Treatment of advanced squamous cell carcinoma of the lung: a review

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Abstract: Lung cancer remains the single deadliest cancer both in the US and worldwide. The great majority of squamous cell carcinoma (SCC) is attributed to cigarette smoking, which fortunately is declining alongside cancer incidence. While we have been at a therapeutic plateau for advanced squamous cell lung cancer patients for several decades, recent observations suggest that we are on the verge of seeing incremental survival improvements for this relatively large group of patients. Current studies have confirmed an expanding role for immunotherapy [including programmed cell death-1 (PD-1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition], a potential opportunity for VEGFR inhibition, and even future targets in fibroblast growth factor receptor (FGFR) and PI3K-AKT that collectively should improve survival as well as quality of life for those affected by squamous cell lung cancer over the next decade.

Keywords: Non-small cell lung carcinoma; squamous cell carcinoma of the lung; epidermal growth factor receptor (EGFR); angiogenesis inhibitors; immunotherapy

Submitted Mar 18, 2015. Accepted for publication Jun 21, 2015.
doi: 10.3978/j.issn.2218-6751.2015.06.07
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.06.07

Not only is lung cancer the most commonly diagnosed cancer internationally, representing approximately 17% of new cancer diagnoses worldwide, but it also bears the highest mortality rate among all cancers (24% of cancer-related mortality worldwide) (1). In the United States (US), lung cancer is the second most commonly diagnosed cancer with an estimated 224,000 new cases in 2014 and remains the leading cause of cancer death in the US (2,3). Of these lung cancer cases, over 85% of them are classified as non-small cell lung cancer (NSCLC), with squamous cell carcinoma (SCC) of the lung comprising approximately 30% (4).

Nearly 80% of all lung cancer cases in men and 90% of cases in women are associated with smoking (5,6). SCC is most strongly associated with smoking in a dose-dependent manner, with one study finding that 91% of SCC was attributed to cigarette smoking (7-9).

With the exception of the newly approved nivolumab, there have been no other US Food and Drug Administration (FDA) approvals specifically for SCC of the lung. Moreover, driver mutations/rearrangements connected with FDA-approved agents in the epidermal growth factor receptor (*EGFR*) and echinoderm microtubule associated protein like 4—anaplastic lymphoma kinase (*EML4-ALK*) are very rarely associated with squamous cell histology. Recently, however, molecular genotyping has led to the application of targeted agents for mutations prevalent in SCC. This overview of the treatment of squamous cell lung carcinoma highlights these recent molecular advances and discusses applications of newer cytotoxic and targeted agents evaluated for the treatment of advanced SCC (*Figure 1*).

Cytotoxic chemotherapy

Cytotoxic chemotherapy for NSCLC has reached a therapeutic plateau as evidenced by the published data from Eastern Cooperative Oncology Group (EGOG)

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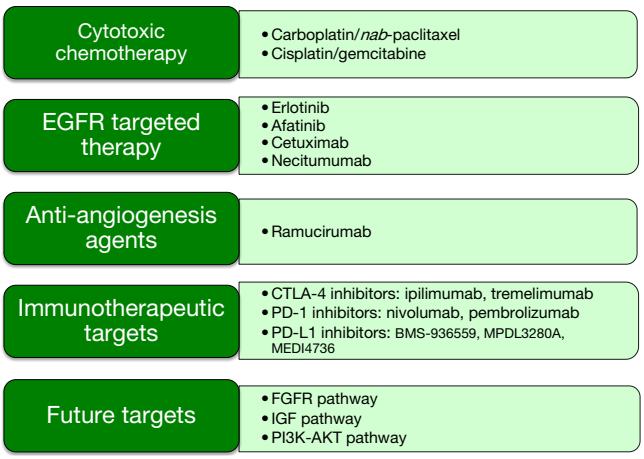

Figure 1 Review of current and potential future therapies for squamous cell carcinoma (SCC) of the lung. EGFR, epidermal growth factor receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; FGFR, fibroblast growth factor receptor; IGF, insulin-like growth factor.

1594 showing equivalent survivals among four different platinum doublet chemotherapies, with outcomes not analyzed by histology (10). Subsequent published data of a large phase III trial of cisplatin/pemetrexed versus cisplatin/gemcitabine, however, did indicate a difference in outcome based on histology (11). In this non-inferiority trial, patients with squamous cell histology received a relative benefit with the treatment of gemcitabine/cisplatin versus pemetrexed/cisplatin. Additional studies identified outcome discrepancies based on histology; a retrospective analysis of a phase III second-line trial revealed inferior survival in squamous cell cancer patients receiving pemetrexed compared with docetaxel and a phase III pemetrexed maintenance trial showed no benefit with pemetrexed maintenance in the squamous cell histologic subset (12,13). Based on the consistency of results across multiple trials indicating shorter survival in those with squamous histology, pemetrexed is not recommended for the treatment of patients with SCC (14).

Recently a large phase III trial comparing carboplatin/paclitaxel (solvent-based) to carboplatin/*nab*-paclitaxel (albumin bound) in stage IIIB and IV NSCLC also found a difference in efficacy based on histology. Though the two arms of the trial had similar survival outcomes, the *nab*-paclitaxel arm had an improved response (the primary endpoint of the trial) compared to the solvent-based paclitaxel arm; however, this benefit was limited to the SCC subset. The SCC subset exhibited a 41% radiologic response in the *nab*-paclitaxel arm compared to a 24% radiologic response in the solvent-based paclitaxel arm. Compared to the solvent-based paclitaxel group, the *nab*-paclitaxel group exhibited a numerically higher median overall survival in SCC (10.7 *vs*. 9.5 months) yet this was not statistically significant (HR 0.89, 95% CI, 0.719-1.101, P=0.284). In addition, the side effect profile in the *nab*-paclitaxel arm was more favorable, with less myalgias, neuropathy, and cytopenias (15). Ongoing studies should clarify the role of *nab*-paclitaxel in the treatment of squamous cell lung cancer patients (NCT identifier 02328105) (16). The lower toxicity profile has also bolstered its role as a potential agent in the maintenance setting (NCT identifier 02027428) (17).

EGFR targeted therapy

In patients with an EGFR activating gene mutation, there is ample evidence to offer first line EGFR tyrosine kinase inhibition (TKI) based on improved progression free survival and overall survival compared with cytotoxic chemotherapy (18-27). EGFR activating gene mutations are found in approximately 20% of adenocarcinomas but the prevalence in squamous cell cancers is considerably less (28). A study from Rekhtman *et al*. in 2012 illustrated that EGFR mutations do not occur in pure SCCs but appear only in mixed adeno-squamous carcinomas (29).

Though the response rate in patients without EGFR activating mutations is low, recent data may support the use of EGFR TKIs for later lines of therapy in wild type patients, including those with SCC (18). A retrospective study examining erlotinib in patients with advanced SCC found that of the 92 patients analyzed (74 of whom were current or former smokers), 16 achieved a partial response and 9 had stable disease. However, only 27 patients actually had molecular analysis performed on tumor specimens, and 2 were found to have EGFR complex mutations (30). The SATURN trial examining the efficacy of erlotinib as maintenance treatment in advanced NSCLC revealed that erlotinib prolonged progression free survival compared to placebo in both EGFR mutation-positive and EGFR mutation-negative tumors. The squamous cell subset analysis failed to reach statistical significance (31). The TAILOR trial comparing erlotinib to docetaxel as second-line treatment of patients with wild-type EGFR stage IV NSCLC showed that docetaxel was more effective than erlotinib (median overall survival was 8.2 months

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for docetaxel versus 5.4 months for erlotinib, and results trended in a similar direction for the SCC subset) (32).

It is possible that with a favorable proteomic signature, patients with wild-type EGFR tumors may have similar overall survival when treated with second-line chemotherapy or erlotinib as presented in the PROSE study using the VeriStrat test. Squamous cell patients were equally represented in both arms of the study (33). The ongoing LUX-Lung 8 trial is a prospective phase III trial comparing EGFR TKIs (afatinib *vs.* erlotinib) in patients with relapsed/refractory stage IIIB or IV SCC with ECOG performance status of 0-1 who had progressed after at least four cycles of platinum-based doublet chemotherapy and had not received prior EGFR TKI. Preliminary data suggest that the median progression free survival and disease control rate are higher for afatinib compared to erlotinib (2.7 *vs.* 1.9 months; 45.7% *vs.* 36.8%, respectively). This is tempered by higher incidences of diarrhea and stomatitis with afatinib (34).

Monoclonal antibodies against EGFR have shown moderate activity in NSCLC. Cetuximab, a recombinant human/mouse chimeric monoclonal antibody against EGFR, showed only minimal survival benefit when combined with cisplatin and vinorelbine (*vs.* chemotherapy alone) in a subset of patients with SCC (9 *vs.* 8.2 months), but this subgroup analysis did not reach statistical significance (35). Necitumumab, an IgG1 monoclonal antibody against EGFR, did not show any evidence that its addition to cisplatin/pemetrexed increased survival in first-line treatment of metastatic non-squamous NSCLC (36). However, outcomes were different when necitumumab was combined with different chemotherapy in a different histologic subset. The addition of necitumumab statistically improved overall survival, progression free survival, and disease control rate when added to cisplatin/gemcitabine in a trial conducted in SCC patients with a median overall survival improvement of 11.5 *vs.* 9.9 months (HR =0.84, P=0.012) (37).

Anti-angiogenesis agents

Bevacizumab, a VEGF inhibitor, has shown efficacy in NSCLC but is not recommended for SCC as it has been associated with life-threatening hemoptysis when used in SCC (38,39). Ramucirumab, a VEGFR2 inhibitor, was recently approved for second-line therapy for stage IV NSCLC based on results from the REVEL trial. The study compared ramucirumab/docetaxel to placebo/docetaxel in patients who progressed on platinum-based chemotherapy. Median overall survival was better (HR 0.86, 95% CI, 0.75-0.98, P=0.023) in the ramucirumab arm (10.5 months) compared to the placebo arm (9.1 months). Median progression free survival was also superior in the ramucirumab arm (4.5 *vs.* 3 months, P<0.0001). The study was not powered for subgroup analysis, though SCC patients made up approximately 25% of the trial and experienced a numeric improvement in median overall survival in the ramucirumab arm (9.5 *vs.* 8.2 months in placebo arm, HR 0.88, 95% CI, 0.69-1.13) (40). Phase II data investigating ramucirumab with paclitaxel/carboplatin as first-line therapy for stage IIIB/IV NSCLC revealed 6-month progression free survival rate of 59%, though 85% of patients had adenocarcinoma and phase II randomized data in the front-line squamous cell population has not been presented (41).

Immunotherapeutic targets

Another potential avenue within the field of targeted therapy for SCC involves immune-checkpoint inhibition. Aberrancies in the HLA-A gene were frequently noted in SCC from the Cancer Genome Atlas Project, suggesting a prominent role for immune evasion for these cancers (34). Pathways further along in study include the programmed cell death ligand 1 (PD-L1) and programmed cell death-1 (PD-1) and the CTLA-4 pathway. Tumors attempt to escape surveillance and detection by expressing PD-L1, which in turn interacts with the PD-1 on T-cells. This interaction leads to suppression of the antitumor T-cell response. Novel therapies are being developed to disrupt this PD-1/PD-L1 checkpoint (*Figure 2*). Two such therapies are nivolumab and pembrolizumab, which are monoclonal antibodies against the PD-1 receptor on T-cells so as to unmask the dormant T-cell antitumor response (42-44). PD-L1 inhibitors (BMS-936559, MPDL3280A, and MEDI4736) are also in development. While PD-1 inhibitors have been most extensively tested in patients with melanoma, new data suggest efficacy in NSCLC as well (45,46). As of October 2014, pembrolizumab has achieved breakthrough therapy designation for EGFR- and ALK- rearrangement-negative NSCLC following platinum-based chemotherapy, based on phase I results from the KEYNOTE-001 study. A total of 282 patients with treatment-naïve or previously treated advanced NSCLC were treated with pembrolizumab once every 3 weeks. The overall response rate (ORR) in the squamous histology group was 18-25% compared to 23% for the non-squamous histology group. At the time of publication of the data, only half of the patients had PD-L1 staining performed; of these, the ORR was 39-47% in patients with strong PD-L1

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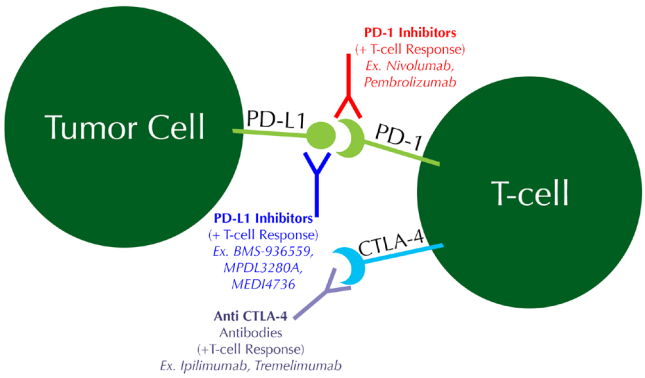

Figure 2 Schematic of immune checkpoint mechanisms. Tumors can express PD-L1, which interacts with PD-1 on T-cells, leading to suppression of the antitumor T-cell response. PD-L1 and PD-1 inhibitors prevent this interaction, unleashing the T-cell antitumor response. Anti-CTLA-4 antibodies bind to CTLA-4 to increase the ratio of effector T-cells to negative regulatory T-cells to achieve the same effect. PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

expression but only 9-16% in patients with weak/negative PD-L1 expression. The progression free survival and overall survival were also longer in patients with PD-L1 strong-positive patients. The median overall survival was found to be 8.2 months, while the median overall survival had not yet been reached in the treatment-naïve group (47).

Nivolumab is still undergoing active trials. A prior phase II open-label, single-arm trial investigating the use of nivolumab in heavily pretreated patients with advanced squamous cell NSCLC (CheckMate-063) showed an 11-month ORR of 15% (95% CI, 9-22%), and all were partial responses. At the time of analysis, 10 of the 17 responding patients had response durations exceeding 6 months. This marks a key advancement over the previously demonstrated 1-year survival rates of 5.5-18% for third-line squamous cell NSCLC (48). A recent phase III trial of nivolumab compared to docetaxel as second-line therapy in patients with squamous cell NSCLC (CheckMate-017) was stopped early because of superior overall survival in the nivolumab arm (49). The 272 patients with advanced or metastatic SCC were randomized to either nivolumab or docetaxel after having progressed on prior platinum-based chemotherapy. The nivolumab arm experienced a 41% overall survival advantage over the docetaxel arm (9.2 *vs.* 6.0 months; HR 0.59, 95% CI, 0.44-0.79, P=0.00025). In contrast to the available pembrolizumab data, nivolumab exhibited improved overall survival compared with second line docetaxel regardless of PD-L1 immunohistochemistry expression (50). These milestone data were responsible for the recent expedited FDA approval of nivolumab specifically for the treatment of patients with advanced SCC who have progressed after platinum-based chemotherapy (51).

CTLA-4 inhibition has also been a topic of research in NSCLC. CTLA-4 is expressed by active cytotoxic T-cells, which acts as a negative regulatory molecule against T-cell response. These T-cells are silenced through interaction with ligands on antigen presenting cells. Anti-CTLA4 antibodies such as ipilimumab and tremelimumab bind to CTLA-4 thereby unleashing the antitumor effect of T-cells and increasing the ratio of effector T-cells to negative regulatory T-cells (52). In a phase II trial comparing the efficacy of paclitaxel/carboplatin alone (control arm) versus paclitaxel/carboplatin with ipilimumab (phased or concurrent) in stage IIIB and IV NSCLC, phased ipilimumab improved immune-related progression free survival (5.7 months for the phased ipilimumab arm *vs.* 4.6 months for the control arm). In comparison to non-squamous NSCLC, the SCC subgroup exhibited an even greater improvement in progression free survival with phased ipilimumab (53).

Future targets

Recent work by the Cancer Genomic Access Research Network has confirmed the complexity of SCC with a somatic mutation rate of 8.1 mutations per megabase, higher than other tumors studied including breast, glioblastoma, colorectal (54). There were only three cases of activating EGFR or KRAS mutations of 178 cases analyzed but the frequency of mutations predicted to have functional effect was over 50%. Targetable pathways such as PI3K/AKT, receptor tyrosine kinase and RAS had frequent alterations with at least one of those pathways altered in 69% of cases. The work also found previously identified targets such as fibroblast growth factor receptor (FGFR) 1 and PIK3CA (amplified in 20%), EPHA2 (mutated in 7%), MET (amplified in 6%), PDGFR (amplified in 8-10%), EGFR and AKT (mutated in 2-5%), some of which are highlighted below (42,55,56).

Fibroblast growth factor receptor (FGFR)

FGFR1 is a member of the FGFR tyrosine kinases, and

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activation is responsible for igniting the PI3K/AKT and RAS/MAPK pathways that stimulate growth and angiogenesis in several cancers (including SCC). FGFR1 is amplified in approximately 20% of SCC, and has shown to be associated with cigarette smoking in a dose-dependent fashion. There is some discordance as to whether FGFR1 amplification serves as a negative prognostic factor in surgically resected SCC with Kim *et al.* and a recent meta-analysis by Chang *et al.* supporting this assertion (55,57-60). Several FGFR inhibitors exist, including cediranib, nintedanib, pazopanib, and ponatinib (46). Cediranib is no longer under investigation given lack of efficacy in an early randomized trial (61). Nintedanib was studied with docetaxel (*vs.* docetaxel and placebo) in advanced NSCLC; overall survival in the nintedanib arm was only significantly improved in the adenocarcinoma patients but not in the total study population (62). Pazopanib (a dual FGFR and VFGFR inhibitor) was under investigation (NCT01208064, recently terminated early) but it has been limited by its heavy toxicity profile (63,64). Ponatinib is still undergoing trials (NCT01935336) but prior studies with head and neck cancer (NCT01761747) have been terminated due to toxicity (65). Novel non-ATP competitive FGFR1 inhibitors derived from nordihydroguaiaretic acid (NDGA) have shown promise in FGFR1 amplified SCC (66).

Insulin-like growth factor (IGF) pathway

The IGF pathway was recently a subject of interest, most notably with the IGF1R monoclonal antibody figitumumab. Initial phase II studies had suggested a benefit in SCC specifically, but two different phase III studies with figitumumab with either chemotherapy or erlotinib were prematurely ended due to excess toxicity and a lack of improvement in overall survival. Though this toxicity seemed to be correlated with low levels of circulating IGF, further progress in this pathway has been slow (55,67,68).

PI3-AKT signaling pathway

The PI3K-AKT signaling pathway is another potential candidate for targeted therapy. PIK3CA copy-number gains occur in 20% of all lung cancers, and frequency is even higher in SCC. PIK3CA mutations occur in approximately 6.5% of SCC. There are several PI3K inhibitors that are being actively developed; these include dual PI3K/MTOR inhibitors, isoform-selective PI3K inhibitors, and pan-PI3K inhibitors (55,69,70).

Conclusions

Lung cancer remains the single deadliest cancer both in the US and worldwide. The great majority of SCC is attributed to cigarette smoking, which fortunately is declining alongside cancer incidence. While we have been at a therapeutic plateau for advanced squamous cell lung cancer patients for several decades, recent observations suggest that we are on the verge of seeing incremental survival improvements for this relatively large group of patients. Current studies have confirmed an expanding role for immunotherapy, a potential opportunity for VEGFR inhibition, and even future targets in FGFR and PI3K-AKT that collectively should improve survival as well as quality of life for those affected by squamous cell lung cancer over the next decade.

Acknowledgements

None.

Footnote

Conflicts of Interest: Benjamin A. Derman, Kathryn F. Mileham, and Marta Batus have nothing to disclose. Philip D. Bonomi discloses clinical trial support from Eli Lilly, Bristol Myers Squibb, and Merck, as well as honoraria for advisory boards from Eli Lilly and Merck. Mary J. Fidler discloses consulting fees from Celgene and Bristol Myers Squibb.

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Cite this article as: Derman BA, Mileham KF, Bonomi PD, Batus M, Fidler MJ. Treatment of advanced squamous cell carcinoma of the lung: a review. Transl Lung Cancer Res 2015;4(5):524-532. doi: 10.3978/j.issn.2218-6751.2015.06.07

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