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New treatment options in advanced squamous cell lung cancer: new drugs, molecular targets and immunotherapy

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Abstract

The past few years have witnessed a rapid shift in the treatments for patients with squamous cell lung cancers (SQ-NSCLC) after the U.S. Food and Drug Administration and the European Medical Agency approval of a number of immune checkpoint inhibitors as second-line therapies for patients with NSCLC. These series of approvals marked the first substantial improvement in overall survival for patients with SQ-NSCLC in over a decade. Further gains have been made more recently with the incorporation of immune checkpoint inhibition in the first-line setting, either as monotherapy or in combination with chemotherapy. These advances have, however, exposed existing deficiencies in the management of this disease. Despite a deeper understanding of the genomic alterations that characterize SQ-NSCLC and years of trial work targeting these alterations, personalized therapies remain out of hand. Also, epigenetic therapies to modulate the expression of lineage-dependent survival pathways and undruggable oncogenes are under investigation. Another important therapeutic approach is to exploit metabolic vulnerabilities unique to SQ-NSCLC. Future studies will continue to focus on identifying targeted approaches to expand the treatment options for our patients.

Keywords:
Squamous cell lung cancer. Drugs. Molecular targets. Immunotherapy.

Resumen

Los últimos años han sido testigos de un rápido cambio en los tratamientos para pacientes con cáncer de pulmón de células escamosas (SQ-NSCLC) después de que la FDA y la EMA aprobaran una serie de inhibidores de puntos de control inmunológico como terapias de segunda línea para pacientes con NSCLC. Esta serie de aprobaciones marcó la primera mejora sustancial en la supervivencia general de los pacientes con SQ-NSCLC en más de una década. Más recientemente se han logrado más avances con la incorporación de la inhibición de los puntos de control inmunológico en el ámbito de la primera línea, ya sea como monoterapia o en combinación con quimioterapia. Sin embargo, estos avances han dejado al descubierto las deficiencias existentes en el tratamiento de esta enfermedad escamosa. A pesar de una comprensión más profunda de las alteraciones genómicas que caracterizan al SQ-NSCLC y de años de ensayos dirigidos a estas alteraciones, las terapias personalizadas siguen estando fuera de control. Además, se están investigando terapias epigenéticas para modular la expresión de vías de supervivencia tumoral y oncogenes con nuevos tratamientos farmacológicos. Otro enfoque terapéutico importante está enfocándose en las vulnerabilidades metabólicas exclusivas del SQ-NSCLC. Los estudios futuros seguirán centrándose en identificar enfoques específicos para ampliar las opciones de tratamiento para nuestros pacientes.

Palabras clave:
Carcinoma escamoso de pulmón. Fármacos. Dianas moleculares. Inmunoterapia.

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INTRODUCTION

Squamous cell lung cancers (SQ-NSCLC) account for 20 %-30 % of all cases of non-small cell lung cancer (NSCLC) diagnosed in the United States (1). Although treatment options for patients with this disease have been historically similar to those for patients with lung adenocarcinomas, the era of personalized medicine, which formally began with the identification of drug-sensitizing epidermal growth factor receptor (EGFR) mutations in 2004, ushered in a widening divide in the management of these two diseases. The steady identification of actionable oncogenic alterations, almost exclusively limited to lung adenocarcinomas, has cemented the routine use of genomic profiling in that disease. The increasing number of targeted therapies matched to these alterations and their impact on progression-free survival (PFS) and overall survival (OS) reinforce the power of genotype-directed therapy. However, most substantial impact on the treatment of patients with SQ-NSCLC has come from the histology-agnostic approach of immune checkpoint inhibition.

As we show in this review, immune checkpoint inhibition has opened the door to new treatment options for patients with SQ-NSCLC, but it has also exposed our relatively poor understanding of the biology of this disease. Our incomplete knowledge of SQ-NSCLC continues to limit what providers can offer patients who have this disease. Drug development in SQ-NSCLC has been challenging due to complex tumor genomics, a limited mechanistic understanding of the interplay of oncogenic pathways, and a lack of representative mouse models. With such high mortality, the development of therapies specific to SQ-NSCLC is urgently needed. In this perspective, we discuss some of the key mechanisms involved in the tumorigenesis of SQ-NSCLC, lessons learned from past attempts at targeted drug development, and emerging therapeutics for advanced metastatic SQ-NSCLC.

ADVANCES IN FRONTLINE THERAPY

The treatment landscape for advanced SQ-NSCLC has changed substantially in the past few years and has witnessed a reshuffling of secondary therapies to the upfront setting. Pembrolizumab, initially approved as a second-line therapy after treatment with platinum doublet chemotherapy, has moved to the first-line setting as a monotherapy option and in combination with platinum doublet chemotherapy. Chemotherapy remains a mainstay for patients with contraindications to immunotherapy (Fig. 1).

Pembrolizumab monotherapy for high PD-L1 expression

KEYNOTE-024 established the use of pembrolizumab monotherapy as the standard of care for patients with 50 % or greater tumoral PD-L1 expression (2). This trial randomly assigned patients with newly diagnosed stage IV NSCLC with high tumoral PD-L1 expression (tumor proportion

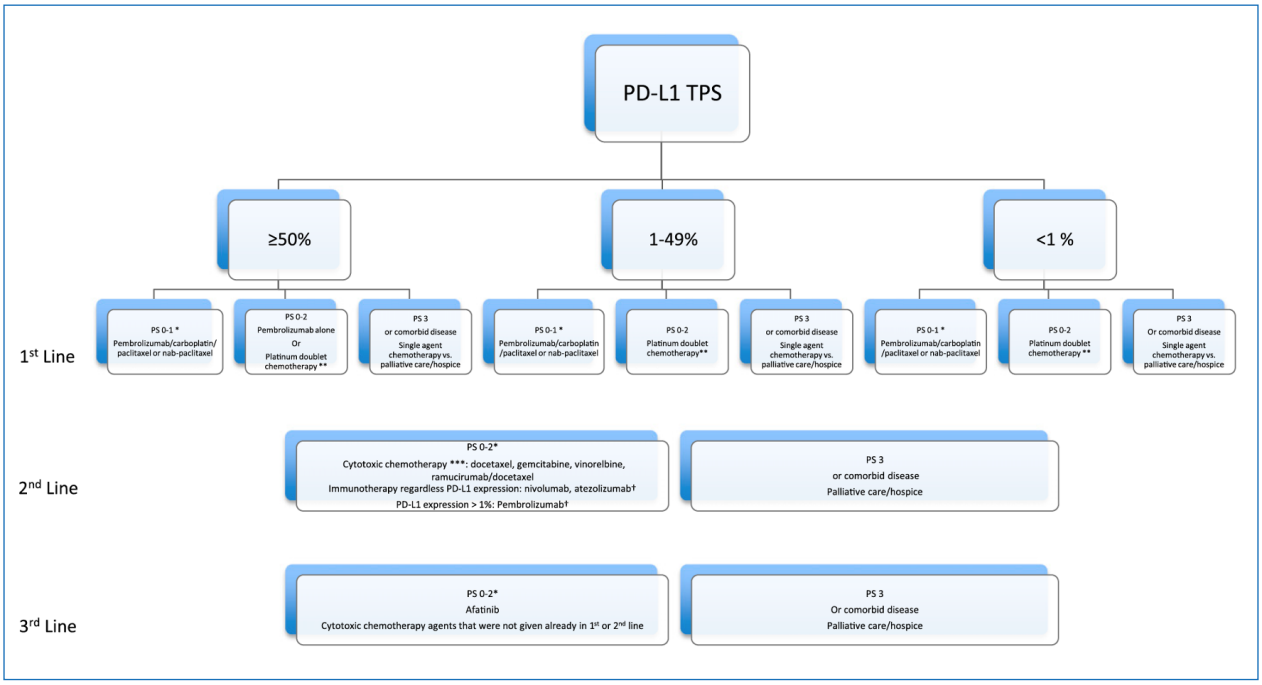

Fig. 1. Treatment algorithm for patients with advanced squamous cell lung cancers.

score, 50 % or greater) to 200 mg of pembrolizumab every 3 weeks for 35 cycles or investigator's choice of platinum doublet chemotherapy. Thirty percent of the 1,653 patient samples tested in the study had 50 % or greater tumoral PD-L1 expression. Eighteen percent of patients enrolled had squamous cell histology. The study met its primary endpoint of improvement in PFS. The median PFS for pembrolizumab was 10.3 months versus 6.0 months for chemotherapy (hazard ratio [HR], 0.50; 95 % CI, 0.37-0.68; $p < 0.001$). The objective response rate (ORR) for patients treated with pembrolizumab was 44.8 % compared with 27.8 % for patients treated with chemotherapy. As of 2017, the median OS for patients treated with pembrolizumab was 30.0 months compared with 14.2 months for patients treated with chemotherapy (HR 0.63; 95 % CI, 0.47-0.86; $p = 0.002$) (3). All patient subgroups, including those with squamous cell histology, derived a survival benefit with pembrolizumab. The improved efficacy came with fewer toxicities overall: 73.4 % of patients in the pembrolizumab group had treatment-related adverse events compared with 90.0 % in the chemotherapy group; the incidence of high-grade treatment-related adverse events was almost halved with immunotherapy (26.6 % vs. 53.3 %). The incidence of grade 3-4 immune-related adverse events was 9.7 % with pembrolizumab and 0.7 % with chemotherapy. These results support the use of pembrolizumab as the new standard of first-line therapy for patients with metastatic SQCLC whose tumors bear 50 % or greater PD-L1 expression.

For patients whose PD-L1 expression is less than 50 %, data from the KEYNOTE-042 study suggest that there is no increased benefit to using pembrolizumab over platinum doublet chemotherapy (4). Although OS was higher in the pembrolizumab arm compared with the chemotherapy arm (median OS, 16.7 months vs. 12.1 months; HR 0.81; 95 % CI, 0.71-0.93; $p = 0.0018$), patients with high tumoral PD-L1 expression primarily drove this result. OS was not significantly different in patients with 1 %-9 % tumoral PD-L1 expression (HR 0.92; 95 % CI, 0.77-1.11).

In contrast to pembrolizumab, first-line nivolumab failed to improve PFS or OS compared with platinum doublet chemotherapy in the CheckMate 026 study (5). This trial used a cutoff for tumoral PD-L1 expression of 5 % or greater. In subgroup analysis, patients with squamous histology who received nivolumab had a higher PFS, but this was not statistically significant (5.1 vs. 4.6 months; HR 0.83; 95 % CI, 0.54-1.26); moreover, OS was identical in both treatment arms. Nivolumab is, as a result, not approved for the treatment of naive metastatic or recurrent NSCLC.

Chemo-immunotherapy combinations

As with lung adenocarcinoma, platinum doublet chemotherapy plus immunotherapy has recently been approved by the U.S. Food and Drug Administration for use as first-line therapy in patients with metastatic SQ-NSCLC. The approval was based on KEYNOTE-407, which randomly assigned 559 patients to four cycles of carboplatin with nanoparticle albumin-bound (nab)-paclitaxel weekly or paclitaxel every 3 weeks plus pembrolizumab or placebo followed by pembrolizumab maintenance or placebo alone for up to 35 cycles (6). Patients were stratified by PD-L1 expression level, taxane choice, and geographic region. The majority of patients were PD-L1 positive (63.1 %) and received paclitaxel (60.1 %). There was an effective crossover rate of 31.7 % in the 281-patient intention-to-treat population. Patients treated with chemotherapy plus pembrolizumab achieved a median OS of 15.9 months versus 11.3 months with chemotherapy alone (HR 0.64; 95 % CI, 0.49-0.85; $p < 0.001$). There was also an improvement in PFS favoring chemotherapy plus pembrolizumab (6.4 months vs. 4.8 months; HR 0.56; 95 % CI, 0.45-0.70; $p < 0.001$). The OS and PFS benefit were present at all levels of PD-L1 expression, with improved survival benefit at higher levels of PD-L1 expression. Neither PFS nor OS was affected by taxane selection. The ORR was also significantly higher with chemotherapy plus pembrolizumab (57.9 % vs. 38.4 %; $p = 0.0008$). The addition of pembrolizumab to platinum doublet therapy did not result in a higher incidence of adverse events. Immune-related adverse events, including infusion reactions, occurred in 28.8 % patients treated with pembrolizumab compared with 8.6 % patients given placebo.

For reasons that remain unclear, the combinatorial benefit seen with pembrolizumab was not reproduced in a similarly structured trial that used atezolizumab as the immune checkpoint inhibitor. IMpower 131 randomly assigned patients with advanced SQ-NSCLC to atezolizumab or placebo plus carboplatin and paclitaxel or nab-paclitaxel for four cycles, followed by maintenance atezolizumab or placebo (7). Although the addition of atezolizumab to chemotherapy resulted in an improvement in PFS compared with chemotherapy (6.5 vs. 5.6 months; HR 0.74; 95 % CI, 0.62-0.87), there was no OS benefit (median OS, 14.6 months for atezolizumab plus chemotherapy vs. 14.3 months for chemotherapy alone; HR 0.92; 95 % CI, 0.76-1.12; $p = 0.41$).

In the CheckMate 9LA study explored first-line nivolumab plus ipilimumab combined with a limited course (two cycles) of chemotherapy to this combination (8). Patients were randomly assigned (1:1) to nivolumab (360 mg intravenously every 3 weeks) plus ipilimumab (1 mg/kg intravenously every 6 weeks) combined with histology-based, platinum doublet chemotherapy (intravenously every 3 weeks for two cycles; experimental group), or chemotherapy alone (every 3 weeks for four cycles; control group). Seven hundred and nineteen patients were randomly assigned to nivolumab plus ipilimumab with two cycles of chemotherapy ($n = 361$ [50 %]) or four cycles

of chemotherapy alone ($n = 358$ [50 %]). (median 14.1 months [95 % CI 13.2-16.2] *vs* 10.7 months [9.5-12.4]; hazard ratio [HR] 0.69 [96.71 % CI 0.55-0.87]; $p = 0.00065$). With 3.5 months longer median follow-up (median 13.2 months [IQR 6.4-17.0]), median overall survival was 15.6 months (95 % CI 13.9-20.0) in the experimental group versus 10.9 months (9.5-12.6) in the control group (HR 0.66 [95 % CI 0.55-0.80]). The most common grade 3-4 treatment-related adverse events were neutropenia (in 24 [7 %] patients in the experimental group *vs* 32 [9 %] in the control group), anemia (21 [6 %] *vs* 50 [14 %]), diarrhea (14 [4 %] *vs* two [1 %]), increased lipase (22 [6 %] *vs* three [1 %]), and febrile neutropenia (14 [4 %] *vs* ten [3 %]). In the subgroup's analysis, the OS was more pronounced in patients with squamous histology vs non-squamous histology [HR 0.64 (0.48-0.84) vs 0.80 (0.66-0.97], respectively (9). This OS benefit seen in patients with SQ-NSCLC was more prominent in patients with PD-L1 < 1 % [median OS 15.3 vs 8.0 moths, HR (95 % CI) 0.50 (0.30-0.83)]. These data further support the use of NIVO + IPI + chemo as an efficacious first-line treatment option for patients with metastatic NSCLC, particularly for those with tumor PD-L1 < 1 % or SQ histology, which are populations with high unmet needs.

OPTIONS BEYOND FRONTLINE THERAPY

The treatment landscape beyond frontline therapy witnessed a remarkable shift in 2018 after the approval of the KEYNOTE 407 regimen. The de facto standard second-line therapies since 2015, which encompassed a series of PD-1/PD-L1 checkpoint inhibitors, have been supplanted by chemotherapy, because most patients will transition to second-line therapy in an immunotherapy refractory state. Nevertheless, given their importance in the management of SQ-NSCLC, data leading to the second-line approval of immunotherapy drugs are reviewed below, as are the modest advances seen with angiogenesis inhibition and EGFR-directed approaches. Current second-line and beyond options are summarized in figure 1.

Immunotherapy approaches

Nivolumab (a PD-1 inhibitor) was the first immune checkpoint inhibitor to be approved in the second-line setting for the treatment of SQ-NSCLC. CheckMate 017, a phase III trial, randomly assigned 272 patients previously treated for advanced SQCLC with platinum therapy to nivolumab or docetaxel (10). Median OS was superior in the nivolumab cohort. The median OS was 9.2 months (95 % CI, 7.3-13.3) with nivolumab versus 6.0 months (95 % CI, 5.1-7.3) with docetaxel. Furthermore, the results of this trial were independent of PD-L1 expression, leading, at least for a time, to optional PD-L1 immunohistochemistry testing after the approval of nivolumab for the treatment of NSCLC in 2015. Similar survival advantages were seen in KEYNOTE 010, which randomly assigned patients whose tumors were PD-L1 positive to pembrolizumab or docetaxel (median OS, 10.4 months vs. 8.5 months) (11). An advantage was seen in all histologic subtypes, including SQCLC, although the results are scaled in magnitude with higher degrees of PD-L1 expression. Atezolizumab, an anti-PD-L1 antibody, was similarly approved on the basis of an OS benefit over docetaxel for metastatic NSCLC in patients who have experienced progression on initial therapy (12). Although nivolumab, pembrolizumab, and atezolizumab are theoretical options in the second-line setting and beyond, their use is expected to decrease because most patients receive treatment with pembrolizumab in the frontline setting, either as monotherapy or in combination with platinum plus taxane chemotherapy.

Chemotherapy and targeted therapy options

Chemotherapy has, as a result, become the second-line option for most patients with advanced SQ-NSCLC, centering on docetaxel as a backbone therapy. This is due, in part, to results from the REVEL trial, which randomly assigned patients with NSCLC following progression on platinum doublet therapy to docetaxel with or without ramucirumab, a monoclonal VEGF receptor 2 antibody (13). All response metrics were superior in the ramucirumab-treated arm. The ORR was 23 % versus 14 % ($p < 0.0001$), median PFS was 4.5 months versus 3.0 months (HR 0.76; $p < 0.0001$), and median OS was 10.5 months versus 9.1 months (HR 0.88; 95 % CI, 0.75-0.98). The regimen was approved by the FDA in 2014 and the EMA in 2019. Offsetting the modest improvement in OS with the addition of ramucirumab to docetaxel are increased costs and some degree of increased toxicity. Exceptions to this algorithm are patients with SQCLC whose tumors bear high PD-L1 expression and who received treatment with pembrolizumab monotherapy. For these patients, platinum doublet chemotherapy remains the standard second-line therapy, followed in the third-line setting and beyond with the other agents discussed in this section.

For the purposes of context related to the use of EGFR inhibitors in this disease, docetaxel was previously shown to be superior to erlotinib for patients who have EGFR wild-type tumors (14), including patients with SQ-NSCLC (median OS, 8.2 months vs. 5.4 months; HR 0.73; 95 % CI, 0.53-1.00; $p = 0.05$). It is against these data that afatinib, an irreversible ErbB receptor family kinase inhibitor, was explored as a second-line therapy in the LUX-LUNG 8 trial, which randomly assigned patients after platinum doublet therapy to afatinib versus erlotinib (15). Median PFS (2.4 months vs. 1.9 months; HR 0.82; $p = 0.043$) and me-

dian OS (7.9 months vs. 6.8 months; HR 0.81; $p = 0.008$) were modestly longer with afatinib, although the ORR was low and not significantly different between the two arms (6 % vs. 3 %; $p = 0.055$). An exploratory analysis was conducted, suggesting that alterations in HER2 family members might predict improved outcomes in patients treated with afatinib (16).

On the basis of the aggregate data, afatinib remains an option in the treatment of patients with advanced SQ-NSCLC as a third-line and beyond treatment option. Other chemotherapy drugs have been explored and remain options as well, including gemcitabine, vinorelbine, and mitomycin, although the clinical benefit of these agents in the third-line setting and beyond remains largely unknown (17-19).

THERAPEUTIC TARGETS IN SQ-NSCLC: THE PAST, PRESENT, AND FUTURE

It was because of this paucity of treatment options that a great deal of optimism surrounded the publication of The Cancer Genome Atlas' results on the comprehensive molecular profiling of a series of 178 resected early stage SQ-NSCLC tumors in 2012 (20). These data, coupled with work from other groups (21,22), identified relatively high-frequency recurrent somatic alterations that encompassed a number of biologic pathways. Genes that exhibited significant amplification or deletion events included SOX2, FGFR1, or WHSC1L1; PGFRA or KIT; and CCND1, CDNK2A, NFE2L2, MYC, CDK6, and PTEN (Fig. 2).

Learning from the past

Following the successes of targeted therapies in lung adenocarcinoma, receptor tyrosine kinases (RTKs) have been heavily investigated in SQ-NSCLC. Unfortunately, the quest to identify a targetable mutation in SQ-NSCLC has been unsuccessful, with many high-profile failures of targeted drugs in late-phase clinical trials. In the biomarker driven phase II LUNG-MAP S1400 study of previously treated SQ-NSCLC patients, the overall response rates to targeted therapies were only 7 % (23). Figure 3 illustrates the number of approved targeted therapies in lung adenocarcinoma compared with SQ-NSCLC.

EGFR and the ERBB family receptors

Among the first to be tested are targeted therapies against the ERBB family receptors, particularly EGFR. Unlike the never smokers in lung adenocarcinoma, sensitizing mutations are rarely identified in SQ-NSCLC, with a reported incidence of only 0 %-5 % (20). Even when an activating mutation is present, the response rates are low (20 %-30 %) with a shorter progression-free survival compared with their lung adenocarcinoma counterparts.

In the absence of activating mutations, EGFR TKIs have nevertheless been tested in SQ-NSCLC. When given to previously treated patients who were unselected for EGFR status, erlotinib demonstrated responses in both squamous and non-squamous lung cancers (24). Responses were enriched among those with EGFR protein expression. Subsequently, afatinib, a second-generation TKI with activi-

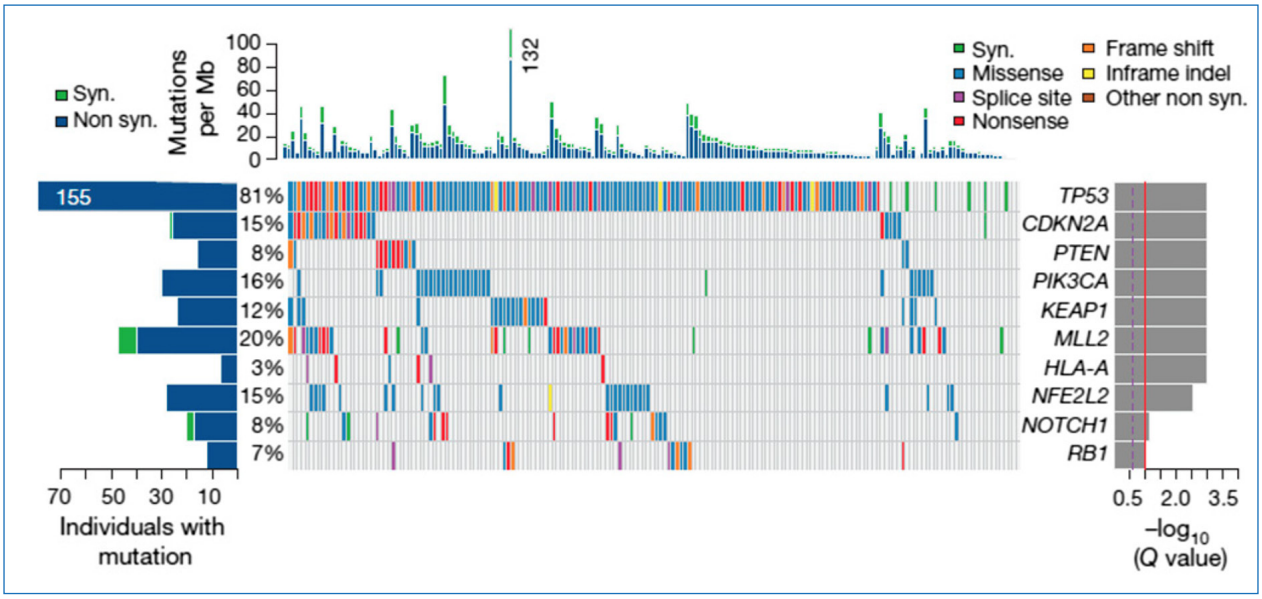

Fig. 2. Significantly mutated genes in squamous cell lung cancers (figure reproduced from Cancer Genome Atlas Research Network) (20).

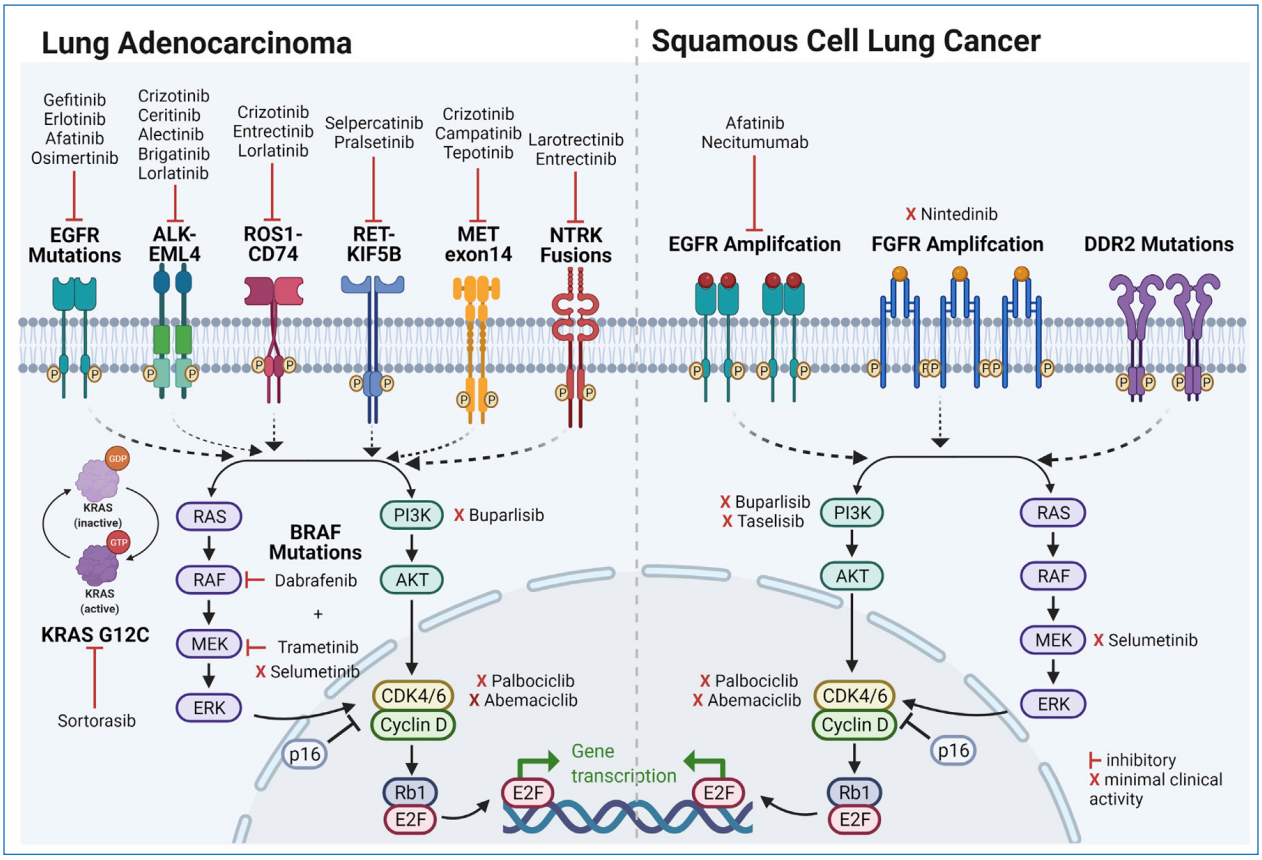

Fig. 3. A multitude of targeted therapies are available for squamous cell lung cancers compared with lung adenocarcinoma.

ty against the entire ERBB family receptors, showed improved survival over erlotinib in the LUX-Lung 8 study, which was specific to SQ-NSCLC (15). In post hoc analyses, there were no associations with EGFR protein expression or copy number. However, the presence of ERBB2 mutations, which were not necessarily located to hotspots, was associated with improved outcome to afatinib compared with erlotinib (16). Afatinib is currently the only EGFR TKI approved for EGFR TKIs as a single agent.

Rather than classical activating mutations, EGFR gene amplification and elevated protein expression are more common in EGFR TKIs (25,26). Consequently, two EGFR monoclonal antibodies, cetuximab and necitumumab, have been investigated for their clinical utility. The addition of cetuximab to chemotherapy was investigated in the phase III FLEX study among SQ-NSCLC patients with EGFR expression and demonstrated a small benefit in OS compared with chemotherapy alone. However, cetuximab had not been adopted into clinical practice due to toxicity (27). Necitumumab, another EGFR monoclonal antibody, showed a similar modest improvement in survival, but was better tolerated with no detriment to quality of life (28). Necitumumab, in combination with chemotherapy, is one of the few targeted therapies that is currently approved (by the FDA only) for SQ-NSCLC.

These data found contextualization in the existing efforts that had been made at characterizing the drugability of some of these pathways and targets. A synthesis of these approaches winnowed the list of potential targets to a handful for initial clinical testing in biomarker-led trials, including FGFR1 amplification, discoidin domain receptors (DDRs), upstream phosphatidylinositol 3-kinase (PI3K) alterations, RAS and CDKN2A/RB1 aberrations.

FGFR

Another RTK that is commonly altered in SQ-NSCLC is the FGFR and its downstream FGF signaling pathway (29,30). Amplifications in FGFR1 are enriched in SQ-NSCLC compared with lung adenocarcinoma and are associated with a worse prognosis (31,32). Altered in about 20 % of SQ-NSCLC, significant efforts have been made to block FGFR signaling. However, nintedanib, an FGFR1 TKI, in combination with chemotherapy, failed to demonstrate any benefit over chemotherapy alone in the phase III LUME-Lung-1 trial (33). This study was again performed in an unselected patient population. Interestingly, subgroup analyses showed that clinical benefit, if any, was seen

among lung adenocarcinoma and not SQ-NSCLC patients (34). Even in a subsequent trial where patients were selected based on a high FGFR copy number > 5, dovitinib, a pan-FGFR inhibitor, still showed minimal benefit (35).

FGFR fusions, which result in constitutive signaling, are less common and are reported in 0.2 % of SQ-NSCLC (36). There are reports of response to erdafitinib, a pan-FGFR inhibitor, in the setting of an FGFR fusion (36). Given the low prevalence and limited data, whether FGFR fusion is a true driver in SQ-NSCLC remains undetermined.

DDR2

Discoidin domain receptors (DDRs) are a family of RTKs with two subtypes that bind collagen and promote cell proliferation and survival (37,38). Altered patterns of DDR protein expression have been described across tumor subtypes (37). The incidence of activating mutations in DDR2 is controversial, and these occur in 0 %-4.4 % in SQ-NSCLC (20). In a subset of tumors with activating DDR2 mutations, Hammerman et al. demonstrated preclinical evidence of DDR2 oncogene addiction and that depletion of DDR2 with RNA interference inhibited tumor growth (37). There were also clinical case reports of patients with DDR2 mutations responding to dasatinib, a multikinase TKI that blocks DDR2 (37). However, many mutations in DDR2 have been identified that are not localized to hotspots (39). DDR2 mutations are also not mutually exclusive with other candidate drivers. These data suggest that, while dysregulation of the DDR pathway is common, the degree of oncogenic addiction to DDR2 is likely low. Currently, there are no DDR2-targeted agents approved or in a clinical trial for SQ-NSCLC.

RAS

KRAS is the most commonly mutated oncogene in lung adenocarcinomas, but the incidence of KRAS mutations among SQ-NSCLC is controversial (40). Reported across studies at rates of 1 %-6 %, some question whether this represents the true incidence of KRAS mutations in pure SQ-NSCLC as opposed to missed adenosquamous carcinomas on small biopsies. The European Thoracic Oncology Platform (ETOP) Lungscape project analyzed 888 patients with resected squamous lung cancers, which makes a missed adenosquamous diagnosis much less likely, and identified KRAS mutations in 6 % of cases (41). Nevertheless, it is not known whether KRAS mutations contribute to SQ-NSCLC growth. With the recent approval of sotorasib for KRAS G12C mutations, more data will become available on whether RAS directed therapies have any benefit in SQ-NSCLC.

PIK3CA

Aberrations of the PI3K-AKT pathway are common across SCC subtypes (40). Several alterations that lead to increased PI3K signaling have been observed in SQ-NSCLC: (1) amplification of PIK3CA (20 %); (2) activating PIK3CA mutations (5 %-16 %); and (3) loss of PTEN, a negative regulator of the PI3K pathway (15 %) (42,43). Unfortunately, clinical trials for inhibitors against PI3K isoforms have been largely negative and were challenged with difficult-to-manage toxicities due to cross-reactivity with wild-type PI3K.

Targeting the cell cycle: CDKN2A/RB1

Loss of cell cycle control can occur with inactivation of CDKN2A and or loss of RB1. Inactivating mutations in CKDN2A are present in up to 72 % of all SQ-NSCLC (Cancer Genome Atlas Research, 2012) (20). CDKN2A encodes the P16 protein, which inhibits CDK4/6 to block phosphorylation of RB1, thereby halting the progression of the cell cycle from G1 to S phase (44). Loss of P16 is heavily involved in the tumorigenesis of squamous carcinomas. The CDK4/6 inhibitors induce cell cycle arrest by blocking phosphorylation of RB1. In cases where the loss of cell cycle control is due to RB1 loss, CDK4/6 inhibitors will have no effect. In a pan-cancer analysis, inactivating CDKN2A mutations and loss of RB1 were mutually exclusive, underscoring the significance of these two genes in cell cycle regulation (44).

CDK4/6 inhibitors have minimal efficacy in SQ-NSCLC, even in selected patients. Two prospective studies investigated palbociclib or abemaciclib in patients with inactivating CDKN2A mutations and had low response rates, albeit in heavily pretreated patients (45,46). The SWOG1400C LUNG-MAP biomarker-directed study enrolled SQ-NSCLC patients with CDK4, CCND1, CCND2, and CCND3 amplifications, all of which were associated with cell cycle dysregulation However, the overall response rate to palbociclib was only 6 % (47).

EPIGENETIC THERAPY IN SQ-NSCLC

Epigenetic aberrations, which are found in approximately half of all human cancers and are thought to be clonal, have a profound role in malignancies (48). DNA methylation and chromatin remodeling have a wide control of gene expression, allowing access of transcriptional factors to activate genes while sequestering inactive loci in inaccessible structures. Recurrent mutations in chromatin protein, such as the Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex, disrupt homeostasis and contribute to tumorigenesis in SQ-NSCLC, both global and locus-specific aberrations in epigenetic regulators have been identified. Global DNA hypomethylation was

seen in SQ-NSCLC, allowing for transcription and activation of oncogenes and contributing to a high mutational burden (49). On the other hand, locus-specific hypermethylation was found to silence tumor suppressor genes, which was associated with a high expression of DNA methytransferase 1 (DNMT1) in smokers. In addition to tumorigenesis, epigenetic aberrations contribute to tumor heterogeneity and lineage plasticity.

Epigenetic therapy had disappointing results in solid tumors in the past. First-generation epigenetic drugs typically inhibit DNMT or histone deacetylase (HDAC) and are troubled by high toxicity and minimal efficacy (50). The DNMT1 inhibitor decitabine failed as monotherapy in clinical trials of lung cancer. However, next-generation epigenetic therapies are more specific with trials designed for a biomarker-selected population. In addition, epigenetic therapies have synergistic properties with other treatments and potentially restore sensitivity in cases of acquired resistance. Figure 4 provides a mechanistic overview of the epigenetic drug targets relevant to SQ-NSCLC.

SOX2 and its epigenetic regulators

SOX2 is a lineage-defining transcription factor and one of the most commonly amplified genes in SQ-NSCLC, reported in up to 60 %-80 % of all tumors (51). Along the development of the invasive carcinoma sequence, SOX2 drives squamous differentiation markers. In human SQ-NSCLC, amplification of SOX2 was found to be an early clonal event, occurring before genome duplication, which suggested involvement in tumor initiation. However, SOX2 is not considered a driver oncogene in the traditional sense since SOX2 alone cannot induce malignant transformation. The generation of SQ-NSCLC in mouse models required SOX2 overexpression in combination with PTEN, CKDN2A/2B, or loss of LKB1. Nevertheless, SQ-NSCLC cell lines show high dependency on SOX2, and in vitro experiments using RNA interference of SOX2 demonstrated impaired tumor growth. Although SOX2 is considered undruggable, its chromatin regulators LSD1 and EZH2 are potential therapeutic opportunities.

LSD1

LSD1 is a histone lysine demethylase (KDM) that frequently participates in cross-epigenetic regulation. Overexpression of KDM is associated with cancer proliferation and invasion (52). In human SQ-NSCLC cell

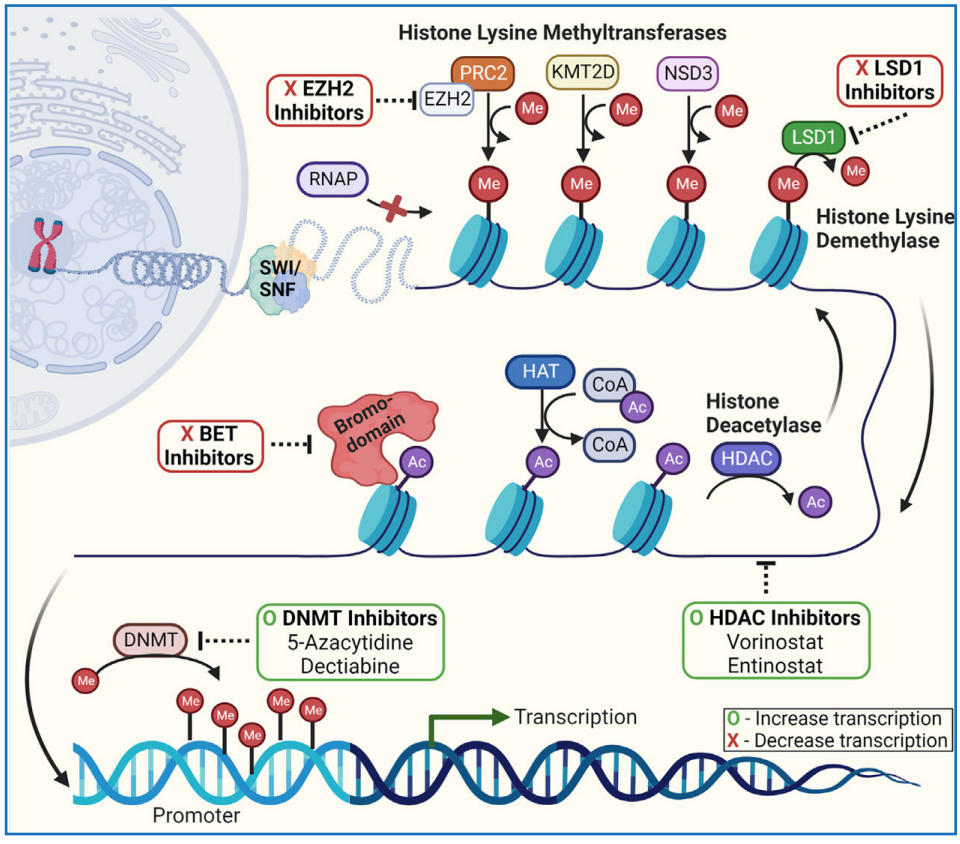

Fig. 4. Epigenetic therapy influences gene expression by allowing or repressing transcription.

lines, SOX2 expression was correlated with increased expression of LSD1 and sensitivity to LSD1 inhibition. A correlation was not seen between sensitivity to LSD1 inhibition and expression of other pluripotent stem cell proteins. Inhibiting LSD1 in SOX2-expressing cells reduces lineage-specific oncogenic potential and promotes cellular differentiation. LSD1 inhibitors, alone or in combination with other epigenetic modifiers, are currently being investigated in clinical trials (NCT05268666).

EZH2

Histone lysine methyltransferases (KMTs) are a class of chromatin regulators with key roles in regulating gene expression related to DNA replication, DNA damage response, and cell cycle progression (52). One of the most well-studied KMTs is EZH2, an enzymatic component of PRC2. Overexpression of EZH2 is common in human NSCLC and associated with squamous histology. EZH2 was also observed to be expressed in human pre-malignant lung lesions with squamous differentiation, with increasing levels from low- to high-grade dysplasia, suggesting a role in SQ-NSCLC tumorigenesis. EZH2 dependency was shown in SOX2-amplified SQ-NSCLC cell lines and was associated with decreased transcription of tumor suppressor genes such as *TGFBR2*. In mouse models, EZH2 elevation was also identified as an epigenetic mechanism for squamous transformation in a KRAS-LKB1 mutant lung tumors in mouse model. In triple-negative breast cancer mouse models, inhibition of EZH2 reduced the expression of SOX2. A promising target for SQ-NSCLC, EZH2 inhibitors are being actively investigated across solid tumors (NCT04390737, NCT04104776, NCT04407741).

THE FUTURE

Predictive biomarkers

Robust predictive biomarkers are necessary for developing effective therapies in SQ-NSCLC. Heterogeneity is inherent to SQ-NSCLC due to their complex genomic landscape. Sub-classifications of SQ-NSCLC will improve therapeutic success. At present, next-generation sequencing (NGS) is recommended for never to light smokers with SQ-NSCLC. We would, however, advocate for comprehensive NGS on all patients. While a single targetable oncogene is unlikely to be identified by NGS, mutations such in KMT2D, PIK3CA, or NFE2L2 can provide insight into tumor behavior and response to therapy, and identify potential clinical trials. In the future, the evaluation of multiple genes that can be combined into a predictive score will be useful to guide therapy.

Current predictive biomarkers for immunotherapy are inadequate. PD-L1 expression appeared less predictive of response in SQ-NSCLC compared with lung adenocarcinoma (53,54). Tumor mutational burden (TMB) is only loosely correlated with outcome in SQ-NSCLC. Biomarkers that allow a more comprehensive assessment of the tumor immune microenvironment (TIME), such as gene expression profiling, are necessary. A T effector gene signature, which encompasses mRNA expression of PD-L1, CXCL9, and IFNγ, was associated with improved OS in the IMpower 150 study (55). But the three-gene T effector signature was not clearly better than PD-L1 expression as the biomarker. In contrast, Wiesweg et al. utilized machine learning to generate a seven-gene score that could predict response to PD-(L)1 inhibitors independent of PD-L1 expression (56). Gene expression profiling on other immune cells, particularly immunosuppressive populations, in the TIME is also important. In renal cell carcinomas, a myeloid signature was uniquely predictive of benefit from the combination treatment with PD-L1 and vascular endothelial growth factor (VEGF) inhibitors. Furthermore, biomarkers evaluating the neoantigen presentation machinery are necessary as inactivating mutations in HLA have been reported in SQ-NSCLC.

Subtyping of SQ-NSCLC into broad categories is also helpful. Wilkerson et al. identified four major clusters of SQ-NSCLC using mRNA expression profiling (57). Each cluster had distinct biological processes: (1) primitive, enriched for RB1 loss; (2) classical, enriched for SOX1-TP63 amplification and KEAP1- NFE2L2 alterations; (3) secretory, with a predominant inflammatory response; and (4) basaloid, enriched for alterations in cell adhesion. In the past, sub-classification efforts have not been widely adopted because they do not correlate with treatment outcomes, which, ironically, are non-selective. As we develop new therapies targeted at specific pathways, efforts in sub-classifying SQ-NSCLC will be immensely helpful in guiding treatment approaches and clinical trial selection.

The molecular complexity of SQ-NSCLC suggests that rational combination therapy based on tumor biology is necessary for effective treatment. At present, many clinical trials in SQ-NSCLC explore combinations with currently available therapies (Table I). Most involve combinations with immune checkpoint inhibitors, which now form the cornerstone of treatment for SQ-NSCLC. To capitalize on the initial successes of immunotherapy, a mechanistic understanding of how the TIME in SQ-NSCLC is shaped by its molecular landscape is needed.

Table I. Current active clinical trials investigating novel combinatory approaches in squamous cell carcinoma of the lung

Target	Drug	Phase	Study population
Targeting DNA repair and immune checkpoints			
PARP and PD-1 inhibitors	Olaparib, pembrolizumab, chemotherapy (NCT03976362)	III	Squamous lung cancer
ATR and PD-1 inhibitors	Berzosertib, pembrolizumab, chemotherapy (NCT04216316)	I/II	Squamous lung cancer
Targeting signal transduction and immune checkpoints			
PIK3CA and PD-1 inhibitors	Copanlisib, nivolumab (NCT03735628)	I/II	NSCLC and advanced solid tumors
SHP2 and PD-1 inhibitors	JAB-3068 (NCT04721223)	I/II	NSCLC and advanced solid tumors
SHP2, CDK4/6 and PD-1 inhibitors	TNO155, partalizumab, ribociclib (NCT04000529)	I	NSCLC and advanced solid tumors
Drugs targetin the epigenome			
DNMT and PD-1 inhibitors	Tetrahydrouridine-decitabine, nivolumab (NCT02664181)	II	NSCLC
DNMT, HDAC, and PD-1 inhibitors	Azacytidine, entinostat, nivolumab (NCT01928576)	II	NSCLC
	Guadecitabine, mocetinostat, pembrolizumab (NCT03220477)	I	NSCLC
EZH2 inhibitors	HH2853 (NCT04390737)	I	Advanced solid tumors
EZH2 and PD-1 inhibitors	SHR2554 + SHR1701 (NCT04407741)	I	Advanced solid tumors
LSD1 and HDAC inhibitor	JBI-802 (NCT05268666)	I	Advanced solid tumors
BET and HDAC inhibitors	ZEN-3694, entinostat (NCT05053971)	I	Advanced solid tumors
BET and PD-1 inhibitors	ZEN-3694, ipilimumab, nivolumab (NCT04840589)	I	Advanced solid tumors
Drugs targeting metabolic abnormalities			
Glutaminase and PD-1 inhibitors	DRP104 (sirpiglenastat), atezolizumab (NTC04471415)	I	NSCLC x with *KEAP1, NFE2L2* or *STK11* mutations
	IACS-6274, pembrolizumab (NCT05039801)	I	NSCLC and advanced solid tumors
IDO and PD-1 inhibitors	IO102-IO103, pembrolizumab (NCT05077709)	II	NSCLC, HNSCC, urothelial cancers

CONCLUSIONS

SQ-NSCLC share many commonalities with SCCs arising from other anatomic sites, and drug discovery in SQ-NSCLC will have far-reaching implications in managing other squamous cancers. Although the search for targeted therapies in SQ-NSCLC has been disappointing thus far, novel approaches to drug discovery by incorporating epigenetics and exploiting metabolic vulnerabilities are promising. In addition, the genomic complexity of SQ-NSCLC may be advantageous for immunotherapies, particularly when combined with biomarker-directed targeted treatments.

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