Algorithm for the treatment of advanced or metastatic squamous non-small-cell lung cancer: an evidence-based overview

N. Daaboul MD,* G. Nicholas MD MSc,* and S.A. Laurie MD*

ABSTRACT

The treatment of squamous non-small-cell lung cancer (NSCLC) is evolving. In the past, the backbone of treatment was chemotherapy, with very few other options available. Fortunately, that situation is changing, especially with a better understanding of tumour biology. Various strategies have been tried to improve patient outcomes. The most notable advance must be immunotherapy, which has revolutionized the treatment paradigm for lung cancer in patients without a driver mutation. Immunotherapy is now the treatment of choice in patients who have progressed after chemotherapy and is replacing chemotherapy as upfront therapy in a selected population. Other strategies have also been tried, such as the addition of targeted therapy to chemotherapy. Targeted agents include ramucirumab, an inhibitor of vascular endothelial growth factor receptor 2, and necitumumab, a monoclonal antibody against epithelial growth factor receptor. Recently, advances in molecular profiling have also been applied to tumours of squamous histology, in which multiple genetic alterations, including mutations and amplifications, have been described. Research is actively seeking targetable mutations and testing various therapies in the hopes of further improving prognosis for patients with squamous NSCLC. Here, we review the various advances in the treatment of squamous NSCLC and present a proposed treatment algorithm based on current evidence.

Key Words Non-small-cell carcinoma of the lung, squamous cell carcinoma, targeted therapy, immunotherapy

INTRODUCTION

Lung cancer is a common malignancy and remains the cancer with the highest mortality rate in Canada[1]. Unfortunately, it is often diagnosed at an advanced incurable stage. Non-small-cell lung cancer (NSCLC) encompasses approximately 85% of lung cancers, with 20% of those cancers being squamous cell carcinoma (SCC)[2]. Squamous cell carcinoma is strongly associated with smoking. Its incidence has been steadily declining over time, mostly because of a parallel reduction in smoking.

Historically, the systemic treatment of advanced SCC was limited to palliative chemotherapy. Appropriate treatment delivery can be challenging because of the general demographics of the disease, with SCC patients tending to be older and to have more comorbidities. In recent years, more therapeutic options have become available. The most noteworthy would be immunotherapy, which has changed the treatment paradigm in NSCLC by improving outcomes. Nonetheless, we are still far from personalized medicine

in SCC of the lung—an approach that has been realized for adenocarcinomas, in which the discovery of driver mutations (such as those in *ALK* and *EGFR*) has allowed for the use of targeted therapy in selected patients. Recently, broader molecular genotyping has led to the description of multiple mutations that are potentially targetable in SCC. Data relating to targeted agents are still limited, and ongoing research is trying to determine the efficacy of such agents in a clinical setting.

Here, we review approved therapies for advanced and metastatic SCC of the lung. We also discuss various targeted therapies that are available or currently being investigated (Table I).

CYTOTOXIC CHEMOTHERAPY IN SCC

Initial Chemotherapy
Doublet chemotherapy, which must include a platinum agent (cisplatin or carboplatin) and which is given for 4–6 cycles, is a standard of care in first-line treatment of SCC

Correspondence to: Scott A. Laurie, The Ottawa Hospital Cancer Centre, 501 Smyth Road, Ottawa, Ontario K1H 8L6.
E-mail: slaurie@toh.ca ■ **DOI:** https://doi.org/10.3747/co.25.3792

TABLE I Targeted therapy agents mentioned in this article

Agent	Target	Side effects (not exhaustive)
Monoclonal antibodies		
Bevacizumab	VEGF-A	Hypertension, neutropenia, bleeding, impaired wound healing, proteinuria, gastrointestinal perforation
Ramucirumab	VEGFR2	Hypertension, neutropenia, bleeding, impaired wound healing, proteinuria, infusion reaction, gastrointestinal perforation
Cetuximab	EGFR	Fatigue, rash, diarrhea, infusion reaction, hypomagnesemia
Necitumumab	EGFR	Fatigue, rash, diarrhea, infusion reaction, hypomagnesemia
Tyrosine kinase inhibitors		
Erlotinib	EGFR	Gastrointestinal symptoms (diarrhea), rash, elevated liver enzymes
Gefitinib	EGFR	Gastrointestinal symptoms (diarrhea), rash, elevated liver enzymes
Afatinib	EGFR, HER2	Gastrointestinal symptoms (diarrhea), rash, elevated liver enzymes
Crizotinib	ALK, MET, ROS1	Rash, diarrhea, elevated liver enzymes, vision disorder, QT prolongation
Multikinase inhibitor		
Pazopanib	FGFR1, VEGFR1–3, PDGFR, Kit	Fatigue, cytopenia, increased liver enzymes, gastrointestinal symptoms (nausea, diarrhea), QT prolongation, hypertension, hair depigmentation
mTOR inhibitor		
Everolimus	mTOR	Fatigue, cytopenia, diarrhea, stomatitis, hypersensitivity syndrome, pneumonitis
Immune checkpoint inhibitors		
Nivolumab	PD-1	Autoimmune side effects including fatigue, infusion reaction, rash, gastrointestinal symptoms (diarrhea, colitis), endocrinopathies (dysthyroidism, adrenal insufficiency), increased liver enzymes, pneumonitis
Pembrolizumab	PD-1	

VEGF = vascular endothelial growth factor; VEGFR2 = vascular endothelial growth factor receptor 2; EGFR = epidermal growth factor receptor (also known as HER1 or ErbB1); HER2 = human epidermal growth factor receptor 2 (also known as ErbB2/*neu*); ALK = anaplastic lymphoma kinase; MET = hepatocyte growth factor receptor; Flt-3 = fms-related tyrosine kinase; FGFR1 = fibroblast growth factor receptor 1; PDGFR = platelet-derived growth factor receptor; mTOR = mechanistic target of rapamycin.

of the lung. In a large meta-analysis, two-drug regimens (compared with single-agent chemotherapy) were associated with significantly increased rates of response and overall survival (os)[3]. Such regimens are generally offered to patients with a good performance status, and randomized studies comparing those regimens with best supportive care have shown a benefit in terms of survival and quality of life[4]. A variety of drugs can be paired with platinum, the most common being paclitaxel, gemcitabine, or vinorelbine. Prolonged administration of this initial chemotherapy is not recommended; although chemotherapy use can have an effect on progression-free survival (pfs), its effect on survival has not been formally demonstrated[5].

No particular platinum-based doublet regimen has been proved to confer a clinically significant advantage over the others[6]. The choice is often based on safety profile and convenience of administration. Treatment intensification by adding a third chemotherapy agent has also not yielded positive outcomes. Response rates were increased, but did not translate into increased survival rates[7]. Histology offers insight into chemotherapy selection, but personalizing chemotherapy in scc of the lung is not yet achievable. Molecular biomarkers such as *ERCC1* and *RRM1* have not helped to identify potential responders in a clinical setting, despite encouraging preclinical data[8,9].

Notably, pemetrexed is not indicated in scc of the lung, whether in the first or subsequent lines of treatment. In a large phase III study comparing cisplatin–gemcitabine with cisplatin–pemetrexed in nsclc[10], the survival benefit observed in the cisplatin–pemetrexed arm introduced pemetrexed as an attractive treatment choice for lung adenocarcinoma, especially given its better tolerability. In contrast, the cisplatin–gemcitabine doublet was associated with better survival in scc. A detrimental effect on survival of cisplatin–pemetrexed was also observed in patients who had received prior chemotherapy. A possible explanation for pemetrexed resistance could be higher expression of one of its targets, thymidylate synthase, in squamous tumours[11].

Maintenance Therapy

Maintenance therapy aims to delay disease progression. Strategies include "switch maintenance" (in which initial chemotherapy is followed by a maintenance drug different from those used in the initial regimen) and "continuation maintenance" (in which a drug used in the initial regimen is continued alone, after the platinum agent has been dropped). Maintenance is offered when a patient experiences a favourable response or stable disease after first-line chemotherapy; patients who progress on their platinum doublet move on to second-line salvage therapy.

Various maintenance strategies using cytotoxic chemotherapy have been studied, including docetaxel[12], gemcitabine, and pemetrexed. Those agents have not been adopted as effective maintenance strategies in scc. For example, with gemcitabine, a longer pfs was noted without an effect on os[13]. The most widely used maintenance chemotherapy in nsclc is pemetrexed[14], but that approach does not apply in scc. In the jmen study, patients with non-squamous histology experienced a 3.2-month significant survival advantage. In contrast, patients with scc derived no benefit from maintenance pemetrexed [hazard ratio (hr): 1.03; *p* = 0.896][15].

Erlotinib was also studied in the maintenance setting. In the saturn trial, a modest improvement in os was observed for erlotinib maintenance compared with placebo (12 months vs. 11 months), but os was not statistically different between the scc (approximately 40% of the population) and the adenocarcinoma patients[16]. The iuno study compared maintenance erlotinib with erlotinib at disease progression in patients with advanced non-*EGFR*-mutated nsclc (36% scc). In contrast to the saturn trial, iuno found that maintenance erlotinib was not superior to second-line treatment (os: 9.7 months vs. 9.5 months; *p* = 0.82) in patients with *EGFR* wild-type lung cancer[17]. After the results of iuno were reported, the U.S. Food and Drug Administration (fda) modified the indication for erlotinib in nsclc, limiting it to *EGFR* mutation–positive tumours[18].

Based on the foregoing studies, maintenance therapy has been restricted mostly to nonsquamous histologies.

Chemotherapy at Progression

Upon disease progression after platinum doublet chemotherapy, patients deemed fit for treatment would, until recently, be offered single-agent docetaxel[19]. This taxane derivative has been proved effective when compared with best supportive care. Treatment with docetaxel is associated with significant prolongation of survival (7.0 months vs. 4.6 months; *p* = 0.047), with the benefits of therapy outweighing toxicity[20]. Compared with best supportive care, docetaxel is also associated with less deterioration in quality of life[21].

For many years, single-agent docetaxel was thus considered the standard second-line treatment at progression. That situation has changed with data now showing that immuno-oncology therapies are more effective than docetaxel in this setting. Docetaxel is now considered a possible treatment after progression on immunotherapy. Notably, docetaxel has not been compared with best supportive care in a third-line setting after immunotherapy failure.

IMMUNOTHERAPY

Immunotherapy has changed the treatment paradigm for nsclc, especially in patients with no driver mutations. It has introduced a new treatment modality for scc of the lung, for which proven and available treatments are not as diverse as they are for adenocarcinoma.

Immuno-oncology therapies include various immune checkpoint inhibitors such as antibodies directed against ctla-4, PD-1, and PD-L1. The fundamental mechanism of those drugs is to stimulate a patient's T-cell immune response to recognize and destroy cancer cells[22]. Carrying a high mutational burden can increase the likelihood of responding to immuno-oncology agents, and scc—because it is related to smoking and exposure to a multitude of carcinogens—is a tumour that ranks among those with the highest mutational burden[23]. Immunotherapy has a toxicity profile different from that of cytotoxic chemotherapy, and it seems to be better tolerated overall.

Immunotherapy in First-Line Treatment

In the keynote-24 trial, pembrolizumab, a PD-1 inhibitor, was associated with improved pfs and os in treatment-naïve patients with 50% tumour-cell staining for PD-L1 (compared with standard doublet chemotherapy)[24]. Pembrolizumab was continued in those patients until progression or unacceptable toxicity. The median pfs of 10.3 months, compared with 6.0 months for those receiving chemotherapy, represented a significant improvement [hr: 0.50; 95% confidence interval (ci): 0.37 to 0.68; *p* < 0.001], with a more favourable toxicity profile. Median survival was not reached in either arm at the time of analysis. The pfs advantage was detected in all histology types, including scc (18% of the entire cohort; hr: 0.35; 95% ci: 0.17 to 0.71). Those positive outcomes were not seen in CheckMate 026, which compared first-line nivolumab, another PD-1 inhibitor, with chemotherapy[25]. That trial did not meet its primary endpoint of pfs (4.2 months vs. 5.9 months, *p* = 0.251). However, less toxicity was observed in the nivolumab arm (grades 3–4 adverse events: 17.6% vs. 50.6%). CheckMate 026 was less restrictive with respect to PD-L1 expression, with 5% being a cut-off for high expression.

The keynote-24 trial is pivotal and will change the first-line treatment of metastatic nsclc without a driver mutation. Health Canada granted approval for pembrolizumab in treatment-naïve patients who have high tumour PD-L1 expression[26] and no contraindications to immunotherapy, the most common being active or recently treated autoimmune disease and interstitial lung disease. That approval has started changing practice, with some guidelines modifying recommendations for patients with advanced nsclc and no driver mutations. Pembrolizumab is now the preferred first-line treatment for patients with 50% or greater PD-L1 expression[27].

Immunotherapy at Progression

Nivolumab was the first immuno-oncology agent approved for the treatment of lung cancer. More specifically with respect to scc, the phase iii CheckMate 017 trial randomly assigned 272 patients with stage iv scc progressing during or after platinum-based chemotherapy to nivolumab or docetaxel. Median os was improved in the nivolumab group (9.2 months vs. 6.0 months; *p* < 0.001; hr: 0.59; 1-year os: 42% vs. 24%).

The immunotherapy response rate is fairly low (<20%); however, it seems that a subset of patients can derive long-term benefit from immunotherapy. In CheckMate 017, efficacy was independent of PD-L1 tumour expression[28], a result that differed from that in CheckMate 057, in which PD-L1 expression was predictive in a population having nonsquamous nsclc[29]. Additionally, in the keynote-010

study, which enrolled 1034 patients, participants experienced a longer os with pembrolizumab than with docetaxel. In that study, PD-L1 tumour expression had to be at least 1%. The median os was 10.4 months with pembrolizumab 2 mg/kg and 8.5 months with docetaxel ($p = 0.0008$). The survival advantage was demonstrated for all histology subtypes, including the scc subset (HR: 0.74; 95% CI: 0.50 to 1.09). The difference was more marked in patients with PD-L1 expression exceeding 50% (approximately 40% of patients), which further validated PD-L1 selection. In such patients, os was significantly longer with pembrolizumab (median: 14.9 months vs. 8.2 months; $p = 0.0002$)[30].

Pembrolizumab has also been granted accelerated approval by the FDA in advanced or metastatic high microsatellite instability or mismatch-repair-deficient solid tumours upon progression, regardless of tumour type[31]. That approval was based on efficacy data, the overall response rate being 39.6% in 149 patients. However, high microsatellite instability seems to be very infrequent in NSCLC[32].

Other anti–PD-L1 agents such as atezolizumab and durvalumab are also active in second- or subsequent-line treatment for lung cancer, including scc. In the phase III randomized OAK study comparing atezolizumab with second-line docetaxel, atezolizumab was associated with a survival benefit regardless of histology or PD-L1 expression. In the squamous subgroup (26%), median os was superior at 8.9 months compared with 7.7 months (HR: 0.73; 95% CI: 0.54 to 0.98)[33].

Currently, nivolumab is approved for the treatment of advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy, regardless of PD-L1 expression. Pembrolizumab, in the second line or beyond, is approved in patients with metastatic NSCLC and PD-L1 expression of 1% or greater. Government funding in Canada has been accepted in various provinces, making nivolumab and pembrolizumab more accessible.

Combination Immunotherapy With or Without Chemotherapy

Studies have demonstrated that specific chemotherapies commonly used in lung cancer can enhance the immunologic response to cancers[34]. That observation has led to research into combinations of immunotherapy and chemotherapy. Adding chemotherapy might add benefit for patients. It can be associated with higher response rates and more durable responses. It could also make combination therapy a treatment of choice for a broader population[35].

Combination immunotherapy could include giving an anti–CTLA-4 agent with a PD-1 or PD-L1 inhibitor. Such agents could be given together with or without standard chemotherapy. Early-phase trials are looking at various combination strategies. For example, in Canada, the Canadian Cancer Trials Group BR.34 trial (NCT03057106 at http://ClinicalTrials.gov) is looking at durvalumab–tremelimumab given with or without chemotherapy in patients with metastatic NSCLC. Another trial, KEYNOTE-021 (NCT02039674), is studying pembrolizumab in combination with chemotherapy or immunotherapy in participants with metastatic NSCLC. Based on a cohort in KEYNOTE-021, pembrolizumab given with carboplatin–pemetrexed was recently approved by the FDA for the first-line treatment of adenocarcinoma. Many combination trials are under way, and more details are expected in the future.

ANTIANGIOGENESIS AGENTS

Blocking neovascularization and tumour proliferation can theoretically reduce tumour growth. Bevacizumab is the most commonly studied antiangiogenesis agent in NSCLC. It targets the vascular endothelial growth factor pathway by inhibiting vascular endothelial growth factor A.

Bevacizumab has shown efficacy in NSCLC. It can also cause massive pulmonary hemorrhage, sometimes fatally so, as reported in earlier trials testing the combination of chemotherapy and bevacizumab[36]. Those events occurred more frequently in scc, which led to the early exclusion of patients with scc from the pivotal bevacizumab trials[37,38], including the randomized trial showing an os improvement of 2 months for paclitaxel–carboplatin plus bevacizumab compared with chemotherapy alone. Squamous-cell histology and the presence of hemoptysis are therefore contraindications to the administration of bevacizumab in NSCLC.

Other antiangiogenic agents have also been tested in NSCLC[39]. Ramucirumab, which binds directly to vascular endothelial growth factor receptor 2, demonstrated modest activity in NSCLC. Although patients with squamous histology could participate in the related trials, patients with major invasion of airway or blood vessels, a cavitating lesion, or a recent history of hemoptysis were notably excluded. The phase III REVEL trial assigned 1253 patients to docetaxel with or without ramucirumab after progression on a platinum doublet[40]. A small but statistically significant difference favoured the combination. The os, PFS, and response rate were all improved. For the squamous-cell subgroup (25% of patients), outcomes were similar but nonsignificant (os: 9.5 months vs. 8.2 months; HR: 0.88; 95% CI: 0.69 to 1.12; $p = 0.319$). Ramucirumab is the only antiangiogenesis drug that has an indication in scc. It has been approved by the FDA[41], but not by Health Canada. An approach using ramucirumab has not been widely accepted because the cost–benefit ratio of the combination seems marginal[42].

ANTI-EGFR AGENTS

Mutations of *EGFR* are very rare in scc and seem to be present only in mixed adenosquamous carcinomas[43]. The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors are usually the treatment of choice for patients with an activating *EGFR* mutation, mostly seen in adenocarcinoma[44]. These targeted agents have revolutionized the care of *EGFR*-positive lung cancer and are conventionally used first[45,46].

However, EGFR tyrosine kinase inhibitors have also been used in patients who progress after chemotherapy, regardless of tumour histology. Chemotherapy is usually more effective than erlotinib for second-line treatment in previously treated patients with NSCLC who have *EGFR* wild-type tumours. In the TAILOR trial, docetaxel was superior to erlotinib in *EGFR* wild-type NSCLC. Median os was 8.2 months compared with 5.4 months ($p = 0.05$), with a similar outcome for the scc subgroup (os HR: 0.57; 95% CI: 0.32 to 1.03)[47]. Nonetheless, in the Canadian-led

BR.21 trial, a survival benefit was shown for EGFR inhibitors compared with placebo in an unselected population that included a squamous-cell subset[48]. The response rate to erlotinib was low at 8.9%, and yet PFS (2.2 months vs. 1.8 months, $p < 0.001$) and OS (6.7 months vs. 4.7 months, $p < 0.001$) were better with erlotinib than with placebo. The benefit was seen mostly in adenocarcinoma patients; in the other histology subtypes, the survival difference was not significant (HR: 0.8; 95% CI: 0.6 to 1.0; $p = 0.7$).

Recently, the LUX-Lung 8 trial compared afatinib, an irreversible ErbB receptor family blocker, with erlotinib as second-line treatment in patients with advanced SCC of the lung after a platinum doublet[49]. The PFS (median: 2.6 months vs. 1.9 months; HR: 0.81; $p = 0.0103$) and OS (median: 7.9 months vs. 6.8 months; HR: 0.81; $p = 0.0077$) were both improved in the afatinib group. The ErbB family of receptors, including EGFR, is overexpressed in SCC, which could explain the outcome benefit seen with afatinib[50]. Afatinib could be an option for fit patients who have progressed on several lines of treatment and who are desirous of further treatment.

Inhibitors of the EGFR pathway also include monoclonal antibodies, of which the most studied are cetuximab and necitumumab. Their effect does not seem to be associated with an activating *EGFR* mutation, and so their use could be warranted in SCC. Cetuximab, a recombinant monoclonal antibody against EGFR, is not currently of use in NSCLC. The FLEX trial randomized 1125 previously untreated patients to cisplatin–vinorelbine with or without cetuximab. No change in outcome was reported. In the SCC subset (more than one third of the population), a trend toward benefit was observed for the combination arm (9 months vs. 8.2 months), but the difference did not reach statistical significance[51].

Investigation into anti-EGFR monoclonal antibody activity continued with necitumumab, a second-generation agent. The SQUIRE trial enrolled 1093 patients with SCC. Patients were randomized to treatment with cisplatin–gemcitabine given with or without necitumumab (days 1 and 8 of a 21-day cycle). Up to 6 cycles of combination therapy were administered, with patients having the possibility of continuing on maintenance necitumumab if they achieved clinical benefit (51% received maintenance for a median of 4 cycles). Compared with chemotherapy alone, the addition of necitumumab was associated with a survival advantage (11.5 months vs. 9.9 months; HR: 0.84; 95% CI: 0.74 to 0.96; $p = 0.01$) and an improvement in the disease control rate (82% vs. 77%, $p = 0.043$)[52].

The SQUIRE study was one of the first trials demonstrating a survival advantage for a new agent combined with doublet chemotherapy in a SCC-only population. The FDA and Health Canada approved necitumumab in combination with cisplatin–gemcitabine for the treatment of patients with metastatic squamous NSCLC who have not received prior therapy for advanced disease[53,54]. The clinical significance of necitumumab seems incremental and modest. The survival benefit of 1.6 months comes with a significantly increased risk of toxicities, which include thromboembolism, hypomagnesemia, and severe skin reactions (grades 3–4 adverse events: 7%, 9%, and 7% respectively with necitumumab vs. 2%, 1%, and 1% with chemotherapy alone).

PRECISION MEDICINE WITH TARGETED THERAPY

Next-generation technologies have provided invaluable information about cancer genomics, including those for lung cancer. The Cancer Genome Atlas project has published a comprehensive genomic characterization of SCC. They sequenced lung samples from 178 patients with SCC and identified a potentially targetable gene or pathway alteration in most of the samples studied[55]. Alterations in the fibroblast growth factor receptor (FGFR) kinase family were common. Mutations in *PIK3CA, PTEN, TP53, CDKN2A, NOTCH1* were also described. That study has opened the door to personalized medicine in SCC[56]. Describing the multitude of genetic aberrations in SCC is beyond the scope of this review; however, the subsections that follow discuss the mutations most often found in SCC—among them, *PIK3CA* mutations, FGFR amplification, *MET* mutations, and the potential targets currently studied in clinical trials.

FGFR1

Amplification of FGFR1 occurs in approximately 20% of patients with SCC of the lung[57]. The FGFR pathway plays a key role in signal transduction in lung cancer. Activation is responsible for igniting the PI3K/AKT and Ras/MAPK pathways that stimulate growth and angiogenesis in several cancers, including SCC[58]. Amplification of FGFR is associated with smoking and confers a worse prognosis[59,60].

Inhibitors of FGFR include nintedanib, pazopanib, and ponatinib, which target multiple tyrosine kinases[61]. Originally, FGFR was thought to be a very promising target because some inhibitors showed activity in preclinical models. However, clinical trials in lung cancer have shown only minimal activity of such inhibitors at the cost of increased toxicities, which include hypertension, gastrointestinal side effects, and rash[62]. For example, results with pazopanib have been disappointing. A clinical trial comparing maintenance pazopanib with placebo after platinum doublet chemotherapy in patients with NSCLC was terminated at the futility interim analysis[63].

The phase III LUME-Lung 1 study, in which nintedanib was combined with docetaxel, assessed the efficacy and safety of the combination as second-line therapy for NSCLC without any molecular selection. In the nintedanib arm, OS was improved only for the adenocarcinoma histology subgroup, but not for the overall cohort (median: 10.1 months vs. 9.1 months; HR: 0.94; 95% CI: 0.83 to 1.05; $p = 0.2720$)[64]. Studies with nintedanib (NCT01346540 and NCT01948141 at http://ClinicalTrials.gov) are continuing in a molecularly selected population with FGFR1 amplification. Other FGFR inhibitors are also in development and remain in the investigational phase[65,66].

PI3K Pathway

Genetic alterations in the *PI3K* family include mutations in *PIK3CA,* amplification of AKT3, and inactivation of *PTEN.* The incidence varies depending on trial reports, but genetic alterations of *PI3K* seem to present in approximately 50% of patients with SCC of the lung. The PI3K pathway is believed to be critical to the signal transduction system regulating essential cellular functions including cell growth and proliferation[67,68]. Various trials have previously tested

everolimus, an inhibitor of the mechanistic target of rapamycin (mTOR) complex 1, with disappointing results[69,70].

Several PI3K inhibitors are being actively developed, including isoform-specific and pan-isoform PI3KCA inhibitors and dual PI3KCA–mTOR inhibitors. None has yet shown impressive results. For example, buparlisib, an oral inhibitor of class I PI3K was deemed futile in a phase II study[71]. Trials investigating other selective PI3K inhibitors such as taselisib are in progress either as single agents or combined with chemotherapy.

c-Met

In NSCLC, multiple mechanisms of *MET* activation have been described. In the recently published phase III MET-lung study, patients with NSCLC were randomized to onartuzumab, an anti-MET antibody, plus erlotinib or to erlotinib alone. Increased expression of the MET protein was not associated with improved PFS or OS in patients who received both agents[72].

Although those results were disappointing, there is now renewed interest in *MET* exon 14 skipping mutation as a potential oncogenic driver. The deletion of the juxtamembrane domain of MET leads to enhanced signalling through the MET receptor pathway. To date, the deletion has been described in adenocarcinoma, in which 3%–4% of tumours harbour the mutation. New data suggest that the mutation could be also detected in SCC, possibly in the adenosquamous variant. Patients with the mutation might respond to c-Met inhibitors. Clinically significant tumour responses have been reported with off-label use of anti-MET tyrosine kinase inhibitors such as crizotinib or cabozantinib[73,74].

Multiple trials are under way evaluating the efficacy of targeted agents in SCC. The Lung-MAP study (NCT02154490 at http://ClinicalTrials.gov) is a lung cancer master protocol for patients with advanced SCC after progression on first-line treatment[75]. It is based on genomic testing of tumours through a next-generation sequencing platform. This collaborative clinical trial, led by SWOG, with Canadian Cancer Trials Group participation, aims to match predictive biomarkers with targeted drugs. Each biomarker is a single-arm phase II study in itself, and the substudies function independently. The primary objective for the studies is overall response rate, which could lead to a phase III trial randomizing a targeted treatment compared with standard-of-care therapy. This initiative is innovative in that it assesses compatibility with various novel treatments, increasing the likelihood of patients receiving a targeted agent. Further, patients without any mutation are offered immunotherapy, including nivolumab alone or a combination of nivolumab and ipilimumab.

SUMMARY

Squamous cell carcinoma is entering the era of precision medicine. Noteworthy developments during recent years are modifying the classical treatment algorithms that previously were based mostly on chemotherapy (Figure 1). Immunotherapy, in first or subsequent lines of treatment, has been a practice-changing development for patients without a driver mutation. Evidence from a randomized
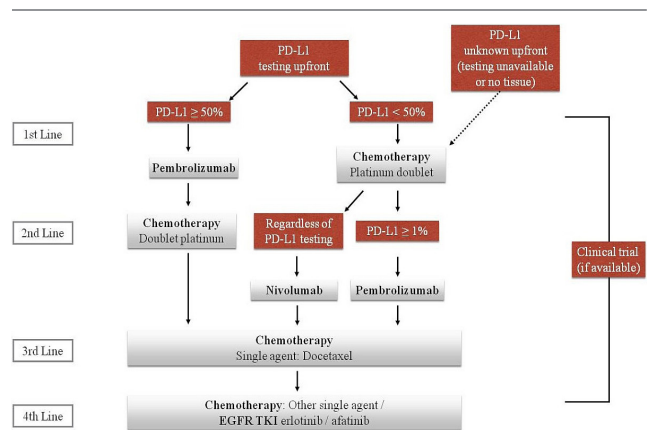
FIGURE 1 The current algorithm for the treatment of small-cell lung cancer. EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

controlled trial now supports first-line treatment with pembrolizumab in patients with high PD-L1 expression. Nonetheless, it is accepted that patients who progress after doublet chemotherapy and who have not previously received immunotherapy are to be offered immunotherapy (for example, nivolumab) regardless of PD-L1 expression. Researchers are looking into the increased benefit such drugs bring and are broadening the spectrum of administration. Thus, multiple ongoing trials are testing combination immunotherapies with or without chemotherapy. Some improvement in outcome has also been seen with ramucirumab and necitumumab combined with chemotherapy, although clinical application of those agents has not yet been widely accepted in Canada because of modest efficacy, significant toxicity, and cost. Lastly, tumour molecular sequencing has described a multitude of new mutations in SCC. Active research will probably provide more insight into the most targetable mutations and potentially effective agents. The discovery of newer treatments is definitely bringing hope to patients with advanced SCC.

CONFLICT OF INTEREST DISCLOSURES

AUTHOR AFFILIATIONS

*Division of Medical Oncology, The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON.

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