3, and they are mutually exclusive to EGFR and KRAS mutations. Mutations are seen in ~2% of patients and are quite similar in both adenocarcinoma and SCC. Approximately 90% of mutations found in lung cancer do not involve the mutation commonly seen in melanoma (V600E), and this may have biologic and therapeutic implications (64, 65).

EML4-ALK is an aberrant fusion gene that encodes a cytoplasmatic chimeric protein with constitutive kinase activity. This gene fusion has potent oncogenic activity in animal models and cell lines, and inhibition of ALK leads to a substantial tumor response. This fusion is uncommon, occurring in ~2% to 7% of cases of NSCLC, and is more prevalent in people who never smoked or in light smokers and in patients with adenocarcinoma. In lung SCC, the estimated prevalence is ~1% (66–68).

Serine/threonine kinase 11 (STK11/LKB1) is a tumor-suppressor gene that phosphorylates AMPK. It regulates cell-cycle arrest, p53-mediated apoptosis, and the induction of cell polarity (69). Somatic mutations of LKB1 are present in 5% of lung SCCs and 23% of adenocarcinomas, and their roles are not clear (70).

### Transcription factor alterations

The p53 gene, located on chromosome 17p13.1, codes for a multifunctional DNA sequence-specific nuclear phosphoprotein that is essential for maintaining the integrity of the genome. In lung cancer, the frequency of p53 mutation is between 30% and 50%. In the COSMIC database, the rate of TP53 mutation in SCC of the lung is 51% (36). The spectrum of somatic mutations observed in p53 in SCC

is characterized by a high proportion of C:G > A:T transversions and is compatible with the mutagenic effects of tobacco carcinogens (71). Loss of p53 pathway function can also be related to HDM2 amplification/overexpression when p53 is wild type.

Sex-determining region Y-Box 2 (SOX2) is a transcription factor that plays a role in squamous differentiation of the esophagus and lung. The amplification of the SOX2 gene is the most frequent chromosome gain seen in SCC of the lung, with a frequency of 23% as shown by single-nucleotide polymorphism arrays and FISH (23, 24, 72). Suppression of SOX2 in amplified SOX2 cells has greater antiproliferative effects compared with other genes on

3q26.33, and SOX2 amplification and overexpression are involved in maintaining stem cell properties in SCC (24, 72).

### Therapeutic Opportunities

The advent of targeted therapies has revolutionized cancer treatment. In lung adenocarcinoma, significant improvements in outcomes can be achieved when targeted therapies are used in populations of patients who have been selected based on the molecular profile of their tumor. Unfortunately, this is not true for patients with lung SCC, whose treatment cannot be selected based on the molecular

**Table 2.** Potential molecularly driven treatment approaches in lung SCC

Compound	Targets	MOA	MT/CT	Ph	Molecularly enriched	HS	NCTID
<b>FGFR1</b>							
BGJ398	Pan FGFR	KI	MT	1	Yes	No	NCT01004224
AZD4547	Pan FGFR	KI	MT	1	Yes	No	NCT00979134
E-3810	Pan FGFR, VEGFR	KI	MT	1	No	No	NCT01283945
FP-1039	FGF	AB	MT	1	No	No	NCT00687505
TKI258	FGFR, VEGFR, PDGFR	KI	MT	1	No	No	NCT01270906
<b>DDR2</b>							
Dasatinib	BCR/ABL, SRC, c-Kit, DDR1-2	KI	MT	2	No	No	NCT00787267 NCT00459342
<b>BRAF</b>							
GSK2118436	BRAF	KI	MT	2	Yes	No	NCT01336634
<b>PI3KCA</b>							
PF-04691502	PI3K, mTOR	KI	MT	1	No	No	NCT00927823
XL147	PI3K	KI	CT	1	No	No	NCT00756847
BKM120	PI3K	KI	MT	2	Yes	Yes	NCT01297491
BYL719	PI3K	KI	MT	1	Yes	No	NCT01219699
XL765	PI3K, mTOR	KI	MT	1	No	No	NCT00485719
PX866	PI3K	KI	CT	1	No	No	NCT01204099
GDC-0941	PI3K	KI	CT	1	No	No	NCT00975182
<b>AKT1</b>							
MK2206	Pan AKT	KI	CT	1	No	No	NCT01147211
			CT	2			NCT01294306
GDC-0068	Pan AKT	KI	MT	1	No	No	NCT01090960
<b>MET</b>							
Crizotinib	MET, ALK	KI	MT	1	No	No	NCT00585195
			CT				NCT01121575
XL184	MET, RET, VEGFR2	KI	MT	2	No	No	NCT00940225
			CT				NCT00596648
MetMAb	MET	AB	CT	3	Yes	No	NCT01456325
Arq197	MET	KI	CT	2	Yes	No	NCT01395758
<b>ERBB2</b>							
MGAH22	Her2	AB	MT	1	Yes		NCT01148849
Lapatinib	EGFR, HER2	KI	CT	1	No		NCT01184482

Abbreviations: AB, antibody; CT, combined therapy; HS, histologic selection or stratification; KI, kinase inhibitor; MOA, mechanism of action; MT, monotherapy; NCTID, National Cancer Trial Identification; Ph, phase of clinical development.

profile of their tumor. However, the detection of new genetic alterations constitutes a window of opportunity to test both new and already approved molecules (Table 2).

FGFR1 is a promising target with a high amplification frequency and encouraging preclinical data. Several FGFR1 TKIs (BGJ398, AZD4547, TKI258, and E-3810, all of which are orally available) are in the early phase of clinical development. E-3810, a dual VEGF/FGFR1 inhibitor, was well tolerated in a phase I trial (73). Moreover, in a phase II trial of TKI258, a 25% disease control rate was achieved at 24 weeks in heavily pretreated patients with breast cancer with FGFR1 amplification (74). FGFR1 looks promising; however, to date, no trials with this target are specifically enrolling SCC patients.

Targeting DDR2 mutations is auspicious. Their frequency is similar to that detected in the EML4-ALK translocation in adenocarcinoma, and many already approved drugs are DDR2 inhibitors. Dasatinib, imatinib, nilotinib, and ponatinib target BCR/ABL, SRC, c-Kit, and multiple Eph kinases, and also inhibit DDR1 and DDR2 (75). Dasatinib was shown to have modest activity in pretreated, unselected patients with NSCLC (76). Although DDR2 is potently inhibited by dasatinib, allowing a target inhibition within the therapeutic window, it is currently not clear whether DDR2 is the relevant target of dasatinib in DDR2-mutant tumors. Ongoing clinical trials are recruiting patients with NSCLC using dasatinib. An interesting finding is that ponatinib is also a potent pan-FGFR inhibitor (77).

Many MET inhibitors are under investigation. Crizotinib is a MET/ALK dual inhibitor that is being tested in combination with the pan-HER inhibitor PF-00299804 in phase I trials. XL 184 is a MET/VEGF2 TKI that achieved a 40% disease control rate in a phase II trial of unselected patients with NSCLC, including patients with SCC (78). In combination with erlotinib, MetMab (an antibody to the MET receptor) showed clinical benefit in a phase II trial in pretreated patients with NSCLC and overexpression of MET (79). ARQ 197 is a MET TKI that improved progression-free survival and overall survival, although this result was more pronounced in the population with nonsquamous histologies (80). Furthermore, although this study involved molecularly unselected patients, there was a trend toward better outcomes in patients with MET amplification.

To date, inhibition of Her2 has not been proved to be effective in NSCLC. Trials testing trastuzumab in Her2-protein-overexpressing NSCLC failed to show clear benefit (81, 82). This could partially be explained by differences in patient selection. MGAH22 is an antiHER2 antibody that is currently under phase I investigation in Her2-overexpressing tumors. Anecdotal activity has been reported with trastuzumab or pan-Her inhibitors (PF-00299804 and neratinib) in patients with NSCLC with Her2-mutated or amplified tumors (43–45).

PI3K amplification and mutations are frequent events in SCC; however, their predictive value for sensitivity to PI3K inhibition is still debated (83). PF-04691502, an oral inhibitor of PI3K/mTOR, is currently in a phase I trial. XL147 is an oral inhibitor of PI3K that has shown signs of

activity in NSCLC, even in patients with no PI3K mutations, in a phase I trial. It has been explored in another phase I trial combined with erlotinib (84). BKM120 is a potent and highly specific oral pan-class I PI3K inhibitor that is currently being evaluated combined with chemotherapy in patients with NSCLC and evidence of an activated PI3K pathway. BYL 719, an oral PI3K inhibitor, is under phase I study in patients harboring PI3KCA mutations. GDC-0941 is currently being tested in a phase I study in combination with erlotinib in unselected patients with NSCLC. Loss of PTEN may render cells dependent on the PI3K-AKT pathway, and this may provide a therapeutic window for small-molecule inhibitors that have been developed to block PI3K signal transmission. Because AKT is downstream of PI3K, its inhibition can be used when the purpose is to inhibit the PI3K-AKT pathway. The E17K mutation found in SCC does not alter the sensitivity of AKT to ATP competitive inhibitors, but it does alter the sensitivity to allosteric kinase inhibitors (85). MK-2206 is an allosteric inhibitor of AKT that is being tested in a phase II trial in lung cancer. GDC-0068 is an oral, selective, ATP-competitive AKT inhibitor that is currently in a phase I trial.

Until now, targeting of p53 has proved to be highly disappointing; however, a new era may emerge with the use of hdm2 inhibitors such as RG7112 and MK-8242, which are currently in the phase I setting. RG7112 was tested in patients with liposarcomas (a frequently HDM2-amplified tumor), but with no prescreening for p53 status (86).

Finally, targeting BRAF was tested in unselected patients with NSCLC. Sorafenib, a multikinase BRAF inhibitor, failed to show a survival advantage when added to first-line chemotherapy in advanced NSCLC (87). GSK2118436, a selective inhibitor of BRAF that showed activity in non-V600 BRAF mutant melanoma, is under investigation in a phase II trial in patients with NSCLC and BRAF mutations (88).

## Conclusions

Although the incidence of adenocarcinoma is on the rise, lung SCC is currently the second most frequent histologic subtype and the leading one in developing countries. Encouraging new treatments have afforded a benefit to patients with adenocarcinoma, but unfortunately the same is not true for SCC. Chemotherapy is still the gold standard for first-line treatment in advanced SCC of the lung. To date, no single phase III trial involving targeted therapies has identified a benefit in this subpopulation; moreover, some trials showed augmented toxicity in comparison with the population with nonsquamous disease.

Increasing information from basic, translational, and clinical research is changing the approach to patient care in cancer. The historical classification of lung cancer is histology based, but modern pathology needs to bring histology and genomics closer together. A correct histologic diagnosis can help guide the choice of a selected pool of aberrations to be screened. The recognition of molecular

subtypes may identify tumors with different biologic behaviors, and molecular profiling together with an appropriate histologic diagnosis potentially can be used to select the right targeted therapy.

Over the past few years, investigators have described many genomic alterations in SCC. Preclinical data for some of these alterations are promising, and it has been shown that many such aberrations can make a cancer cell become addicted to a specific pathway. How much of this molecular deciphering will translate to actionable targets and therapeutic success remains to be established. Amplification of MET or FGFR1, both of which are found frequently in SCC of the lung, makes the amplified cells become dependent on that pathway, and clinical data concerning MET and FGFR1 inhibition are encouraging. Dasatinib and imatinib inhibit cells carrying DDR2 mutations, which are detected more often in SCC than in adenocarcinoma. In the short term, the molecular characterization of patients with SCC in modern profiling platforms will therefore be as important as deciphering the molecular

genetics of adenocarcinoma. Patients with SCC of the lung should not be denied molecular testing, because such an approach may provide new therapeutic opportunities for such patients. Patients with SCC of the lung harboring specific molecular defects that are actionable (i.e., FGFR1, DDR2, and PI3K) should be enrolled in prospective clinical trials targeting such defects.

#### Disclosure of Potential Conflicts of Interest

R. Thomas receives consulting and lecture fees from Sanofi-Aventis, Merck, Roche, Boehringer Ingelheim, AstraZeneca, and Atlas-Biolabs. No other potential conflicts of interest were disclosed.

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