Squamous-cell carcinoma of the lung: molecular subtypes and therapeutic opportunities

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Abstract

Lung cancer is the leading cause of cancer-related death worldwide. Squamous-cell carcinoma (SCC) of the lung is, ranking behind adenocarcinoma, the second most frequent histological subtype in non-small cell lung cancer. Encouraging new treatments have afforded benefits to patients with adenocarcinoma (ie bevacizumab, EGFR tyrosine kinase inhibitors, ALK inhibitors) but, unfortunately, the same is not true for SCC. However, many genomic abnormalities are present in SCC and there is growing evidence of their biological 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 (ie FGFR1 amplification, DDR2 mutation, PI3K amplification, etc) should be enrolled in prospective clinical trials targeting such molecular defects.

Translational relevance: Squamous-cell carcinoma (SCC) of the lung is the second most frequent histology in non-small cell lung cancer. Over the last decade new approaches targeting specific pathways in NSCLC have emerged but very few advances were made in the treatment of squamous-cell carcinoma. Advances in translational research demonstrate significant differences in molecular pathways among subtypes of NSCLC and these genomic alterations have significant effects in tumor growth. Thus, molecular characterization of SCC is essential to understand the biological relevance and the true frequency of each alteration. Patients with SCC of the lung harboring specific molecular defects that are actionable (ie FGFR1 amplification, DDR2 mutation, PI3K amplification, etc) should be enrolled in prospective clinical trials targeting such molecular defects.
Introduction:

Lung cancer is the leading cause of cancer-related death 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 histological subtypes accounting for 50% and 30% of NSCLC cases respectively. Although, the incidence of lung SCC is decreasing as consequence of changes in tobacco consumption habits, SCC is still a major health issue.[3;4] Despite the recognition of histological subtypes, the concept of “one size fits all” governed decisions for many years.[5] Encouraging new treatments have afforded benefits to patients with adenocarcinoma (ie bevacizumab, EGFR tyrosine kinase inhibitors, ALK inhibitors) but, unfortunately, the same is not true for SCC. A correct histological diagnosis is increasingly important since it may predict response and toxicity to different therapies.[6;7]

Trials evaluating targeted therapies have failed to identify any benefits in SCC patients and the standard frontline treatment administered to these patients is chemotherapy doublets. Moreover, figitumumab, an antibody targeting insulin-like growth factor-1 receptor, combined with chemotherapy demonstrated non-significantly worse survival when compared to chemotherapy alone on a phase III trial.[8] Remarkably, patients with SCC are at higher risk of complications for bleeding if exposed to bevacizumab. It is important to note that vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) combined with chemotherapy have all had their development plan halted in the SCC subtype due to higher mortality rates. Bleeding as well as cavitation are also induced by VEGFR TKI, but this is probably not the only explanation for increased toxicity in the SCC subtype. Thus SCC represents an important field where new therapeutic options are awaited.

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

Histological subtypes of squamous cell carcinoma
Squamous-cell carcinomas 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 the 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 non-small cell lung carcinoma, since large cell carcinoma is not accepted as a diagnosis in small specimens. An immunohistochemical (IHC) panel together with a mucin stain can help identify NSCLC subtypes. The expression of p63, and its N-terminal truncated P40 lacking TTF1 expression, are quite constant phenotypical traits which allow NSCLC subtypes to be distinguished from adenocarcinoma. The expression of p63 is strong and diffuse in SCC which is a particular transcriptional factor of this histological type.

The WHO classification (2004) recognizes 4 variants among SCC, 2 of which have a specific clinicopathological significance and deserve to remain in the forthcoming classifications: 1) the papillary variant shows endobronchial obstructive growth with sometimes limited intraepithelial spread and invasion may be difficult to assess; 2) the basaloid variant (BC) is characterized by a basal bronchial stem cell proliferation shows basaloid pattern predominance and minimal areas of squamous differentiation. BC/SCC is difficult to recognize as SCC on small biopsy specimens: p63, cytokeratins (CKs) 5/6 and the CKs 1, 5, 10 and 14 recognized by the antibody CK34beta E12 are the hallmarks of this very aggressive variant with high mitotic index. Patients with this variant have significantly shorter survival than those with others stage I-II SCC. The other 2 variants have no clinical relevance: clear cell is considered as a cell change more than as a pattern and can occur in all histological categories and the small cell variant is not recognized as being different from the basaloid variant.

**Molecular subtypes in squamous cell carcinoma:**

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 alterations (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, since normal cells in their vicinity do not bear the respective alteration.

We will classify the molecular alterations according to their therapeutic targets: membrane receptor alterations, signaling pathway alterations and transcription factor alterations. We have used any of the following 2 criteria before reporting the abnormalities: 1) a frequency of the molecular event above 10%; 2) a molecular alteration for which there is clinical evidence of objective responses when modulating it by a molecular targeted agent registered or under clinical development. Table 1 and Figure 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 physiological functions and there is evidence of deregulated signals in the pathogenesis of many different cancer types. It signals downstream through four different pathways: RAS-RAF-MAPK, PI3K-AKT, signal transducer and activator of transcription (STAT) and phospholipase Cγ (PLCγ).[22] That tumor growth is dependent on FGFR1 activation was demonstrated in lung cancer cell lines with FGFR1 amplification and mice engrafted with FGFR1-amplified cells.[23] Treatment with specific blockers resulted in tumor growth inhibition or shrinkage. In lung SCC, the frequency of
FGFR1 amplification by FISH (Figure 2) is of 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 once activated, it interacts with Src and Shc.[26;27] Mutations may alter kinase activity, ligand binding or DDR2 localization.[28;29] Mutations were found in 11 of 290 (3.8%) SCC samples.[30] Lung SCC cell lines harboring DDR2 mutations are selectively killed by RNA interference or dasatinib. In addition, tumors established from a DDR2 mutant cell line are sensitive to dasatinib in xenograft models. By contrast, xenografts with non-mutant tumors are insensitive to dasatinib in xenograft models. This response was also seen in a pretreated SCC patient carrying a DDR2 mutation had a long-term response on erlotinib plus dasatinib suggesting that DDR2 mutations may be clinically relevant.

MET is a proto-oncogene that encodes a transmembrane tyrosine kinase receptor for the hepatocyte growth factor (HGF). MET amplification is 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 about 2% for adenocarcinoma and somewhat lower for SCC. This may be due to the fact that there is low-level copy number gain of MET in a much higher percentage of the tumors but it is not clear what the biological implications are. In lung cancer the estimated frequency of mutations is low, 1% for the SCC and 2% for the adenocarcinoma and MET-mutated cells reveal enhanced ligand-mediated proliferation and significant in vivo tumor growth.[36;37]

The human epidermal growth factor 2 (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 (FISH vs IHC) and cutoff values. Studies report overexpression in 10-35% of NSCLC, which is lower when the cutoff is IHC 3+ (3% to 9%). Amplification is higher in adenocarcinoma than in SCC and it confers sensitivity to gefitinib.[38-42] Mutations in ERBB2 gene are rare, 2% in
adenocarcinoma and 1% in SCC and they are associated with resistance to EGFR inhibitors and sensitivity to Her2-targeted therapy.[43-49]

**Signaling pathway alterations:**

Phosphatidylinositol 3-kinase catalytic alpha \( (\text{PI3KCA}) \) encodes for the class IA PI3Ka catalytic subunit p110α. Mutation are seen in around 2-3% of SCC, however, the precise frequency remains to be determined in sufficiently powered studies that are currently ongoing.[36;50-52] Mutational status of PI3KCA is not mutually exclusive to EGFR or KRAS.[53] PIK3CA 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] Since the PIK3CA gene is located closely 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 a protein kinase B alpha (PKBα) which is involved in the PI3K signal transduction pathway.[55] The somatic mutation E17K in the AKT1 gene was found in 1% of lung SCC but not in adenocarcinoma.[56]

The phosphatase and tensin homolog (PTEN) is a phosphatase that has a tumor suppressor role. In the cytoplasm it plays a role of a phosphatase: it dephosphorylates PIP3 into phosphatidylinositol-3,4-bisphosphate (PIP2) consequently inhibiting PI3K-AKT signaling.[57] Additionally, nuclear compartmentalization of PTEN is a key component of its tumor suppressive activity as it positively regulates APC/C-CDH1, in a phosphatase-independent manner, to promote the downregulation of its targets and tumor suppression.[58] The loss of PTEN activity leads to hyperactivation of the PIK3-AKT pathway. PTEN loss can occur at genomic level or by alternative mechanism as promoter hypermethylation, alternative splicing of pre-mRNA, and posttranslational modifications. The rate of PTEN inactivation at protein level is more frequent than that identified at genomic level; promoter methylation is found in 35% of PTEN negative NSCLC.[59;60] PTEN mutations are described in 10% of
lung SCC samples whereas they are found in 2% of adenocarcinomas.[36;61] At genomic level PTEN loss is seen in 8-20% of both histological subtypes.[59;62]

The B-RAF protein is a cytoplasmatic serine/threonine kinase that plays an important role in the RAS-MAPK signalling pathway.[63] B-RAF 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 around 2% of patients and are quite similar in both adenocarcinoma and SCC. About 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 possesses potent oncogenic activity both in animal models and cell lines and inhibition of ALK leads to a substantial tumor response. This fusion is uncommon, occurring in about 2-7% of NSCLC, and is more prevalent in never or light smokers and in patients with adenocarcinoma. In lung SCC the estimated prevalence is around 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 SCC and in 23% of adenocarcinomas and their roles are not clear.[70]

**Transcription factor alterations**

The p53 gene, located in 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%. The rate of TP53 mutation in SCC of the lung is 51% in the COSMIC database.[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 SNP arrays and FISH.[23;24;72] Suppressing SOX2 in amplified SOX2 cells has the largest antiproliferative effects compared to others genes in the 3q26.33 and SOX2 amplification and overexpression is involved in the maintenance of stem cell properties in SCC.[24;72]

**Therapeutic opportunities:**

The advent of targeted therapies revolutionized cancer treatment. In lung adenocarcinoma significant improvements in outcomes occur when targeted therapies are used in populations 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 profile of their tumor. However, the detection of new genetic alterations constitutes a window of opportunity to test new, as well as already approved molecules (Figure 3 and 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 orally available drugs, are in 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 breast cancer patients with FGFR1 amplification.[74] FGFR1 looks promising although, to date, there are still no trials specifically enrolling SCC patients.

Targeting DDR2 mutations is striking. Their frequency is similar to the one detected in the EML4-ALK translocation in adenocarcinoma and many already approved drugs are DDR2 inhibitors. Dasatinib, imatinib, nilotinib and positinib target BCR/ABL, SRC, c-Kit, multiple Eph kinases and also inhibit DDR1 and DDR2.[75] Dasatinib had modest activity in pretreated, unselected NSCLC patients.[76] Although DDR2 is potently inhibited by dasatinib
allowing a target inhibition within the therapeutic window, for the time being, it is not clear whether it 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 dual inhibitor MET/ALK that is being tested combined 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 NSCLC which included SCC patients.[78] MetMAb, an antibody to the MET receptor, in combination with erlotinib demonstrated clinical benefit in a phase II trial in pretreated NSCLC patients with overexpression of MET.[79] ARQ 197 is a MET TKI that improved PFS and OS although this result was more pronounced in the population with non-squamous histologies and although this were molecularly unselected patients, there was a trend towards better outcomes in patients with MET amplification.[80]

To date, inhibition of Her2 has not been proven 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 investigation in phase I in Her2-overexpressing tumors. Anecdotal activity has been reported with trastuzumab or pan-Her inhibitors (PF-00299804 and neratinib) in NSCLC patients with Her2-mutated or amplified tumors.[43-45]

PI3K amplification and mutations are frequent events in SCC although their predictive value towards sensitivity to PI3K inhibition is still debated.[83] PF-04691502, an oral inhibitor of PI3K/mTOR, is currently in phase I. 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 activated PI3K pathway. BYL 719, an oral PI3K inhibitor, is under phase I study in patients harboring PIK3CA mutations. GDC-0941 is currently being tested in phase I combined with erlotinib in unselected NSCLC patient. Loss of PTEN may render cells to depend on PIK3-AKT pathway and this may signalize a therapeutic window for small molecule inhibitors developed to block PI3K signal transmission. As AKT is downstream PI3K its inhibition can be used when the purpose is to
inhibit 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 phase I.

P53 targeting has proven up to now highly disappointing. A new era may emerge with hdm2 inhibitors. These are currently in the phase I setting and encompass RG7112 and MK-8242. RG7112 was tested in patients without pre-screening for P53 status but with liposarcomas (a frequently HDM2-amplified tumor).[86]

Finally, targeting B-RAF was already tested in unselected NSCLC. Sorafenib, a multikinase B-RAF inhibitor, failed to show a survival advantage when added to frontline 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 NSCLC patients with BRAF mutations.[88]

**Perspectives:**

Even though the incidence of adenocarcinoma is on the increase, lung SCC is the second histological 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 frontline treatment in advanced SCC of the lung. To date, no single phase III trial involving targeted therapies had identified benefit in this subpopulation and moreover some trials found augmented toxicity when compared to the population with non-squamous disease.

Growing knowledge from basic, translational and clinical research has changed 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. Nowadays, a correct histological diagnosis can help in the choice of a selected pool of aberrations to be screened. The recognition of molecular subtypes may identify tumors with
different biological behavior, and molecular profiling together with an appropriate histologic diagnosis can potentially be used to select the right targeted therapy.

Over the last years many genomic alterations have been described in SCC. For some of them, preclinical data is promising and many aberrations can make the cancer cell to become addicted to a specific pathway. How much of this molecular deciphering will translate in actionable targets and therapeutic success is yet to be established. Amplification of MET or FGFR1, both frequent in SCC of the lung, makes amplified cells to 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 paves the way for new therapeutic opportunities for these patients. Patients with SCC of the lung harboring specific molecular defects that are actionable (ie FGFR1, DDR2, PI3K) should be enrolled in prospective clinical trials targeting such defects.

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Table 1 Frequency of Selected Genetic Abnormalities in NSCLC

<table>
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<th>Genetic abnormality</th>
<th>Gene location</th>
<th>Squamous Cell Carcinoma</th>
<th>Adenocarcinoma</th>
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<td>TP53[^36;71]</td>
<td>17p13.1</td>
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<td>36%</td>
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<tr>
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Table 2 Potential molecularly driven treatment approaches in lung SCC. MOA: mechanism of action; MT: monotherapy; CT: combined therapy; Ph: phase of clinical development; Mol. Enriched: molecularly enriched; HS: histologic selection or stratification; NCTID: National Cancer Trial Identification; KI: kinase inhibitor; AB: antibody

<table>
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<th>Compound</th>
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Figure 1 Frequencies of potentially actionable/targetable genetic abnormalities present in squamous-cell carcinoma of the lung
Figure 2. FGFR1 FISH amplified SCC cells. White arrows show some of the amplified cells.
Reference List


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